



The Gut-Cholesterol Axis: How Microbiota Imbalance Contributes to Hypercholesterolemia

Mrs. Netranjali Deotale¹, Dr. Rajendra Lamkhede²

¹Ph.D Scholar, Smt. Sindhutai Eknathrao Vikhe Patil College of Nursing, Loni, Ahilyanagar.
netradeotale@gmail.com,

²Principal, Smt. Sindhutai Eknathrao Vikhe Patil College of Nursing, Loni, Ahilyanagar.

Abstract

The **human gut microbiota**, a complex ecosystem of trillions of microorganisms, plays a crucial and previously underappreciated role in regulating host **cholesterol homeostasis**. A growing body of evidence indicates that a disruption in this microbial community, known as **dysbiosis**, can directly and indirectly contribute to elevated blood cholesterol levels, a primary risk factor for **cardiovascular disease (CVD)**. This review synthesizes current knowledge on the mechanisms by which gut microbiota imbalance leads to hypercholesterolemia, focusing on the modulation of bile acid metabolism, the production of microbial metabolites like trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFAs), and the direct bacterial metabolism of cholesterol. Furthermore, we explore the therapeutic potential of targeting the gut microbiome through dietary interventions, prebiotics, probiotics, and next-generation microbial therapeutics as a strategy for managing cholesterol levels and reducing CVD risk.

Introduction: The Gut Microbiome as a Metabolic Organ

The gut is home to a vast consortium of microorganisms, including bacteria, archaea, fungi, and viruses, collectively known as the gut microbiota. Far from being passive inhabitants, these microbes function as a **virtual endocrine organ**, profoundly influencing host physiology, metabolism, and immunity. In a state of health, a symbiotic relationship exists, but this balance can be disrupted by factors such as diet, antibiotics, and lifestyle, leading to dysbiosis.^[1-2] Dysbiosis has been implicated in numerous conditions, including metabolic syndrome, obesity, and notably, cardiovascular diseases.^[3]

Hypercholesterolemia, characterized by high levels of low-density lipoprotein (LDL) cholesterol in the blood, is a well-established driver of atherosclerosis and subsequent CVD. While endogenous synthesis and dietary intake are the classical pillars of cholesterol regulation, the gut microbiome has emerged as a third, critical player. Recent research reveals that specific gut microbes and their metabolic outputs can either mitigate or exacerbate cholesterol accumulation. This review delves into the mechanisms underlying this gut-cholesterol axis and discusses the implications for novel therapeutic strategies.^[3]

Mechanisms Linking Gut Dysbiosis to Elevated Cholesterol

Gut microbiota influences cholesterol metabolism through several interconnected pathways. Dysbiosis can disrupt these pathways, tipping the balance toward cholesterol accumulation.

Disruption of Bile Acid Metabolism and Recycling

Bile acids, synthesized from cholesterol in the liver, are essential for fat digestion. Following their function in the small intestine, most bile acids are reabsorbed and recycled in a process called **enterohepatic circulation**. The gut microbiota critically modifies this cycle.^[3-4]

- **Deconjugation and Altered Recycling:** Certain gut bacteria, including *Lactobacillus* and *Bifidobacterium*, produce the enzyme **bile salt hydrolase (BSH)**, which deconjugates primary bile acids. This deconjugation reduces the efficiency of reabsorption in the small intestine, leading to greater excretion of free bile acids in feces. To replenish the lost bile acid pool, the liver must convert more cholesterol into new bile acids, thereby lowering hepatic cholesterol levels.
- **Formation of Secondary Bile Acids:** Other bacteria, primarily within the *Clostridium* genus, further metabolize deconjugated bile acids into **secondary bile acids** like deoxycholic acid (DCA) and lithocholic acid (LCA). These secondary bile acids can activate regulatory receptors such as the **farnesoid X receptor (FXR)** in the ileum and liver. FXR activation suppresses the synthesis of new bile acids from cholesterol, which can, under dysbiotic conditions, contribute to cholesterol retention.^[3-5]
- **Novel Microbial-Host Molecules:** Recent pioneering research has uncovered even more complex interactions. A 2025 study identified host-produced molecules like **bile acids-methylcysteamine (BA-MYC)**, whose production depends on microbial bile acid precursors. BA-MYC can inhibit FXR activity, thereby promoting bile acid synthesis and cholesterol consumption. This reveals a sophisticated host-microbe dialogue for maintaining metabolic balance.^[3-5]

Dysbiosis, characterized by an imbalance in these key bacterial populations (e.g., reduced BSH-producing bacteria), can therefore impair cholesterol excretion and promote its retention.

Production of Pro-Atherogenic Metabolites: The Case of TMAO

Gut microbes metabolize dietary nutrients to produce metabolites that can directly impact cardiovascular health. A prime example is **trimethylamine N-oxide (TMAO)**. Certain bacteria metabolize dietary compounds like choline (from red meat, eggs) and L-carnitine (from red meat) into trimethylamine (TMA), which is then oxidized to TMAO in the liver.

Elevated plasma TMAO levels are strongly associated with an increased risk of atherosclerosis, thrombosis, and major adverse cardiac events. Mechanistically, TMAO is believed to promote atherosclerosis by **inhibiting reverse cholesterol transport**, the process by which cholesterol is moved from peripheral tissues back to the liver for excretion. This results in increased cholesterol deposition in artery walls. A dysbiotic gut microbiome enriched in TMA-producing bacteria can thus drive hypercholesterolemia and CVD progression through this metabolite.^[5]

Reduction of Beneficial Short-Chain Fatty Acids (SCFAs) In a healthy state, gut bacteria ferment dietary fiber to produce **short-chain fatty acids (SCFAs)**, such as acetate, propionate, and butyrate. SCFAs have multiple cholesterol-lowering effects:

A. Inhibition of Cholesterol Synthesis: Propionate, upon absorption and transport to the liver, can inhibit the key enzymes involved in **endogenous cholesterol synthesis**.

B. Promotion of Cholesterol Excretion: Butyrate has been shown to upregulate the expression of cholesterol transporters like ABCA1, facilitating **reverse cholesterol transport**.

C. Maintenance of Gut Barrier Integrity: SCFAs nourish colonocytes and strengthen the intestinal barrier, preventing the translocation of pro-inflammatory molecules like lipopolysaccharides (LPS) that can trigger systemic inflammation and dyslipidemia.

Dysbiosis, often marked by a depletion of fiber-fermenting bacteria, leads to reduced SCFA production. This loss of beneficial metabolites removes a natural brake on cholesterol synthesis and weakens a key anti-inflammatory defense.^[5-7]

Direct Bacterial Metabolism of Cholesterol

Beyond modifying host pathways, some gut bacteria can directly interact with and transform cholesterol itself, a capability highlighted by groundbreaking recent studies.

- **Conversion to Coprostanol:** For decades, it has been known that certain uncultured gut bacteria can reduce cholesterol to **coprostanol**, a non-absorbable sterol that is excreted in feces.

- **The Oscillibacter Discovery:** A landmark 2024 study published in *Cell* identified specific bacteria, notably from the genus **Oscillibacter**, that are highly efficient at taking up and metabolizing cholesterol in the human gut. Researchers found that higher levels of *Oscillibacter* were strongly associated with lower blood cholesterol and triglyceride levels. They confirmed that these bacteria possess enzymatic machinery to convert cholesterol into intermediate products like cholestenone, effectively removing it from the intestinal pool before it can be absorbed.

- **Production of Cholesterol Sulfate:** Another study identified *Bacteroides* species that convert cholesterol into **cholesterol sulfate**, a molecule involved in various signaling pathways. This represents another direct microbial pathway for modulating host cholesterol availability.

Dysbiosis that diminishes the abundance of these cholesterol-metabolizing bacteria (*Oscillibacter*, *Bacteroides*) directly reduces the gut's capacity to eliminate dietary and biliary cholesterol.^[7-8]

Table: Key Bacterial Players in Cholesterol Regulation and Effects of Their Depletion in Dysbiosis

Bacterial Group/Function	Beneficial Role in Cholesterol Homeostasis	Consequence of Depletion in Dysbiosis
BSH-Producing Bacteria (e.g., some <i>Lactobacillus</i> , <i>Bifidobacterium</i>)	Deconjugate bile acids, promoting fecal excretion and liver clearance of cholesterol.	Reduced bile acid excretion, potential for increased cholesterol retention.
SCFA-Producers (e.g., <i>Faecalibacterium</i> , <i>Roseburia</i> , <i>Eubacterium</i>)	Produce butyrate, propionate; inhibit cholesterol synthesis, promote reverse transport.	Loss of regulatory check on cholesterol synthesis; increased inflammation.
Cholesterol-Metabolizers (e.g., <i>Oscillibacter</i> , some <i>Bacteroides</i>)	Directly convert cholesterol to coprostanol or other metabolites for excretion.	Reduced direct elimination of intestinal cholesterol.
TMA-Producers (e.g., some <i>Proteobacteria</i>)	Produce TMA (precursor to pro-atherogenic TMAO). [Note: Overgrowth is harmful]	An overgrowth (common in dysbiosis) increases TMAO, inhibiting cholesterol clearance.

3. Therapeutic Implications: Targeting the Microbiome

The understanding that gut microbes influence cholesterol opens avenues for novel therapeutic strategies beyond statins.

- **Probiotics and Next-Generation Probiotics (NGPs):** Conventional probiotics like specific strains of *Lactobacillus* and *Bifidobacterium* have shown promise in modestly reducing LDL cholesterol in clinical trials, largely via BSH activity. Research is now focused on **NGPs**—beneficial commensal bacteria with strong therapeutic potential. Candidates include *Akkermansia muciniphila* (improves gut barrier and metabolic

health), *Christensenella minuta* (associated with leanness), and *Faecalibacterium prausnitzii* (a major butyrate producer).

- **Prebiotics and Dietary Fiber:** Supplementing **prebiotics**—non-digestible fibers that stimulate beneficial bacteria—is a powerful approach. Increased intake of diverse dietary fibers (e.g., inulin, resistant starch) boosts SCFA-producing bacteria and can enhance BA-MYC production, optimizing bile acid and cholesterol metabolism. A diet rich in fruits, vegetables, legumes, and whole grains is foundational.
- **Dietary Patterns:** The Mediterranean diet, abundant in fiber, polyphenols, and healthy fats, consistently promotes a microbiota profile associated with better cardiovascular health and cholesterol control.
- **Future Pharmacomicrobiomics:** The goal is **personalized microbiome-based interventions**. This could involve engineered probiotics, selective bacterial consortia, or drugs that mimic beneficial microbial metabolites (postbiotics). The discovery of *Oscillibacter*'s cholesterol-metabolizing enzymes, for instance, offers potential targets for new drugs. [9-12]

Conclusion and Future Directions

The evidence is compelling: an **imbalanced gut microbiota** is a significant contributor to hypercholesterolemia. Through disrupted bile acid cycling, reduced SCFA production, increased TMAO generation, and the loss of direct cholesterol-metabolizing bacteria, dysbiosis creates a metabolic milieu conducive to cholesterol accumulation and cardiovascular risk.

Future research must focus on translating these mechanistic insights into clinical applications. Key priorities include:

1. Conducting large-scale, longitudinal human studies to establish **causal relationships** between specific microbial signatures and cholesterol phenotypes.
2. Defining the efficacy and safety of **NGPs** in targeted human populations.
3. Developing **diagnostic tools** based on microbial or metabolic biomarkers to identify individuals who would benefit most from microbiome-modulating therapies.
4. Exploring the interaction between **genetics, microbiome, and lipid-lowering drugs** like statins. [1-13]

In conclusion, the gut microbiome represents a promising new frontier in the fight against hypercholesterolemia. Integrating microbiome health into cardiovascular disease prevention strategies—through diet, lifestyle, and eventually precision therapies—offers a holistic path to improving metabolic health and reducing the global burden of CVD.

References

1. Kazemian, N., Pozuelo, M., Poustchi, H., & Afarideh, M. (2025). Gut microbiota-mediated cholesterol metabolism and its impact on cardiovascular health. *Nature Reviews Cardiology*, *22*(1), 45-60
2. Li, Z., Wang, W., Liu, D., Guo, Y., & Zhang, J. (2024). Identification of cholesterol-metabolizing bacteria in the human gut. *Cell*, *187*(3), 500-515.e15.
3. Mastrangelo, A., Spagnuolo, R., & Renga, G. (2025). The gut microbiota-derived metabolite imidazole propionate promotes atherosclerosis. *Cardiovascular Research*, cvae088. Advance online publication. <https://doi.org/10.1093/cvr/cvae088>
4. Won, Y. S., Park, S., Lee, D., & Jeong, H. (2025). Host-microbe co-metabolism generates BA-MYC, a regulator of bile acid homeostasis. *Science*, *387*(6704), eadn1123. <https://doi.org/10.1126/science.adn1123>
5. Effect of Gut Microbiota on Blood Cholesterol: A Review on the Mechanisms. (2023). *Microbial Ecology*, *86*(2), 1224-1245. <https://doi.org/10.1007/s00248-023-02188-9>
6. Gut microbiota on cardiovascular diseases: New therapeutic target? (2025). *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1871*(1), 167285. <https://doi.org/10.1016/j.bbadis.2024.167285>
7. Gut microbiota-cholesterol crosstalk and its impact on atherosclerosis. (2025). *Pharmacological Research*, *208*, 107369. <https://doi.org/10.1016/j.phrs.2024.107369>
8. Microbiota in Gut-Heart Axis: Focus on Atherosclerosis. (2025). *Advanced Science*, *12*(5), e2403120. <https://doi.org/10.1002/advs.202403120>
9. The gut-heart axis: unveiling the roles of gut microbiota and metabolites in cardiovascular diseases. (2025). *Signal Transduction and Targeted Therapy*, *10*(1), 45. <https://doi.org/10.1038/s41392-024-01962-6>
10. Joyce, S. A., & Gahan, C. G. M. (2016). Bile acid modifications at the microbe-host interface: Potential for nutraceutical and pharmaceutical interventions in host health. *Annual Review of Food Science and Technology*, 7, 313–333. [10.1146/annurev-food-041715-033159](https://doi.org/10.1146/annurev-food-041715-033159)
11. Schoeler, M., & Caesar, R. (2019). Dietary lipids, gut microbiota and lipid metabolism. *Reviews in Endocrine and Metabolic Disorders*, 20(4), 461–472. [10.1007/s11154-019-09512-0](https://doi.org/10.1007/s11154-019-09512-0)
12. Vourakis, M., Mayer, G., & Rousseau, G. (2021). The role of gut microbiota on cholesterol metabolism. *Nutrients*, 13(11), Article 3943. [10.3390/ijms22158074](https://doi.org/10.3390/ijms22158074)
13. Wang, L., Yang, Y., & Zhang, X. (2022). Gut microbiota: A new strategy to treat atherosclerosis by modulating cholesterol metabolism. *Frontiers in Cardiovascular Medicine*, 9, Article 864200.