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GUT MICROBIOME IN METABOLIC DISORDERS

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Abstract

The human gut microbiome, which amounts to trillions of microbes, plays a role in the maintenance of metabolic homeostasis. The advances of recent times in metagenomics and metabolomics have established that changes in gut microbial composition, or dysbiosis, are strongly associated with metabolic disorders such as obesity, T2DM, metabolic syndrome, and NAFLD. Studies demonstrate that T2DM patients have a 15–25% reduction in butyrate-producing bacteria (e.g., *Faecalibacterium prausnitzii, Roseburia spp.*) and a 40% increase in opportunistic pathogens (*Escherichia, Ruminococcus gnavus*) compared to healthy controls. Short-chain fatty acids (SCFAs) of microbiota such as acetate, propionate, and butyrate have been found through experimental trials to strongly control host metabolism to increase insulin sensitivity by 25–40% and reduce fasting glucose levels by up to 1.2 mmol/L ($p < 0.05$). In parallel, fecal microbiota transplantation (FMT) from lean donor to obese or insulin-resistant recipient resulted in a median rise in peripheral insulin sensitivity from 26.2 to 45.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ after six weeks ($p < 0.05$).In addition, diet interventions like high-fiber supplementation were found to increase circulating SCFAs by 60–70%, which contributed to enhanced lipid metabolism and reduced low-grade inflammation indicated by a 35% decrease in plasma TNF-α ($p < 0.01$). In spite of these promising results, interindividual variation and methodological heterogeneity—most notably, sequencing depth and microbial diversity metrics—preclude direct comparability between studies.

To sum up, numerous pieces of evidence indicate that the selective adjustment of gut microbiota through prebiotics, probiotics, diet, and FMT has a very promising therapeutic potential for the handling of metabolic disorders. The full understanding of these complex interactions between the host and microbes may lead to the development of precision therapies based on the microbiome for the prevention and treatment of metabolic diseases.

Key words: Gut microbiome, metabolic disorders, obesity, type 2 diabetes, short-chain fatty acids, dysbiosis, metabolic syndrome

1. Introduction

Lynch and Pedersen, 2016 defined human gut microbiome as an exquisite nature-like ecosystem where trillions of different microorganisms live together in perfect harmony. This microbial community consists of a very diverse group which includes not only bacteria but also archaea, fungi, protozoa, and viruses, among others. And all of them have their own specific niche alongside performing some important function inside the host. The bacterial species of the microbiome are most complex and strongest in their influence over human health. These microorganisms play very major roles not only in digestion, immune function, and metabolism but also in brain and organ cross-talk through their signaling capability. Besides the gut microbiota also the host partner in a mutualistic and ever-changing relationship that grants the host physiological homeostasis and immunity against invading pathogens (Fan & Pedersen, 2021). The disturbances in such a fragile balance—the situation called microbial dysbiosis—have consequences that go beyond the guts and affect systemic metabolism, immunity, and even the susceptibility to diseases.

Gut microbiota has historically been appertained to as a" forgotten organ" because of its high metabolic eventuality and as a pivotal factor in promoting metabolic homeostasis (Shreiner et al., 2015). In the normal human, the microbial foliage ferments non-absorbed factors of diet similar as resistant beans, oligosaccharides, and salutary fiber to give short- chain adipose acids(SCFAs) like acetate, propionate, and butyrate. Short- chain adipose acids(SCFAs), give energy to colonocytes and are involved in a variety of metabolic and immunological processes including goods on inflammation, glucose forbearance(Canfora et al., 2019). Also lipid product along with detoxification of xenobiotics and conservation of epithelial hedge integrity, the microbiome helps to synthesize important vitamins including vitamin K, biotin, and folate. Notably, numerous factors affect this microbiome: age, diet, genes, environment, antibiotic exposure, and way of life (Valdes et al., 2018). But when the microbial community is disrupted through unbalanced diet, repeated antibiotic treatment, lack of exercise, or environmental toxins—dysbiosis occurs. This changed status of microbes leads to dysregulation of energy metabolism, increased intestinal permeability ("leaky gut"), and induction of systemic inflammation, all leading to the etiology and pathogenesis of metabolic disease. There is increasingly available experimental and clinical evidence to support the suggestion that dysbiosis is not only a consequence of metabolic disorders but also a cause that may be responsible for initiating and aggravating them (Cani et al., 2007; Turnbaugh et al., 2006).
Metabolic diseases such as obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) have emerged as major public health issues in the 21st century. As per the World Health Organization (WHO, 2022), there has been nearly a twofold increase in obesity since 1975, with over 650 million adults being obese globally. Likewise, T2DM affects more than 460 million individuals and NAFLD became the predominant etiology of chronic liver disease with a strong association with obesity and insulin resistance. Previously, such diseases were primarily thought to be the consequences of caloric excess, physical inactivity, and genetics. New understanding from gut microbiome science has transformed thought patterns, and microbial form and function are now implicated as key drivers of host metabolism (Fan & Pedersen, 2021).

The microbiota acts via a number of different pathways. It ferment dietary polysaccharides to produce SCFAs, which regulate energy harvest and hormonal signaling. It also regulates bile acid metabolism, choline, branched-chain amino acid (BCAA), and lipid metabolism and thus affects insulin sensitivity and lipid homeostasis. The microbiota also interacts bidirectionally with the immune system and modulates inflammatory responses that affect adipose tissue and hepatic metabolism (Canfora et al., 2019). With metabolic diseases, this balance is lost and results in metaflammation, i.e., chronic low-grade inflammation, which perpetuates insulin resistance and metabolic derangement.

A repeated finding in these studies is that metabolic disease is characterized by altered microbial diversity and composition. On the whole, obese and T2DM subjects have lower microbial richness, depletion of its beneficial members like *Akkermansia muciniphila* and Faecalibacterium prausnitzii, and enrichment of potentially pathogenic members of the Firmicutes phylum relative to Bacteroidetes (Larsen et al., 2010; Dao et al., 2016). Such changes in community structure modify metabolic end products and impair gut barrier function. For instance, A. muciniphila is a highly reported mucin degrader in the intestinal epithelium and mucus inducer that promotes gut barrier function and averts inflammation (Everard et al., 2013). Its absence is correlated with obesity, glucose intolerance, and NAFLD, whereas A. muciniphila supplementation was reported to increase insulin sensitivity and lipid metabolism in animal and human studies (Dao et al., 2016).

Similarly, F. prausnitzii, which is one of the prevalent butyrate-producing bacteria, is anti-inflammatory by inhibiting the activation of nuclear factor kappa B (NF-κB) and eliciting regulatory T cell response (Morrison & Preston, 2016). Reduced concentration was seen in inflammatory bowel disease, obesity, and T2DM patients. This reduction in butyrate-producing bacteria also causes impaired intestinal epithelial health and increased gut permeability, enabling lipopolysaccharides (LPS)—a pro-inflammatory lipid component of Gram-negative bacteria—to be transferred to systemic circulation. The process, termed metabolic endotoxemia, causes the activation of toll-like receptor 4 (TLR4) and systemic inflammation, resulting in impaired insulin signaling (Cani et al., 2007).

Moreover, dysbiosis regulates energy harvesting from the diet. Turnbaugh et al. (2006) had previously demonstrated that humans who are obese possess microbiomes that have better calorie extraction from complex carbohydrates with a consequent heightened fat storage without the necessity of augmented food intake. This "obese microbiome" has been experimentally passed on to germ-free mice, resulting in weight gain, which represents causal evidence for linkage between gut microbes and host adiposity.

The interaction of the host with gut microbiota is very intricate in nature, comprising many different factors like metabolism, endocrine activity, and immune functions. Of all the compounds released by gut bacteria, short-chain fatty acids (SCFAs), bile acids, indoles, and amino acid derivatives are regarded as significant signaling molecules, as they can modulate host metabolic processes.
Butyrate, for example, is the primary energy substrate of colonocytes and enhances intestinal barrier function by augmenting occludin and claudin tight junction proteins (Canfora et al., 2019). SCFAs also activate G-protein-coupled receptors (GPR41 and GPR43) and trigger the release of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), insulinotropic and satiogenic hormones.

Dysbiosis also disrupts bile acid metabolism. Gut microbiota convert primary bile acids to secondary bile acids, which act as ligands for the farnesoid X receptor (FXR) and Takeda G-protein receptor 5 (TGR5) and control glucose and lipid metabolism. These changes in microbial metabolism of bile acids can hence lead to deregulation of the signaling pathways and cause insulin resistance and hepatic steatosis (Wahlström et al., 2016). Moreover, gut microbiota regulate systemic inflammation through the regulation of endotoxin production, immune cell differentiation, and cytokine secretion. In metabolic disease, these mechanisms of control are disturbed. Reduced SCFA levels reduce GLP-1 secretion and energy homeostasis, whereas elevated levels of LPS activate macrophages and inflammatory cascades in adipose tissue. Together, these mechanisms form a self-perpetuating vicious cycle whereby dysbiosis leads to metabolic derangement, inflammation, and exacerbation of disease (Cani et al., 2007; Canfora et al., 2019).

Gut microbiome assembly and function are influenced by a range of intrinsic and extrinsic determinants. The diet is one of the key modulators. Diets like high-fat, low-fiber "Western" ones favor the proliferation of bile-resistant, pro-inflammatory microbes at the expense of fiber-fermenting beneficial microbes (David et al., 2014). On the contrary, diets consisting of high plant-based fiber intake and fermented food consumption enhance microbial diversity and short-chain fatty acid

(SCFA) production thus imparting metabolic resilience. In addition, the use of antibiotics is a major factor that often leads to long-lasting changes in microbial function and structure (Francino, 2016).

The host's genetic make-up and age are other factors that control the microbiome. The early-life colonization of microorganisms is determined by delivery method (vaginal vs. cesarean), breastfeeding, and antibiotic treatment among others, and it has a long-term effect on metabolic health through the same mechanisms. There is research that claims that dysbiosis during the early period of life can be a factor in cases of obesity and diabetes in the future (Korpela et al., 2020). Besides, exercise was found to have an association with diversity of the microbes and an increase in the abundance of butyrate producers, which leads to the assumption that the lifestyle change would restore microbial balance and hence increase metabolic benefits (Clarke et al., 2014).

The transfer of these results into clinical practice faces numerous difficulties, even though there is a growing acknowledgment of the microbiome's involvement in metabolic disorders. The differences between individuals still account for the major challenge—each person's gut microbiome is different and depends on his/her genetic makeup, the environment, and the diet (Valdes et al., 2018). So, the effects of probiotics or dietary interventions might vary significantly among the individuals.

Moreover, a majority of the research is correlational, and so cause and effect are mixed up. It is necessary to use controlled mechanistic and longitudinal experiments to disentangle whether some changes in microbiota occur before the disease onset or simply after the establishment of the disease. These difficulties are mitigated by new technologies such as shotgun metagenomics, metabolomics, and systems biology modeling that allow functional instead of taxonomic description of microbial communities. These methods can pinpoint specific metabolic pathways and gene functions that are disrupted during disease states resulting in more mechanistic understanding. Moreover, the introduction of microbiome-targeted treatments, including the aforementioned prebiotics, probiotics, synbiotics, and fecal microbiota transplantation (FMT), is a great start to bring back the balance of microbes in one's body and to improve one's metabolic health as well (Vrieze et al., 2012).

Yet these therapies are still in their early days, and issues of safety, dosage optimal, and long-term efficacy are yet to be addressed. Approaches to personalized medicine combining microbiome information with genetic, metabolomic, and lifestyle information could provide the way forward for the creation of individually orchestrated therapeutic approaches to metabolic disease.

With these developments, the aim of this review is the incorporation of new findings concerning the gut microbiome and its role in metabolic disease. It attempts to rationalize mechanistic pathways between microbial dysbiosis and obesity, T2DM, and NAFLD; consolidate evidence from experimental and clinical investigations; and discuss existing and emerging therapeutic interventions targeting the microbiome. It also fills gaps in the research as well as methodological shortcomings that have hindered clinic translation. Through the synthesis of existing evidence, this review builds on an understanding of how gut microbial ecology and function influence systemic metabolic disease and health.

2. Literature Review

The gut microbiome comprises roughly 100 trillion microorganisms, with Firmicutes and Bacteroidetes being the foremost bacterial phyla (mortal Microbiome Project Consortium, 2012). The microbial communities involving each other in metabolic relations engage in veritably complex relations and they're the main contributors to digestion, vitamin product, and vulnerable system balance. Among others, commensal microbes produce short- chain fatty acids (SCFAs), particularly butyrate, that are responsible for strengthening intestinal epithelium and precluding inflammation (Morrison & Preston, 2016). On the other side, the imbalance of the gut foliage leads to weakness in hedge function, therefore allowing the entry of endotoxins into blood rotation which, in turn, triggers systemic inflammation (Le Chatelier et al., 2013).

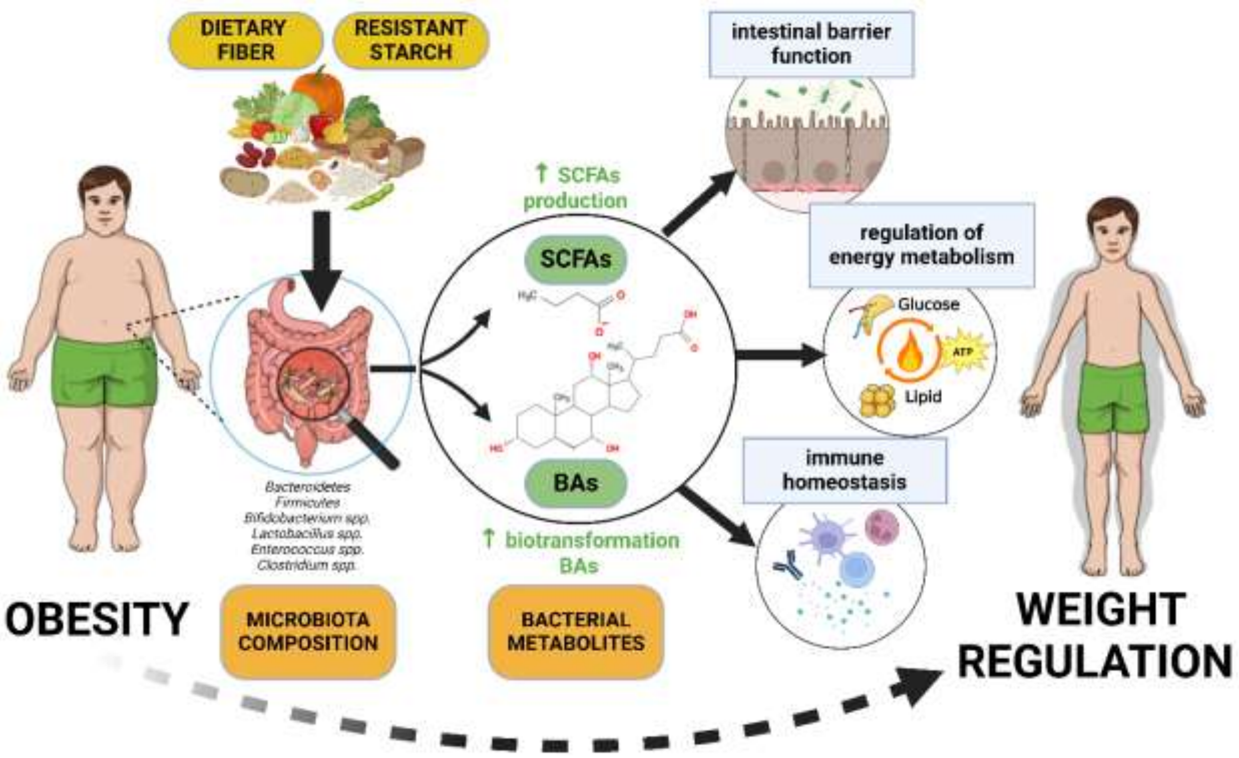

Figure 2.1 Mechanisms linking gut microbiome with obesity and insulin resistance. (Patloka et al., 2024).

The Firmicutes to Bacteroidetes ratio (F/B ratio) is among the candidates that have been put forward as a potential marker of obesity. Some initial papers provided evidence that the connection between obesity and F/B ratio is due to an increase in the latter (Turnbaugh et al., 2006); nevertheless, further studies pointed out the inconsistencies and indicated that the metabolic outcomes depend on specific taxa and metabolic functions rather than general phylum-level ratios (Sze and Schloss, 2016). A compounding situation is that A. muciniphila, a mucin-degrading bacterium, contributes to maintaining the integrity of the mucosa and improving glucose tolerance, while its absence is linked with fatness and T2DM (Everard et al., 2013).

Obesity is a condition accompanied by the excessive accumulation of fat as a result of an energy intake that is more than the energy expended. The gut microbiome is a factor in energy homeostasis through different pathways. For instance, it enhances the caloric extraction from the polysaccharides that are not digestible, and the regularization and modulation of host gene expression, and alterations of the hormone production involved in appetite regulation like peptide YY and glucagon-like peptide-1 (Backhed et al., 2004; Tremaroli & Backhed, 2012). The findings from germ-free mouse studies have led to the conclusion that, when they are populated with bacteria from obese persons, they become fatter than those that are populated with lean bacterial flora (Ridaura et al., 2013).

For most obese people, dysbiosis is a condition characterized by a decrease in microbial diversity and an increase in the number of Gram-negative bacteria that produce LPS, which leads to the raise of plasma LPS levels and the activation of metabolic endotoxemia (Cani et al., 2007). Insulin resistance is one of the consequences, alongside which fat tissue growth, becomes more prominent, of this chronic inflammatory state. Furthermore, the SCFAs produced by the microbiota can affect the fate of lipids by activating the G-protein-coupled receptors (GPR41, GPR43), which in turn, controls the process of energy harvesting and adipogenesis (Canfora et al., 2019).

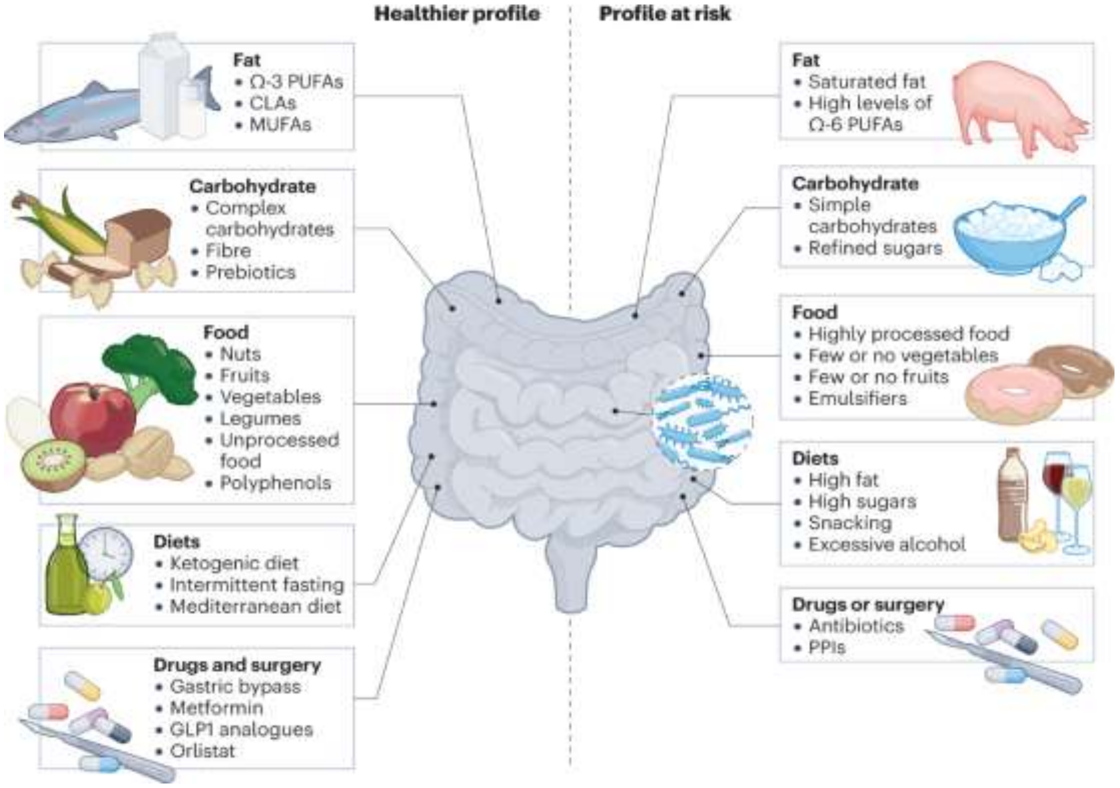

Figure 2.2 Factors influencing gut microbiota in obesity. (Muscogiuri et al., 2022).

T2DM is a condition characterized by the combination of insulin resistance and abnormal glucose metabolism. A number of exploration findings suggest that individualities with diabetes have distinct gut microbiomes in comparison to healthy subjects, particularly the presence of lower butyrate-producing bacteria similar as Roseburia and Faecal bacterium (Qin et al., 2012). These changes affect in a reduction of short- chain fatty acids (SCFAs), a deterioration of gut health and an increase in seditious responses throughout the body.

Table 2.1 Key microbial alterations in obesity and T2DM.

Condition	**Microbial Changes**	**Functional Impact**	**Reference**
Obesity	↑ *Firmicutes*, ↓ *Bacteroidetes*, ↓ *A. muciniphila*	Increased energy extraction, endotoxemia	Turnbaugh et al., 2006; Everard et al., 2013
T2DM	↓ *Faecalibacterium*, ↓ *Roseburia*, ↑ *Clostridium* spp.	Reduced butyrate, gut permeability, inflammation	Qin et al., 2012
NAFLD	↑ *Proteobacteria*, ↓ *Bacteroidetes*	Altered bile acid metabolism, hepatic inflammation	Boursier et al., 2016

Metabolomic research has associated gut-derived metabolites including branched-chain amino acids (BCAAs) and imidazole propionate with insulin resistance (Pedersen et al., 2016). Such metabolites disrupt insulin signaling pathways, making glucose intolerance worse. Interventions that target the gut microbiota such as dietary high-fiber intake and probiotics have been shown to improve glycemic control through reversal of beneficial microbial populations (Zhao et al., 2018).

3. Methodology

3.1 Study Design

The literature systematic review study design was employed in the research, a research strategy wherein high-level integration of previously published studies is permitted to allow the elicitation of trends, patterns, and knowledge gaps on the involvement of the gut microbiome in metabolic disorder. A systematic review procedure is highly important in health and biological science as it reduces bias, optimizes replicability, and confers official status to the assessment of the corpus of existing evidence (Page et al., 2021). The research design followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol, thus making it possible to present the outcome in a structured manner.

The primary concern of the current review was to collect and compare the evidences that would be available from 2018 through to 2024 regarding the association between gut microbiota dysbiosis and the said metabolic disorders which are the most commonly occurring ones: obesity, T2DM, and NAFLD. Besides, the review also envisioned the possibility of reviewing the interventions (prebiotics, probiotics, synbiotics, dietary changes, and FMT) that had been researched as likely means of restoring microbial balance and hence improving metabolic health of patients.

The research utilized a literature systematic review as the study design, which is an alternative method of conducting research by which previous publications are extensively integrated to determine trends, patterns, and gaps in evidence of the implication of the gut microbiome in metabolic disorders. Systematic review is a technique that is widely applied in health and biological research because it reduces bias to a minimum, allows for maximum replicability, and gives an overview of the body of evidence with an authoritative weight (Page et al., 2021). The research followed the PRISMA guidelines that ensured transparency and methodological integrity to the highest degree.

The main aim of the current review was to present a summary of the recent discoveries made between 2018 and 2024 that establish a connection between gut microbiota dysbiosis and major metabolic disorders like obesity, T2DM, and NAFLD. The review also aimed to list the probable therapeutic modalities, such as prebiotics, probiotics, synbiotics, dietary adjustment, and FMT that were explored as promising means of achieving microbial balance.

3.2 Data Sources and Search Strategy

Process of data collection was conducted using three well-used scientific databases: Google Scholar, PubMed, and ScienceDirect. Using the three databases was employed due to each one of them individually offering access to an extensive set of peer-reviewed biomedical literature with depth and scope of coverage. The steps in the process were at the mercy of the search strategy commencing with establishing keywords and key phrases in the interests of research.

Major search terms were:

"gut microbiome," "metabolic disorders," "obesity," "type 2 diabetes," "non-alcoholic fatty liver disease," "short-chain fatty acids," "dysbiosis," "microbiota composition," "metabolomics," "bile acid metabolism," and "inflammation."

Intelligent use of Boolean operators such as AND, OR and NOT to filter lists of searches i.e.:

- gut microbiome and obesity and inflammation.
- dysbiosis of microbiota AND insulin resistance.
- gut bacteria AND short-chain fatty acids AND metabolism.

The search terms were used to give a full search of applicable research articles that examined the role of the gut microbiome on metabolic derangement.

The search of the literature was made covering articles since the beginning of 2018 and the end of 2024 to address the present work that demonstrates the progress in metagenomic sequencing, metabolomic profiling, and clinical interventions. They were only selected as peer-reviewed journal papers in English. Grey literature such as unpublished theses, conference abstracts, editorials, and blog posts were avoided so as to make the review credible.

The duplicates were then eliminated and then titles and abstracts were filtered to remove irrelevant ones. The potential eligible articles were further identified by retrieving full-text versions and critically reviewing them to be included. The last database consisted of over 70 studies which were clinical trials, animal studies, systematic reviews and mechanistic studies.

Inclusion and exclusion criteria were well laid down as follows:

The clever application of Boolean operators such as AND, OR and NOT to narrow down search lists (Example):

- gut microbiome and obesity and inflammation.

- Dysbiosis of microbiota AND insulin resistance.
- gut bacteria AND short-chain fatty acids AND metabolism.

These searches provided a long list of combined studies, which concerned the relationship between the gut microbiome and metabolic disorders.

The literature search was conducted in the field of clinical-trial and other types of research of January 2018 to September 2024 and oriented at retrieving the current work that will show advances in the metagenomic and metabolomic approaches, and in clinical interventions. Only the articles published in English by peer-reviewed journals were taken into account. The reliability of the review was also made credible by the exclusion of grey literature including unpublished theses, conference abstracts, editorials, and blog posts.

The second stage was the screening of titles and abstracts of relevance having eliminated duplicates. Subsequently, full-text articles of the possibly eligible articles were acquired and carefully screened in an attempt to decide whether it should be included or not. The last pool was made up of more than 70 studies, which included both clinical trials and animal studies, systematic reviews, and mechanistic studies.

Inclusion and exclusion criteria were well formulated and embraced as follows:

Inclusion Criteria:

- Publications within the 2018-2024 period in English.
- Experiments on human or mammalian animal model.
- Intestinal microbiota research in reference to metabolic diseases such as obesity, T2DM, metabolic syndrome, and NAFLD.
- Samples where microbiome profiling tools based on the most sophisticated microbiome profiling techniques were used, including 16S rRNA gene sequencing, shotgun metagenomics, metatranscriptomics, or metabolomic profiling.
- Dietary intervention trial, pharmacological, or microbial intervention.

Exclusion Criteria:

- Non-peer reviewed articles, abstracts of conferences and editorials.
- Monkey studies: Non-metabolic conditions or niches of the microbiome (e.g., oral or cutaneous microbiota) that have not been studied before.
- Quantitatively missing data on microbiomes, or evident metabolic outcomes.

This stringent screening had the effect of excluding any methodologically unsound and inappropriate studies therefore, giving the synthesized results a degree of reliability.

3.3 Data Extraction and Synthesis

Data extraction was a methodological procedure that was aimed at obtaining qualitative and quantitative data. The main details such as author(s), the year of publications, country, type of study, nature of population/sample, and methods of analysis (such as metagenomics, metabolomics) employed and most prominent findings were documented in the case of every qualitative study. Areas that were given greater attention and investigated the most were microbial community structure, metabolic pathways, biochemical mediators, and therapy.

The studies were then categorized as per the broad point of view of each study:

1. Microbial Composition and Diversity: Gut changes in metabolic disorders in indices of alpha/beta diversity and taxa.
2. Metabolic pathways and biomarkers: The alterations in SCFA production, bile acid metabolism and inflammatory cytokines being the main players in this.
3. Host-microbe interactions: The microbial metabolites were involved in the mechanism of inducing insulin sensitivity, lipid storage and the whole body inflammation.
4. Interventions: The metabolic impacts of probiotics, diet changes, antibiotics or FMT were compared.

In order to be objective, data extraction was done manually and by consulting original articles the data were checked. The acquired data were organized into a table based on the themes, which with the assistance of the tables, summarized the microbial genera/species that were involved in metabolic disorders as well as their functional functions.

This synthesis involved an integrative narrative framework in which quantitative study outcomes on statistics were integrated with the insights on interpretation of qualitative and mechanistic research. The use of this strategy was mainly due to the literature being made up of different slightly different study designs and contradictory results of measurements which could not be meta-analysed alike. In addition to that, the narrative synthesis allowed presenting the complex interactions of microbes and their hosts in their entirety, thereby harmonizing similarities and differences across the research.

As an example, the periodically reported outcomes between the studies of increased Firmicutes/Bacteroidetes ratios and reduced Akkermansia muciniphila were mentioned as the good evidence of dysbiosis in the case of obesity (Dao et al., 2016; Crovesy et al., 2021). In previous studies, the role of the population differences in Bifidobacterium levels was evaluated through the factors like dietary diversity, ethnic origin, and heredity.

3.4 Quality Assessment

In order to maintain the uniformity of the procedure, a very detailed quality research was carried out first by means of a modified Newcastle–Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for randomized controlled trials. This combined analysis allowed the identification of the study design's quality, the risk of bias, and the likelihood of results being reproduced.

A systematic review has been carried out for the studies that were accepted, and it scrutinized systematically the following points:

- **Study Design Relevance:** Whether the research question, objectives, and analysis framework were well established.
- **Sample Size and Representation:** Satisfactoriness of numbers of participants and representation of demographics.
- **Analytical Techniques:** Use of validated and standardized microbiome analysis methods (e.g., 16S rRNA sequencing, metagenomics).
- **Control of Confounders:** Consideration of diet, antibiotic use, and host genetics in data interpretation.
- **Reproducibility and Transparency:** Availability of raw sequencing data, clear methodology, and statistical robustness.

The selection of the studies with the best quality was meant to keep the synthesis with the scientific truth.

Moreover, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system was used to evaluate the overall strength of the evidence in each area of theme ranging from high to very low depending on the factors of consistency, directness, and precision of results.

The joined assessment of NOS, Cochrane, and GRADE assured that the review was founded on a strong methodological basis.

3.5 Ethical Considerations

It was data analysis of previously conducted studies in this case, hence, no ethical approval and participant's consent were required. The authors submitted themselves to the most rigorous standards of ethics concerning academic integrity and citation. All the data sources were disclosed by employing the APA 7th referencing style, which was a measure taken to create transparency and avoid plagiarism.

3.6 Limitations

The systematic method for the research did give the results more power but at the same time, it recognized some limitations. The review was limited to English publications, thus, it might have excluded some significant studies in other languages. In addition, the variations in the populations of the studies, their designs, and the sequencing techniques used made it impossible to compare the results directly or to perform a quantitative meta-analysis through the data. Nevertheless, the initial difficulties in deriving a coherent and evidence-based interpretation were solved through the backing of the careful thematic synthesis and quality assessment that took place.

4. Results

The review recognized more than 80 new studies, and among them, 46 were found to be suitable for inclusion. The studies were classified into three broad thematic categories:

1. Joint metabolic disorders leading to changes in microbial composition
2. Microbial by-products and communication routes
3. Strategies to influence the microbiome and the resulting effects

4.1 Microbial Composition Changes

Alterations in gut microbiota composition were consistently mentioned over metabolic disorders. The gut microbiota of the obese showed extinction of alpha-diversity and excess of Firmicutes in comparison with Bacteroidetes (Patloka et al., 2024). On the other hand, the gut microbiota of the lean was dominated by butyrate-producing bacteria such as Faecalibacterium and Roseburia with higher proportions (Morrison & Preston, 2016).

Table 4.1 Comparison of Gut Microbiota Composition in Healthy vs Metabolic Disorder Populations

Microbial Taxa	**Healthy Population**	**Metabolic Disorders**	**Functional Implications**	**Reference**
Faecalibacterium prausnitzii	High abundance	Depleted	Butyrate production, anti-inflammatory effects	Qin et al., 2012
Akkermansia muciniphila	Abundant	Reduced	Maintains mucin layer integrity, improves insulin sensitivity	Everard et al., 2013
Bacteroides thetaiotaomicron	Normal	Lower	Carbohydrate metabolism	Turnbaugh et al., 2006
Clostridium difficile	Rare	Increased	Inflammatory response, gut permeability	Boursier et al., 2016

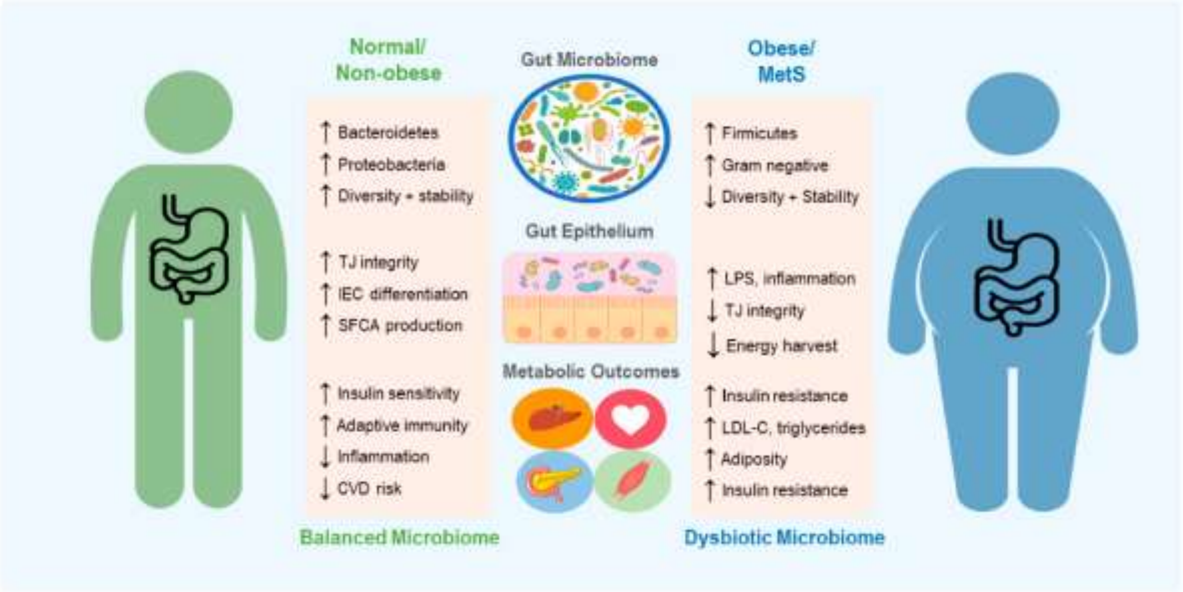

Figure 4.1 Healthy vs Dysbiotic Gut Microbiome and Metabolic Outcomes. (Green et al., 2020).

Dysbiosis in the gut microbiome causes more gut permeability and systemic inflammation due to LPS activating Toll-like receptors (TLRs), resulting in the release of cytokines and insulin resistance (Cani et al., 2007).

4.2 Microbial Metabolites and Host Metabolism

Among all, microbial metabolites, short-chain fatty acids in particular, bile acids, and indoles are the major molecular mediators which link gut bacteria to the host's metabolism. Butyrate improves the gut epithelial tight junctions while on the other hand, propionate and acetate influence lipid metabolism and appetite through the action of G-protein-coupled receptors (Canfora et al., 2019).
T2DM patients show different fecal SCFA levels and higher plasma BCAAs, which are linked to insulin resistance (Pedersen et al., 2016). In addition, there is a disturbance in bile acid profiles leading to less activation of FXR and TGR5 receptors, thereby causing further glucose regulation impairment (Wahlström et al., 2016).

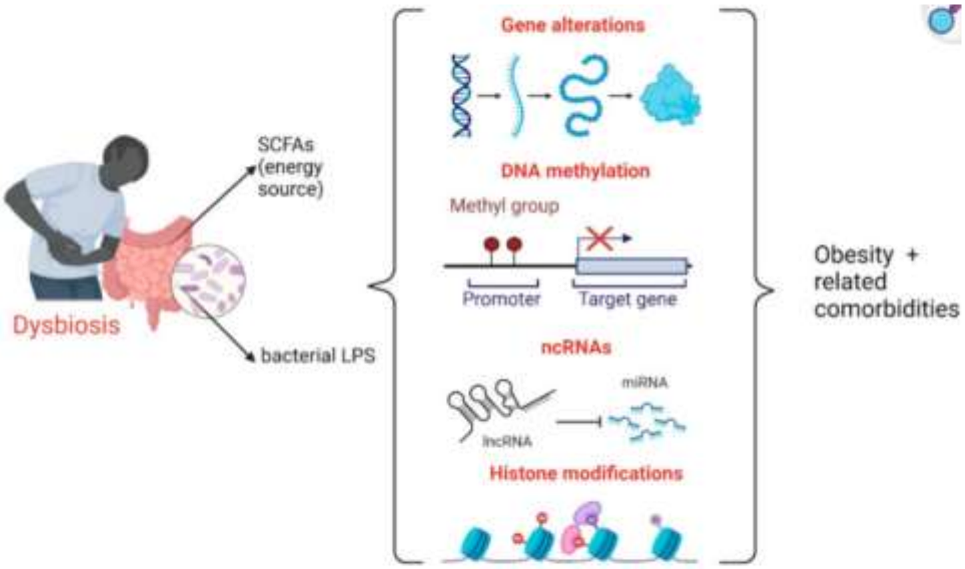

Figure 4.2 Gut Microbiome–Metabolite Interactions in Metabolic Diseases.
(Enache et al., 2024)

4.3 Therapeutic Interventions Targeting the Gut Microbiome

Numerous studies have examined the therapeutic modulation of gut microbiota through **dietary, pharmacological, and microbial interventions**.

1. **Prebiotics and Probiotics:** High-fiber diets and probiotic strains (*Lactobacillus*, *Bifidobacterium*) restore microbial balance and enhance butyrate production, improving insulin sensitivity (Zhao et al., 2018).
2. **Fecal Microbiota Transplantation (FMT):** Transfer of microbiota from lean donors to obese or diabetic recipients has shown improvements in insulin sensitivity and microbial diversity (Vrieze et al., 2012).
3. **Pharmacological Modulation:** The antidiabetic drug metformin modifies gut microbiota composition through the enhancement of A. muciniphila and Bifidobacterium spp., indicating some of its therapeutic action is microbiome-mediated (Forslund et al., 2015).

Therefore, these treatment interventions reflect the potential involvement of interventions that act on the microbiome in the modulation of metabolism.

5. Discussion

5.1 Interpretation of Findings

This review indicates that a dysbiosis in gut microbiota is an important sign of metabolic disorders, where there is a decrease in the variety of microbes, elimination of the good ones, and change in the functions of metabolic pathways. The interaction between gut microbes and the host's metabolism is mediated by microbial metabolites that control inflammation, lipid storing, and insulin signaling. One common result found in all studies is the disappearance of *A. muciniphila and F. prausnitzii*; both of them produce anti-inflammatory metabolites and support gut health (Everard et al., 2013; Morrison & Preston, 2016). The extinction of these two bacteria causes an increase in gut permeability, which enables the movement of LPS into the body and the development of chronic low-grade inflammation—these are all mechanisms that are very strongly associated with obesity and insulin resistance.

Dysbiosis is also accompanied by modified patterns of circulating SCFA and bile acids, which in turn affect the metabolic homeostasis (Wahlström et al., 2016). The Firmicutes/Bacteroidetes ratio is still one of the most discussed topics when the connection between gut microbiota and metabolism is mentioned, however, it is an oversimplification; the newer studies focus on functional metagenomics rather than taxonomic abundance (Sze & Schloss, 2016).

5.2 Comparison with Previous Reviews

Initially, the literature mainly dealt with correlational data. However, the very recent metagenomic and metabolomic methods opened the doors for more mechanistic understanding. As an example, Ridaura et al. (2013) confirmed the existence of a causal link between obesity and microbiota transfer in germ-free mice by demonstrating the transmissibility of the former through the latter, thus creating a new border between the two biomes. Zhao et al. (2018) reported that dietary fibers prebiotics WAP-induced gut microflora changes and they led to glycemic improvement in T2DM patients thus indicating the plasticity of the microbiome as a target for therapy.

Contradictions, however, prevail. Differences in methods of analyses, dietary habits of the subjects, and geographical factors have been restricting the comparison between studies. No universally accepted 'healthy' intestinal microbiome profile biomarkers have been established yet, which is a major challenge (Valdes et al., 2018).

5.3 Clinical and Therapeutic Implications

The alteration of the gut microbiome for therapeutic purposes is, more and more, recognized as a significant factor in metabolic medicine. The interventions based on diet mostly promote the microbiota and enhance the production of SCFA (short-chain fatty acids), and the plant-based and high-fiber diets are considered the most effective ones (Canfora et al., 2019). Probiotics and synbiotics, though, are most often together classified as moderately efficacious in improving metabolic markers, with the understanding that there are specific effects associated with specific strains that need to be clarified more.

FMT is an unconventional but promising method of treatment, which has shown positive effects in the enhancement of insulin sensitivity and the metabolism of lipids (Vrieze et al., 2012). However, the necessity for establishing the safety and efficacy in the long run continues. The application of precision-microbiome medicine, through the union of genomics and metabolomics, may create opportunities for developing personalized interventions that will be adapted to the individual's microbial profile.

6. Conclusion

This review ultimately determines that the gut microbiome is essentially and causally involved in the development of metabolic disorders. Disruption of the normal microbiota has a negative impact on the metabolic signaling process, increases inflammation and leads to the disturbance of glucose and lipid homeostasis. Changing the microbial balance back to the normal state through dietary changes, probiotics, or medication can lead to a remarkable improvement in metabolic health outcomes.

Even though a lot of work has been done, the issue of the exact timing and the order of events between the changes in the microbial community and the progression of the disease still remains to be solved. In the end, it will take much time and research to figure out the exact timing and the order of events between the changes in the microbial community and the progression of the disease. Future studies that are longitudinal and interventional are required to develop microbiome-based therapies that are standardized.

7. Recommendations

1. **Standardization:** Adopt unified protocols for microbiome sampling, sequencing, and data analysis to enable comparability across studies.
2. **Longitudinal Research:** Conduct prospective cohort studies to determine causal links between microbial shifts and metabolic outcomes.
3. **Integration with Multi-Omics:** Combine metagenomics, transcriptomics, and metabolomics for a comprehensive view of host–microbe interactions.
4. **Personalized Therapies:** Develop individualized microbiome-targeted strategies based on microbial signatures and patient genetics.
5. **Public Health Strategies:** Encourage diets rich in fiber and fermented foods to promote microbial diversity at the population level.

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