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REVIEW

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The impact of microbiome modulation on neutrophil levels and cardiovascular disease prevention

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ABSTRACT

Cardiovascular disease (CVD) continues to be a major worldwide health issue, mainly caused by inflammatory pathways. Neutrophils are crucial immune cells that have a significant impact on inflammation and tissue damage in the cardiovascular system. High levels of neutrophils play a key role in causing atherosclerosis, unstable plaques, and vascular damage, making high neutrophil counts a reliable indicator of higher cardiovascular disease risk. Recent research has concentrated on the gut microbiome, which is a complicated collection of microorganisms that impacts different bodily functions, such as immune regulation. Metabolites originating from the microbiome, like SCFAs and TMAO, can either enhance or reduce inflammation and have a notable effect on neutrophil activity. Although the potential for microbiome-based interventions to influence immune responses and lower the risk of CVD is impressive, numerous studies are constrained in their scope and duration, lacking a standardized method for comprehending these interactions. This review seeks to examine how changing the microbiome can affect neutrophil behavior and inflammation, highlighting the importance of ongoing clinical research and comprehensive, multi-omics methods to fully understand the benefits of using microbiome strategies for preventing and managing CVD.

KEYWORDS

Cardiovascular disease (CVD); Gut microbiota; Neutrophils; Short-chain fatty acids (SCFAs); Inflammation; Dysbiosis

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Introduction

Cardiovascular disease (CVD) is a significant global health issue, primarily driven by inflammatory processes that can lead to severe complications. Within the immune response, neutrophils play a critical role in mediating inflammation and contribute to tissue damage in the cardiovascular system. Excessive neutrophil activity is associated with the development of atherosclerosis, plaque instability, and vascular injury, establishing elevated neutrophil counts as a reliable predictor of increased CVD risk [1]. In recent years, the gut microbiome—a diverse collection of microorganisms in the gastrointestinal tract—has garnered significant attention in scientific research. This microbiome significantly influences various physiological functions, particularly immune regulation. The metabolites produced by the gut microbiome, such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), are critical factors in modulating inflammation and immune responses [2]. Specifically, SCFAs exert anti-inflammatory effects, while TMAO has been implicated in promoting inflammation and enhancing neutrophil activity [3].

Although the potential of microbiome-based interventions to effectively modulate immune responses and significantly lower CVD risk warrants further investigation, many studies often exhibit limitations in design and duration, hindering the development of a standardized approach to understanding the complex interactions between the microbiome, neutrophils, and cardiovascular health. To address these knowledge gaps, it is essential to undertake long-term clinical studies and adopt integrated, multi-omics approaches that combine genomic, metabolomic, and microbiomic data. These studies may elucidate how targeted microbiome strategies can optimize neutrophil activity and improve cardiovascular health. Ultimately, understanding these mechanisms could lead to innovative preventive strategies in CVD management, emphasizing the therapeutic potential of microbiome modulation. This comprehensive exploration of the microbiome's influence on inflammation and neutrophil regulation highlights the importance of interdisciplinary research in tackling CVD [4,5].

The Role of Neutrophils in Cardiovascular Disease

Overview of neutrophils and inflammation

Neutrophils, also called polymorphonuclear leukocytes, are crucial white blood cells for the innate immune system, known for their rapid travel to damaged tissues, they are the first responders to infection or injury locations. Upon being activated, neutrophils use different methods such as phagocytosis, degranulation, and generating reactive oxygen species (ROS) to get rid of pathogens and cellular waste. Even though rapid neutrophil activation is important for getting rid of infectious agents, if it continues for too long it can cause tissue damage and play a role in chronic inflammatory conditions like CVD [6].

Neutrophil-mediated vascular damage

In the context of CVD, neutrophils play a significant role in the development and progression of atherosclerosis. Following endothelial injury, neutrophils are recruited to the site of inflammation, where they release pro-inflammatory cytokines, chemokines, and enzymes that can damage surrounding tissues. This process contributes to endothelial dysfunction, which is a precursor to atherosclerosis [7].

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Specifically, neutrophils can enhance the uptake of lipids by macrophages and promote foam cell formation, a hallmark of atherosclerotic plaque development. The accumulation of neutrophils within the arterial wall can exacerbate plaque instability, increasing the risk of thrombosis and acute cardiovascular events such as myocardial infarction.

Neutrophil counts as a risk factor

Several epidemiological studies have found a connection between higher levels of neutrophils and a greater risk of cardiovascular issues. An example is the elevated neutrophil-to-lymphocyte ratios, which have been recognized as predictive indicators for negative cardiovascular events, such as death in individuals with coronary artery disease and heart failure [8]. Increased levels of neutrophils could indicate inflammation in the body and act as a marker for the severity of a disease. Additionally, chronic disorders like obesity, diabetes, and chronic kidney disease, which are linked to higher neutrophil activity, exacerbate the risk of heart disease.

Neutrophil Extracellular Traps (NETs)

Recent research has emphasized that neutrophils contribute to cardiovascular disease through the formation of neutrophil extracellular traps (NETs) [9]. NETs consist of DNA and antimicrobial proteins that form networks to capture and eradicate pathogens. However, NETs can also enhance blood clotting and inflammation in blood vessels. Finding NETs in atherosclerotic plaques is linked to plaque rupture and thrombosis, highlighting neutrophils' dual function in fighting infection and causing heart problems.

Therapeutic implications

The function of neutrophils in CVD has important treatment implications. New approaches to preventing and treating cardiovascular diseases may be found by focusing on neutrophil activation and recruitment. Potential therapeutic approaches include the use of anti-inflammatory agents that modulate neutrophil function, as well as interventions aimed at improving endothelial health and reducing systemic inflammation [10].

The Gut Microbiome and Immune Modulation

Gut Microbiome composition

The gut microbiome, found in the gastrointestinal tract, is made up of a variety of organisms such as bacteria, viruses, fungi, and archaea. This community plays a vital role in maintaining the host's health, especially by regulating their immune system. A diverse and robust microbiome enhances the immune response, while dysbiosis, marked by a reduction in beneficial bacteria and a rise in harmful ones, is linked to inflammatory conditions like CVD [11].

Microbiome's role in immune system modulation

The gut microbiome plays a crucial role in shaping the immune system, impacting both innate and adaptive immune reactions. Microbial byproducts, like SCFAs generated when fermenting dietary fibers, are essential for regulating immune function. Short-chain fatty acids (SCFAs) can support anti-inflammatory pathways, increase regulatory T cell (Treg) production, and decrease pro-inflammatory immune cell activation [12]. This communication between the microbiome and the immune system is essential for keeping balance and avoiding too much inflammation.

Link between gut microbiota and systemic inflammation

Dysbiosis has been associated with higher levels of systemic inflammation, which may play a role in the development of a range of diseases, such as CVD. For instance, an unbalanced gut microbiota could cause the release of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which can encourage vascular inflammation. Moreover, dysbiosis also impacts the integrity of the intestinal barrier, enabling microbes to pass through into the blood, leading to systemic inflammation and increasing the risk of cardiovascular issues [13].

Impact of diet on the Gut Microbiome

The diet has a crucial impact on regulating the gut microbiome. Diets rich in fiber from fruits, veggies, and whole grains support the growth of helpful microbes, boosting SCFA production and enhancing immune function [14]. On the other hand, diets rich in processed foods, sugars, and unhealthy fats may result in dysbiosis and heightened inflammation. New studies highlight how modifying one's diet can influence the gut microbiome to support heart health and reduce inflammation.

Therapeutic potential of microbiome modulation

Modifying the gut microbiome shows potential for treating cardiovascular disease and inflammatory conditions. Probiotics, which are live beneficial bacteria, are being studied for their ability to reestablish microbial equilibrium and enhance immune response [15]. Certain bacteria types, including *Lactobacillus* and Bifidobacterium, have demonstrated potential in clinical studies for their capacity to decrease inflammation. Prebiotics, such as undigestible fibers that support good gut bacteria, can contribute to a balanced microbiome [16]. Moreover, synbiotics, which merge probiotics and prebiotics, show promise in improving gut health and decreasing systemic inflammation.

Microbiome and Neutrophil Dynamics in Cardiovascular Disease

Microbiome-neutrophil interactions

The interactions between the gut microbiome and neutrophils provide key insights into inflammation's role in CVD. Neutrophils, a type of white blood cell and first-line defense of the immune system, are responsible for responding quickly to infection or injury. However, when neutrophils become overly active, they can contribute to tissue damage and chronic inflammation—both of which are significant in the development and progression of CVD [17]. The gut microbiome, consisting of trillions of microbes, influences neutrophil function by modulating systemic inflammation. This microbiome-neutrophil relationship is crucial in determining the body's inflammatory balance and, subsequently, cardiovascular health.

Role of Gut Microbiota in neutrophil activation

Research shows that the gut microbiome can regulate neutrophil function. Certain types of bacteria, such as specific strains of *Lactobacillus* and Bifidobacterium, can either boost or

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hinder the activation of neutrophils through different methods. For example, the fermentation of dietary fibers by gut bacteria produces short-chain fatty acids (SCFAs) such as butyrate, which help create an anti-inflammatory setting that could potentially decrease heightened neutrophil activity. On the other hand, an unhealthy gut flora, known as dysbiosis, may cause an elevated release of inflammatory substances like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [18]. This can boost the migration and stimulation of neutrophils, worsening vascular inflammation. Table 1 studies the comparative analysis of beneficial metabolites and harmful metabolites.

Table 1. Comparative analysis of beneficial vs. harmful microbial metabolites.

Type	Microbial Metabolites	Source	Effect on Neutrophils	Impact on Cardiovascular Health
Beneficial Metabolites	Short-Chain Fatty Acids (SCFAs): Acetate, Propionate, Butyrate	Produced by fermentation of dietary fibres (e.g., fruits, vegetables, whole grains)	Reduces neutrophil activation by promoting anti-inflammatory pathways and increasing Treg production.	Positive Impact: Lowers inflammation, reduces endothelial dysfunction, and lowers blood pressure.
	Indole and Derivatives	Breakdown of tryptophan by gut bacteria	Reduces neutrophil recruitment to vascular tissues and inhibits excessive inflammation.	Positive Impact: Lowers vascular inflammation, and supports endothelial integrity.
	Bile Acid Metabolites	Conversion of bile acids by gut bacteria	Modulates neutrophil response by reducing oxidative stress.	Positive Impact: Reduces cholesterol levels, and lowers cardiovascular risk.
	Polyphenol Metabolites	Derived from plant-based foods	Exerts antioxidant effects, reducing neutrophil-mediated oxidative stress.	Positive Impact: Lowers arterial stiffness, and improves lipid profiles.
	Sulfate-Reducing Metabolites	Sulfur-containing foods	Regulates neutrophil migration and prevents overactivation.	Positive Impact: Maintains vascular function in balance.
Harmful Metabolites	Trimethylamine N-oxide (TMAO)	Metabolism of dietary choline, L-carnitine (from red meat, eggs, dairy)	Enhances neutrophil activation and recruitment, promoting inflammation.	Negative Impact: Increases atherosclerosis risk, and promotes plaque rupture.
	Lipopolysaccharides (LPS)	Produced by Gram-negative bacteria during bacterial death	Triggers systemic inflammation and neutrophil activation.	Negative Impact: Promotes vascular inflammation, and increases CVD risk.
	Hydrogen Sulfide (H_2S) (in excess)	Produced by sulfate-reducing bacteria	Exacerbates oxidative stress and endothelial dysfunction.	Negative Impact: Promotes hypertension, and leads to vascular damage.
	Branched-Chain Amino Acids (BCAAs)	Fermentation of proteins	Increases neutrophil activity, contributing to insulin resistance.	Negative Impact: Associated with metabolic syndrome, promotes CVD risk.
	Phenylacetylglutamine (PAG)	Metabolism of amino acids by gut bacteria	Enhances neutrophil adhesion to endothelial cells.	Negative Impact: Increases thrombosis risk, associated with myocardial infarction.

Mechanisms of Interaction

Microbial metabolites and neutrophil modulation

Short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, are metabolites produced by gut bacteria during the digestion of dietary fiber. These SCFAs promote an anti-inflammatory environment, which can reduce neutrophil activation and dampen excessive inflammatory responses [19]. Butyrate, for instance, has been found to enhance the production of regulatory T cells, which help keep neutrophil activity in check. This anti-inflammatory influence of SCFAs supports a balance in neutrophil activation, lowering the risk of vascular damage that often accompanies CVD.

Conversely, the metabolite trimethylamine N-oxide (TMAO) has pro-inflammatory effects. TMAO is produced when gut bacteria metabolize certain nutrients, such as choline,

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found in foods like red meat [20]. Higher levels of TMAO in the blood are associated with increased neutrophil activation, which can exacerbate inflammatory responses within blood vessels, thereby contributing to the progression of atherosclerosis.

Dysbiosis and systemic inflammation

Dysbiosis, an imbalance in the gut microbiome where harmful bacteria outnumber beneficial species, can heighten systemic inflammation by disrupting the gut barrier. When the integrity of the gut barrier weakens, microbial components like lipopolysaccharides (LPS) can enter the bloodstream. LPS, a pro-inflammatory molecule, activates neutrophils and other immune cells, fueling systemic inflammation [21].

In CVD, chronic low-grade inflammation driven by dysbiosis increases neutrophil recruitment to vascular tissues, where they may exacerbate plaque formation within the arteries [22]. Over time, this heightened neutrophil activity can destabilize plaques, elevating the risk of thrombosis and acute cardiovascular events such as myocardial infarction.

Neutrophil extracellular traps

Neutrophil extracellular traps (NETs) are made up of DNA, enzymes, and antimicrobial proteins that neutrophils release to trap pathogens. Even though NETs play a role in the immune system, an overproduction of NETs can lead to inflammation and blood clotting issues, especially in blood vessels. Dysbiosis-induced neutrophil activation increases NET formation, which has been detected within atherosclerotic plaques [23]. The presence of NETs in these plaques is linked to their instability, creating a higher risk of rupture and subsequent cardiovascular events.

Potential for therapeutic intervention

The interaction between the microbiome and neutrophils opens avenues for therapeutic strategies to manage CVD. By modulating the gut microbiome, it may be possible to reduce neutrophil-driven inflammation. Dietary interventions rich in fiber, probiotics (beneficial bacteria like *Lactobacillus* and *Bifidobacterium*), and prebiotics (non-digestible fibers that nourish beneficial bacteria) have shown promise in restoring microbiome balance. These approaches could decrease the levels of pro-inflammatory metabolites like TMAO while increasing anti-inflammatory SCFAs, reducing neutrophil activation, and potentially lowering cardiovascular risk [24].

Impact on cardiovascular health

Neutrophils are integral to the inflammatory response associated with CVD. They contribute to the progression of atherosclerosis through mechanisms such as the formation of neutrophil extracellular traps (NETs), which can promote thrombosis and plaque destabilization [25]. The modulation of neutrophil activity by the gut microbiome highlights a potential pathway for therapeutic intervention. Restoring microbial balance through dietary adjustments or probiotics may help regulate neutrophil activity and mitigate cardiovascular risk.

Clinical implications

The modulation of the gut microbiome through probiotics, prebiotics, and synbiotics has emerged as a promising approach for reducing CVD risk. Each of these interventions offers unique benefits by influencing gut health, managing inflammation, and promoting a favorable lipid profile, which together can help in the prevention of CVD. Here's a deeper look into how these supplements work, based on findings from recent clinical studies:

1. Probiotic supplementation trials

Probiotic supplements contain live beneficial bacteria that can positively impact the gut microbiome when consumed regularly. In particular, strains such as *Lactobacillus* and *Bifidobacterium* are being studied for their ability to improve cardiovascular health. These probiotics are known to support digestive health, but they also play a broader role in managing inflammation and improving lipid profiles—both of which are essential in reducing CVD risk.
Clinical trials have demonstrated several key benefits:

- **Lipid profile improvement:** Some probiotic strains help lower levels of LDL cholesterol, the "bad" cholesterol linked to plaque buildup in arteries. By reducing LDL, probiotics can help slow or prevent the progression of atherosclerosis, a primary cause of CVD [26].
- **Reduction in inflammatory markers:** Persistent inflammation increases the likelihood of CVD, and probiotics aid in reducing inflammation by supporting the proliferation of beneficial bacteria that create anti-inflammatory compounds. For example, some probiotic strains can help increase the production of short-chain fatty acids (SCFAs) such as butyrate, which may decrease the function of pro-inflammatory molecules.
- **Mechanisms of action:** Probiotics exert their benefits by creating a healthier, more balanced microbiome that supports immune regulation and reduces the potential for inflammation-driven vascular damage. This reduction in systemic inflammation not only protects blood vessels but also promotes healthier blood pressure levels and overall cardiovascular function.

2. Prebiotics and dietary fiber

Prebiotics are indigestible fibers that serve as nourishment for helpful gut bacteria. Unlike probiotics, which add live bacteria to the microbiome, prebiotics nourish the existing beneficial microbes, helping them thrive. Many studies are showing that increasing prebiotic intake, particularly through dietary sources like fruits, vegetables, and whole grains, can significantly influence cardiovascular health.

Research findings highlight the following benefits:

- **Enhanced SCFA production:** Beneficial gut bacteria create SCFAs such as acetate, propionate, and butyrate through the digestion of prebiotics. SCFAs possess anti-inflammatory characteristics and aid in maintaining a well-regulated immune reaction, leading to a decrease in the persistent inflammation commonly linked to CVD [27]. Butyrate is especially recognized for its function in fortifying the gut barrier and decreasing the transfer of pro-inflammatory substances into the bloodstream.
- **Blood pressure and inflammation regulation:** Prebiotics have been linked to enhancements in blood pressure and markers of inflammation. The growth of anti-inflammatory bacteria is promoted by fermenting prebiotic fibers, ultimately resulting in decreased cardiovascular risk and

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lower blood pressure. For instance, consuming a diet high in fiber has been linked to lower levels of C-reactive protein, which is an indicator of inflammation within the body.

- **Gut Microbiota composition improvement:** Prebiotics selectively promote the growth of beneficial bacteria over harmful species, thereby contributing to a more balanced and resilient microbiome. This healthier gut environment supports the production of metabolites that aid in vascular health, further underscoring the cardiovascular benefits of a fiber-rich diet.

3. Synbiotics and combined approaches

Synbiotics are products that combine probiotics and prebiotics, offering a synergistic approach to enhancing gut health [28]. By delivering both beneficial bacteria and the nutrients needed to support their growth, synbiotics can potentially provide more comprehensive benefits for cardiovascular health.

Research into synbiotic interventions reveals promising outcomes:

- **Greater microbiota diversity:** Synbiotics increase the diversity of microbial species within the gut, which is a key indicator of gut health. A diverse microbiome is associated with a more stable ecosystem that resists inflammation and supports balanced immune responses. This diversity is especially important for reducing CVD risk, as a varied microbiome can better manage inflammatory triggers.
- **Enhanced SCFA production:** Synbiotics have been shown to promote SCFA production more effectively than probiotics or prebiotics alone. SCFAs help modulate inflammation and improve vascular function by supporting endothelial health, the layer of cells that lines blood vessels. This effect is beneficial for managing blood pressure and reducing the risk of atherosclerosis [29].
- **Improved Cardiovascular risk factors:** Studies indicate that synbiotics can improve multiple cardiovascular risk factors, including blood lipid profiles, inflammatory markers, and blood glucose levels. By combining probiotics that reduce LDL cholesterol with prebiotics that support anti-inflammatory bacteria, synbiotics offer a holistic approach to managing the metabolic aspects of cardiovascular health.

Limitations of Current Studies

This section addresses the challenges and limitations of the existing research on microbiome modulation for cardiovascular prevention. It discusses issues such as small sample sizes, short intervention durations, variability in individual microbiomes, and the need for a clearer understanding of the underlying biological mechanisms. The focus is on identifying gaps that future research should address to strengthen the evidence base.

Challenges in Current Research

The current research on microbiome modulation for cardiovascular disease prevention faces several challenges and limitations. One significant issue is the small sample sizes in many studies, which can limit the generalizability of findings to broader populations. Additionally, short intervention durations often fail to capture long-term effects on cardiovascular health, leaving gaps in understanding the sustained benefits of probiotic and prebiotic supplementation. Variability in individual microbiome composition, influenced by factors such as diet, genetics, and lifestyle, complicates the interpretation of results and may lead to inconsistent outcomes [30]. Furthermore, there is a lack of detailed mechanistic understanding regarding how specific microbial changes translate into cardiovascular benefits, hindering the development of targeted therapies. Lastly, many studies do not adequately control for confounding factors, which can skew results related to cardiovascular endpoints. Addressing these limitations is crucial for advancing the field and establishing effective microbiome-based interventions for cardiovascular health.

Conclusions

The current research indicates the potential benefits of microbiome modulation—through probiotics, prebiotics, and synbiotics—for preventing cardiovascular disease, several key challenges require systematic investigation to fully realize these interventions. Notably, many studies suffer from limited sample sizes, short durations, and significant variability in individual microbiomes, complicating the applicability of findings across diverse populations. Additionally, the mechanisms by which changes in gut microbiota influence cardiovascular health outcomes remain inadequately understood. Future research should focus on larger, longer-term clinical trials with specific demographic and clinical parameters to clarify these relationships and establish evidence-based guidelines for the application of microbiome modulation as a strategy for reducing cardiovascular risk. By addressing these gaps, researchers can improve the understanding of the interplay between gut health and cardiovascular well-being, ultimately leading to more targeted therapeutic options.

Disclosure statement

No potential conflict of interest was reported by the author.

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