WJMER

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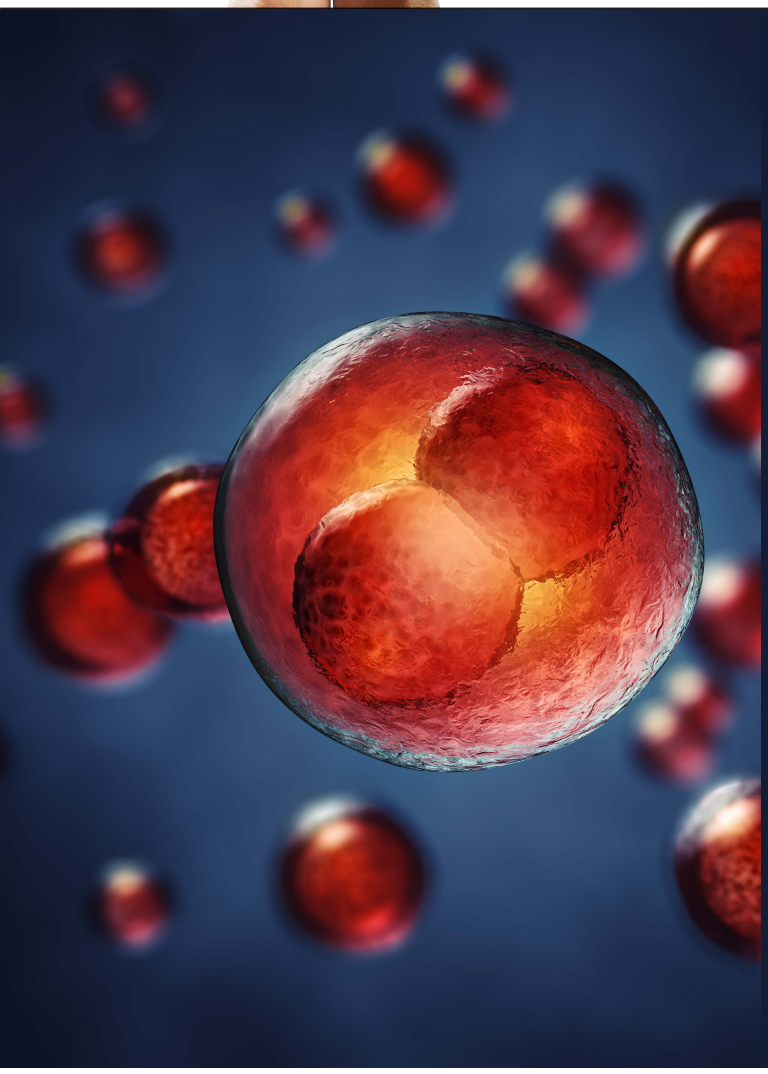

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Introduction

The World Journal of Medical Education and Research (WJMER) (ISSN 2052-1715) is an online publication of the Doctors Academy Group of Educational Establishments. Published on a quarterly basis, the aim of the journal is to promote academia and research amongst members of the multi-disciplinary healthcare team including doctors, dentists, scientists, and students of these specialties from around the world. The principal objective of this journal is to encourage the aforementioned, from developing countries in particular, to publish their work. The journal intends to promote the healthy transfer of knowledge, opinions and expertise between those who have the benefit of cutting edge technology and those who need to innovate within their resource constraints. It is our hope that this will help to develop medical knowledge and to provide optimal clinical care in different settings. We envisage an incessant stream of information flowing along the channels that WJMER will create and that a surfeit of ideas will be gleaned from this process. We look forward to sharing these experiences with our readers in our editions. We are honoured to welcome you to WJMER.

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A WELCOME MESSAGE FROM THE EDITORS

Dear Reader,
It is our great pleasure to bring you the thirty-third edition of the *World Journal of Medical Education and Research (WJMER)*. This edition presents a diverse collection of scholarly articles spanning cardiovascular science, medical education, pharmacology, public health, and student wellbeing. Together, these contributions reflect the continued commitment of researchers and educators worldwide to advancing evidence-based practice, educational innovation, and interdisciplinary healthcare research.

The opening article by Orjichukwu *et al*. presents a comprehensive review that explores the relationship between the gut microbiome and heart failure. The authors discuss how gut dysbiosis and microbiota-derived metabolites, including trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFAs), contribute to inflammation, endothelial dysfunction, and cardiac remodelling. The paper also highlights emerging therapeutic approaches, such as dietary modification, probiotics, and microbiome-targeted interventions, while emphasising the need for further longitudinal and translational research into the gut-heart axis.

In the following article, Hunter *et al.* address the growing need for financial literacy within medical education. The authors argue that many medical students and junior doctors enter clinical practice with limited understanding of personal finance, management of debt, taxation, and investment. The paper advocates for curricular reform and the incorporation of practical financial education tools into undergraduate and postgraduate medical training to better prepare future clinicians for the financial realities of professional life.

Farooq et al. compare the effectiveness of the flipped classroom teaching method with traditional lecture-based teaching amongst undergraduate medical students. Their study demonstrates the benefits of active and student-centred learning approaches, highlighting improvements in learner engagement, participation, and conceptual understanding within the flipped classroom model. The findings contribute to the growing body of literature that supports innovative pedagogical strategies in medical education.

Another contribution investigates the awareness of medical students in Damascus regarding the efficacy and safety of GLP-1 receptor agonists for weight loss in non-diabetic individuals. The study explores students' understanding of the clinical applications, benefits, and potential risks associated with these increasingly prominent pharmacological agents. The findings highlight areas where further education may be required to ensure safe and evidence-based prescribing practices in future clinical practice.

The review by Shaji *et al*. examines patterns of antibiotic utilisation and adverse drug event risks in special populations. The authors discuss the complexities of antibiotic prescribing in vulnerable groups, including paediatric, geriatric, pregnant, and immunocompromised patients. Emphasising antimicrobial stewardship, the paper outlines the importance of individualised treatment approaches to minimise adverse events while addressing the growing global challenge of antimicrobial resistance.

The final article by John *et al*. focuses on an intensive mentoring approach for underperforming MBBS students, evaluated using the Dundee Ready Education Environment Measure (DREEM) questionnaire. The study demonstrates how structured mentoring and targeted academic support can positively influence learner confidence, engagement, and perceptions of the educational environment. The findings reinforce the importance of supportive educational interventions in promoting academic success and student wellbeing.

We sincerely hope that you find each article in this edition educational, insightful, and thought-provoking. Together, these contributions showcase the breadth of contemporary research within medical education and healthcare, while reflecting WJMER's ongoing commitment to fostering academic excellence, innovation, and global collaboration.

Ms Karen Au-Yeung
Associate Editor

Dr Rebecca Williams
Associate Editor

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Review Article
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World Journal of Medical Education and Research:
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Microbiome and Heart Failure: A Comprehensive Review of Gut Health and Microbiota-Derived Metabolites in Heart Failure Progression

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Abstract:
A multifaceted clinical disease, heart failure (HF) is typified by decreased cardiac function and systemic symptoms caused by anatomical or functional abnormalities in the heart. Although traditional studies have concentrated on hemodynamic and neurohormonal processes, new data highlights the vital role that the gut microbiota and its byproducts play in the pathogenesis of HF. An imbalance in the microbial structure known as gut dysbiosis is common in HF patients and is linked to increased gut permeability, systemic inflammation, and changed bioactive metabolite synthesis. Prominent metabolites generated by the microbiota, including phenylacetylglutamine, short-chain fatty acids (SCFAs), secondary bile acids, and trimethylamine N-oxide (TMAO), have a major impact on endothelial function, cardiac remodelling, and inflammation. Together with gut-derived lipopolysaccharides, these metabolites interact with host systems to exacerbate the course of HF. Further impacting HF outcomes are comorbidities such as diabetes, obesity, and chronic renal disease, which intensify gut dysbiosis. The importance of metabolites originating from the microbiota in the progression of HF is highlighted in this review, which summarizes recent findings regarding the gut-heart axis. Additionally, it investigates how dietary changes, probiotics, prebiotics, and multi-omics techniques can all be used to improve the management of HF. This thorough analysis emphasizes the necessity of integrative therapy approaches and longitudinal research to better address the complex link between HF and the gut microbiota.

Key Words:
Gut microbiome; Heart failure; Microbiota-derived metabolites; Trimethylamine N-oxide (TMAO); Short-chain fatty acids (SCFAs)

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Introduction

Heart failure represents a clinical syndrome distinguished by specific signs and symptoms arising from a structural and/or functional cardiac abnormality, which ultimately leads to a decrease in cardiac output and/or increased intra-cardiac pressure (both at rest and during periods of stress) [1]. Some clinical manifestations of heart failure encompass fatigue, peripheral oedema, elevated jugular venous pressure and shortness of breath[2]. It is estimated that heart failure impacts approximately 64 million individuals globally[3]. There are several risk factors correlated with heart failure; some of the most prevalent include a sedentary lifestyle, hypertension, diabetes, smoking and hyperlipidaemia[4]. However, understanding these factors is crucial because they can help in formulating preventive strategies. Although many individuals may not recognize the implications of these risk factors, this awareness could potentially lead to better health outcomes.

By the year 2017, over 64.3 million individuals were affected by HF on a global scale, which corresponds to an estimated age-standardized prevalence rate of 831.0 and 128.2 per 100,000 individuals in terms of years lived with disability (YLDs)[5]. Notably, the highest prevalence rates were recorded in Central Europe, North Africa and the Middle East[5]. By 2019, it was estimated that the prevalence of heart failure had escalated to 17 per 1,000 individuals across 13 European nations[6]. In the United States, utilizing data derived from the National Health and Nutrition Examination Survey (NHANES), it was determined that approximately 6.0 million adults aged 20 years and older were living with HF, which represented a prevalence of 2.4% among Americans by 2012[6]. The financial ramifications associated with the management of heart failure have been increasing over the years; in the USA alone,

approximately $30.7 billion was earmarked for the management of HF patients in 2012. This figure is projected to rise by 127% to $69.8 billion by 2030[7]. However, the implications of these rising costs extend beyond mere financial metrics, as they encapsulate the broader challenges faced by healthcare systems globally.

In general, the economic burden imposed by HF on a global scale is considerable; it has, however, been trending upwards over time. For instance, in 2012 alone, it is estimated that a total cost exceeding $108 billion was expended worldwide[8]. This upward trajectory is concerning, because it reflects not only the increasing prevalence of HF but also the growing strain on healthcare systems. Although some interventions may mitigate these costs, the overall financial impact remains significant.

The global disparity in the quality of life experienced by patients suffering from HF is indeed pronounced. Health-related quality of life (HRQL) among these individuals is particularly low in Africa, contrasting sharply with the elevated levels observed in Western Europe (mean ± SE, 39.5 ± 0.3 vs 62.5 ± 0.4, respectively). This stark difference is highlighted by alarming statistics: 4460 (19%) deaths and 3885 (17%) hospitalizations attributable to heart failure were documented across 40 nations, spanning eight distinct world regions[9]. Impairments in physical function, cognitive abilities and mental health—most notably depression—are especially pronounced in older patients experiencing acute decompensated heart failure, particularly those over the age of 60[10]. In the United States, a comprehensive study assessing 15 chronic conditions revealed that individuals with heart failure exhibited the lowest age-adjusted quality-adjusted life years (QALYs). This finding was further complicated by significant gender disparities; men demonstrated lower age-adjusted QALYs in comparison to women (1.1–1.5 vs 1.5–2.2 years, respectively)[11]. However, it is essential to recognize the multifaceted nature of these issues, because they encompass not only medical implications but also broader social determinants of health. Although the statistics are disheartening, they serve to underscore the urgent need for targeted interventions to improve the quality of life for these vulnerable populations.

Moreover, data derived from the Health and Retirement Study spanning the years 1998 to 2014 revealed that the weighted overall disability-adjusted life years (DALYs) linked to heart failure and hypertension were quantified at 62,630 and 378,849 years, respectively, among middle-aged and older adults within the United States[12]. Insufficient strategies aimed at controlling and preventing hypertension significantly jeopardize productivity; employees often encounter absenteeism or endure presenteeism (i.e., diminished efficiency at work)[13]. This particular phenomenon, consequently, reduces Productivity-Adjusted Life Years (PALY) and results in financial detriments to Gross Domestic Product (GDP)[14] In summary, these findings expose the substantial burden and pivotal significance of heart failure on a worldwide scale. Thus, it is imperative that endeavours to understand the risk factors, underlying mechanisms and management strategies remain critically important; however, obstacles endure due to the intricate nature of these issues. Although notable advancements have been achieved, the necessity for further exploration remains urgent.

The gut microbiota represents a dynamic and integral component of the human body, acquired at birth, which performs essential functions within its metabolic, structural, neurological and immunological frameworks. It also exerts significant influence on both physical and mental health. Studies[15] have demonstrated that the gut microbiota can be involved in the pathogenesis and progression of cardiovascular diseases (CVDs), including HF[16]. Furthermore, both the gut microbiota and its associated metabolites have been implicated in HF[17]. Various CVDs—such as hypertensive heart disease, atherosclerosis, myocardial infarction, heart failure and arrhythmia—have been linked to altered intestinal flora[18]. Moreover, gut microbial fermentation metabolites play a role in the development, prevention, treatment and prognosis of CVDs; these metabolites include trimethylamine N-oxide (TMAO), short chain fatty acids (SCFAs), secondary bile acids (BAs) and gases such as hydrogen sulphide (H_2S), carbon dioxide (CO_2) and nitric oxide (NO)[19]. The relationship between gut microbiota and the biological processes that influence CVD risk is complex; however, it is crucial to understand these interactions because they could inform potential therapeutic strategies[20].

However (there is a paucity of data on the effects of gut microbiota-associated metabolites in HF); thus, the need for an in-depth review arises to understand their role in HF. This understanding is crucial (because it could help develop and accelerate therapeutic potential in the future). Although research is limited, the implications could be significant. But we must proceed with caution, as the complexities of these interactions are not yet fully elucidated. This paper presents a thorough examination of the gut microbiota's role and its metabolites in the progression of HF. The investigation synthesizes contemporary evidence that correlates gut dysbiosis, microbial-derived metabolites, and systemic inflammation with HF pathophysiology. It underscores the influence of metabolites such as TMAO, SCFAs, and secondary bile acids on cardiac remodelling and immune

responses, thus emphasizing their potential as biomarkers and therapeutic targets. Furthermore, the paper delves into the interaction between gut health and comorbidities, including diabetes and obesity, which exacerbate HF outcomes. By integrating insights derived from dietary, probiotic, and multi-omics approaches, it suggests innovative strategies for modulating gut microbiota to manage HF, highlighting the necessity for multidisciplinary research and longitudinal clinical trials. The paper is systematically organized as follows: Section 1 provides an overview of HF, its global burden, and its intricate relationship with gut microbiota, thereby stressing the imperative for a comprehensive review. Section 2 delves into the multifaceted functions of the microbiome and its correlative impact on host health. Section 3 elucidates the various metabolites, such as TMAO, SCFAs, bile acids, and phenylacetylglutamine, articulating their significant roles in the progression and prognosis of HF. Section 4 summarizes a plethora of studies that establish a connection between gut microbiota and HF; however, Section 5 discusses a range of interventions, including probiotics, prebiotics, dietary modifications, faecal microbiota transplantation, and renal denervation. Although these interventions are promising, they highlight the necessity for future research priorities, which should encompass personalized approaches and multi-omics methodologies. Section 6 concludes by underscoring the critical importance of integrating gut microbiota research into the management of HF as well as emphasizing the imperative for multidisciplinary efforts to enhance our understanding of this complex interplay.

Science of the Gut Microbiome: Present Knowledge

The gut microbiome functions at a pivotal intersection between the host organism and its surrounding environment, effectively modulating host physiology in ways that can be astonishingly individualized[21]. The degree of similarity in gut microbiome composition among individuals irrespective of familial connections is significantly low. As depicted in Figure 1, numerous factors assume crucial roles in sculpting the microbiome and nurturing this diversity; however, in contrast to host genetics, environmental determinants such as dietary practices and pharmacological interventions appear to exert a much more substantial influence[22]. Furthermore, Figure 1 elucidates the predictable transformations in the microbiome across the human lifespan, underscoring the fragile balance between the microbiome's resilience and its malleability when faced with perturbations. This intricate interplay is essential for understanding the complexities of microbiome dynamics in human health.

The composition of the gut microbiome is predominantly shaped by environmental influences (such as diet, medications and lifestyle choices); host genetics contribute to this shaping, albeit to a lesser extent. However, although alterations in these environmental factors can precipitate microbial shifts, the microbial community generally exhibits a remarkable degree of stability and resilience. This stability is only disrupted by substantial perturbations, particularly after the toddler years when the adult microbiome becomes "established" and remains relatively stable until advanced age.

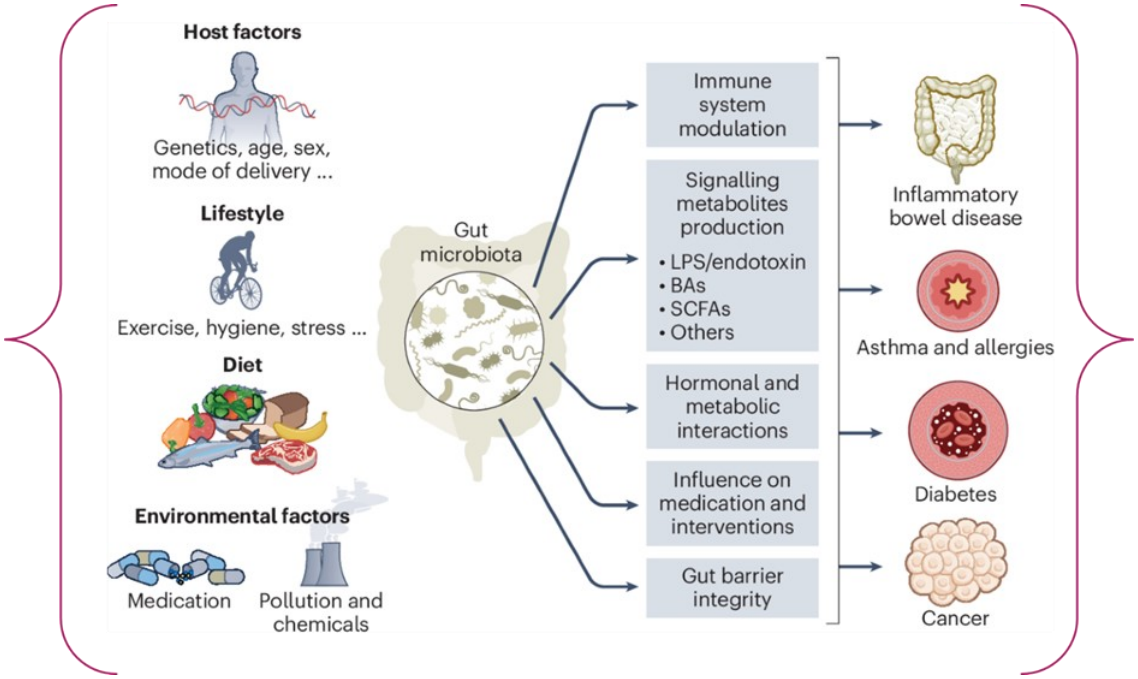

***Figure 1**: Lifetime Gut Microbiome and Key Environmental and Host Determinants*

Method	Principle	Strengths	Limitations
Culturomics	Traditional approach where live microorganisms are cultivated on selective media under controlled conditions.	- Cost-effective - Widely accessible - Allows detailed phenotypic analysis (e.g., pathogenicity, antibiotic resistance, metabolic functions) - Suitable for aerotolerant organisms and rare bacteria poorly represented in databases.	- Labor-intensive - Limited to cultivable microbes - Results influenced by media and conditions - Challenges in studying strict anaerobes or capturing microbe interactions in mixed communities.
Polymerase Chain Reaction (PCR)	Sequencing-based method targeting specific microbial genes for detection and quantification (e.g., qPCR, RT -PCR).	- Rapid and widely available - Cost-effective - Provides absolute abundance of target taxa - High dynamic range.	- Targets limited number of genes/microbes - Unable to detect unknown taxa - Susceptible to PCR biases - Results depend on primer and probe specificity.
16S rRNA Gene Sequencing	Amplification and sequencing of hypervariable regions of the 16S rRNA gene, followed by matching reads to reference databases.	- Commonly used for taxonomic profiling - Identifies cultured and uncultured microbes at the genus level - Relatively rapid and cost-efficient - Well-developed bioinformatic pipelines.	- Provides relative abundance only - Low resolution at species/strain level - Limited to bacteria and archaea; fungi require specialized primers - Cannot distinguish live versus dead microbes - Lacks functional insights.
Shotgun Metagenomics	High-throughput sequencing of all DNA fragments in a sample, followed by computational assembly and taxonomic/functional annotation.	- Identifies bacteria, archaea, viruses, and fungi - Provides species and strain-level resolution - Offers functional potential characterization - Requires minimal DNA input (<1 ng).	- Computationally intensive - Costly (though decreasing) - Requires advanced bioinformatics - Sequencing host DNA may confound results - Reproducibility remains uncertain.
Meta-transcriptomics	Sequencing of RNA transcripts to analyse microbiome gene expression.	- Enables real-time profiling of microbial activity - Quantitative and high resolution - Integrates functional insights with metagenomics for comprehensive analysis.	- Technically complex and costly - RNA instability poses challenges - Requires paired metagenomic data for optimal interpretation - Limited correlation with meta-proteomic outputs.

Method	Principle	Strengths	Limitations
Meta-proteomics	Mass spectrometry (MS)-based quantification of microbiome-derived proteins and peptides.	- Provides functional insights into microbial protein expression. - Can reveal host-microbe protein interactions.	- Technically challenging - Requires high-quality reference libraries - Limited sensitivity for low -abundance proteins.
Metabolomics	Identification and quantification of microbial metabolites using chromatography and MS.	- Rapid and versatile - Suitable for various sample types (e.g., feces, urine, plasma) - Facilitates discovery of both known and novel metabolites - Low sample requirement.	- Targeted metabolomics identifies known compounds but misses unknowns - Untargeted methods are less quantitative and challenging for metabolite annotation - Limited ability to link metabolites to specific microbial taxa.
Multiomics	Integration of multiple data types (e.g., genomics, transcriptomics, proteomics, metabolomics) from the same or concurrent samples.	- Offers a comprehensive systems-level view of microbiome-host interactions - Generates novel hypotheses.	- Costly and computationally demanding - Analytic methods and pipelines are still being standardized.

Table 1*: Analytical Methods for Microbiome Research*

Table 1 offers a comprehensive overview of the most common methodologies, emphasizing their strengths and weaknesses. These approaches can be employed in research involving either humans or animals. By promoting a reductionist framework for hypothesis testing, animal models especially those that use germ-free subjects lacking resident microbiota have greatly enhanced our comprehension of the microbiome-host relationship. However, the transfer of these findings to human applications has faced challenges; in addition to their failure to completely capture the intricacies of human biology and its numerous environmental factors, animal research has shown that some microbiome-host interactions are specific to particular host species. This indicates that the crucial element for effective human translation is the meticulous selection of model systems that authentically replicate the disease characteristics of concern, at both the host and microbiome levels. Relevant instances can be observed in porcine models of metabolic syndrome and HF with preserved ejection fraction, where both host and microbiome physiology, along with their reactions to disturbances, closely resemble those encountered in humans[23].

Gut Microbiome: A Tool for Optimizing Heart Failure Therapy

The interplay between pharmacological agents and gut microbiota constitutes a bidirectional relationship; specifically, medications have the capacity to modify the microbiome[24], whereas microbial entities can influence the pharmacokinetics and pharmacodynamics of various drugs[25]. A precision medicine framework that acknowledges these critical interactions holds the potential to enhance HF therapies, thereby enabling patients to utilize medications that yield individualized benefits while minimizing adverse effects. Numerous widely prescribed cardiovascular agents, such as beta-blockers, RAS inhibitors, digoxin, calcium-channel blockers, statins and antiplatelets, are metabolized by gut microorganisms. For instance, digoxin - an agent indicated for the management of chronic HF and atrial fibrillation - is selectively inactivated by a prevalent gut microbe, Eggerthella lenta; however, this inactivation occurs exclusively via strains possessing a specific gene[26]. The suppression of this

gene in murine models led to increased serum levels of digoxin. Furthermore, it was a protein-rich diet that resulted in the downregulation of this gene[26], thereby demonstrating the downstream modulation of pharmacological effects not solely by gut microbiota but also through intricate microbiome-dietary interactions.

Microbiome profiles possess the potential to forecast drug responses and inform therapeutic decisions. A compelling demonstration of this methodology emerges from the realm of oncology. The antitumor efficacy of immune checkpoint inhibitors (ICIs) is influenced by the gut microbiome and its intricate interactions with the immune system. Distinct microbiome profiles have been correlated with varied ICI responses (27). Certain microbiome signatures have already been effectively utilized in patients afflicted with lung cancer to anticipate future ICI responses (28). A comparable strategy could be adopted in the context of chronic heart failure (HF), where microbiome profiles might be harnessed to predict clinical outcomes related to specific HF treatments. This could facilitate the development of more personalized therapeutic regimens. However, the complexities inherent in the microbiome-immune system relationship necessitate careful consideration, because understanding these interactions could lead to significant advancements in patient care.

Microbiome-targeting therapies may indeed become an integral component of future HF treatment strategies. Probiotics - defined as foods and dietary supplements harbouring live microorganisms - engage with the gut microbiota, thereby beneficially modifying host physiology. Certain probiotics might specifically modulate pathogenic processes that are dysregulated in HF, as evidenced in a rodent model where the administration of Lactobacillus - and Bifidobacterium-containing probiotics resulted in significantly enhanced cardiac function. However, the GutHeart trial - a randomized investigation assessing the efficacy of the probiotic yeast Saccharomyces boulardii in individuals with stable HFrEF - revealed no notable improvement in cardiac function when compared with standard care[29]. Although these findings are disheartening, the negative outcomes of GutHeart should prompt a recalibration of our approach toward evaluating probiotics. This recalibration necessitates the identification of microbiome “probiotypes” that can provide appropriate ecological niches for distinct probiotics, prior to assessing the clinical efficacy of these interventions.

The Gut Microbiota's Role in Pathology and Physiology

The human gastrointestinal tract functions as a dynamically balanced micro-ecosystem, wherein more than 2,000 species and approximately 100 trillion microbes, predominantly bacteria, viruses, and fungi, exist and coevolve with us (this is an intricate symbiotic relationship)[30]. Bacteria constitute the majority of the gut microbe species, with over 90% represented by Bacteroidetes and Firmicutes, subsequently followed by Actinobacteria, Tenericutes, and Proteobacteria[31]. It is noteworthy that the gut microbiota typically establishes itself in the oxygen-devoid, nutrient-abundant ascending colon, which serves as an optimal habitat for survival. Although the gut microbiota begins to colonize and mature from the moment of birth, its composition and functionality can be influenced by various external factors. Through the breakdown of dietary components and the synthesis of vital vitamins like B and K, the gut microbiota supports the host's growth, metabolism, and other developmental processes. However, the gut microbiota's production of short-chain fatty acids (SCFAs) through the fermentation of dietary fibre offers the host protection in a variety of ways, such as influencing the immune system and providing energy for enterocytes[32]. Furthermore, by secreting signals that encourage epithelium renewal and the induction of intestinal vascular remodelling, microorganisms help to maintain intestinal growth and integrity[33]. This interaction emphasizes how important the gut microbiota and its metabolites are to maintaining the host's health. The change in gut microbiota composition and function, known as gut dysbiosis, is caused by a number of reasons, including antibiotic abuse, intestinal inflammation, cold stimulation, and other variables. But according to a number of studies, gut dysbiosis is connected to a wide range of illnesses, such as human cancer, irritable bowel syndrome, and cardiovascular disease. It has also been connected to the newly discovered coronavirus disease 2019 (COVID-19). This syndrome contributes to the development of cardiovascular illnesses by impairing the integrity of the gut barrier, increasing intestinal inflammation, and increasing the absorption of microbial products and metabolites into the host's circulation. Mechanical findings into the impact of gut microbiota in cardiovascular disorders span from inflammation, immunology, and vascular function modulation to reactive oxygen species (ROS) regulation and lipid metabolism[34]. Overall, the gut microbiota has a role in disease pathogenesis, including cardiovascular disease.

Gut Metabolites Associated with HF

The gut microbiota performs an essential role in the intricate degradation of carbohydrates, proteins and, to a somewhat lesser extent, fats alongside various other biomolecules, which includes the fermentation of non-digestible substrates[35]. Certain

metabolites produced via this elaborate process have been linked to heart failure[36]; however, the most consequential among them will be explicated in detail in the subsequent sections. Although this association necessitates additional scrutiny, it remains imperative to contemplate the ramifications of these metabolic byproducts. Because their functions can be diverse, comprehending them is of utmost importance.

Short-chain fatty acids (SCFAs): protective roles and mechanisms in HF

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are largely found in the colon; nonetheless, they have the capacity to circulate throughout the body, exerting a variety of physiological effects[37,38]. SCFA-producing bacteria, such as Faecalibacterium prausnitzii, as well as members of the Lachnospiraceae and Ruminococcaceae families, were found to be significantly lower in individuals with HF. These bacterial communities are required for the formation of butyrate; hence their presence suggests possible cardio protective benefits[39]. In the context of various cardiovascular diseases (CVDs), a lower prevalence of butyrate-producing species has been associated with an increased risk of developing atherosclerosis. Though preclinical studies suggest that increasing dietary SCFA intake may improve heart function, the precise processes and effects of SCFAs for HF remain unknown, and further study is needed to clarify these complicated interactions [40].

Short-chain fatty acids (SCFAs) are known for their immunomodulatory capabilities, which affect cardiac structure and function, primarily via activating anti-inflammatory regulatory T cell systems[41]. Furthermore, SCFAs may modulate blood pressure, possibly leading to the development of HF; however, more research is needed to substantiate this link. Notably, SCFAs, particularly butyrate, play an important role in gut barrier integrity by promoting intestinal epithelial cell differentiation, repairing damaged mucosa, increasing tight junction protein expression, stimulating mucus production, and reducing inflammation induced by circulating exogenous substances. These consequences may also include responses to external stresses, which could reverse negative alterations[42]. Butyrate is thought to activate hypoxia-inducible factor (HIF) in the colon, maintaining the effectiveness of the gut barrier in the physiologically hypoxic environment of the area. Reduced SCFA levels may be a contributing factor to the progression of HF, according to findings of increased gut permeability in HF patients[39]. Despite these results, there is still a substantial lack of research on the function of SCFAs in decompensated heart failure, with no studies, as far as we are aware, examining their effects on patient outcomes in this particular patient group.

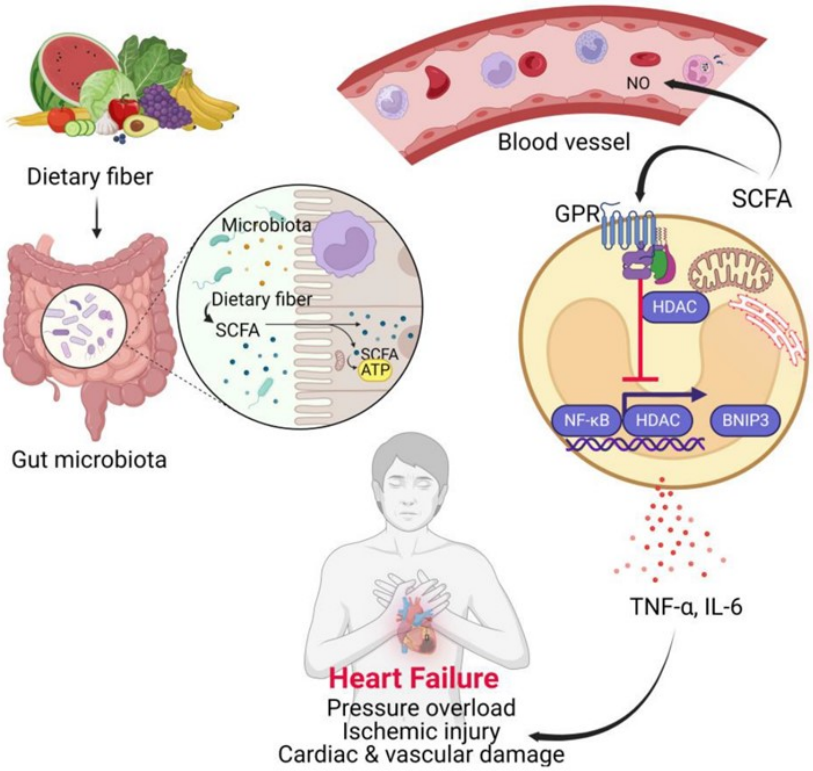

Figure 2: *The role of SCFAs in heart failure.*

The role of short-chain fatty acids (SCFAs) in the context of heart failure presents an intriguing area of inquiry. These compounds are synthesized from dietary fibre through the fermentation processes conducted by gut microbiota. SCFAs serve a vital function by providing energy to enterocytes and various innate immune cells. However, their influence extends beyond mere energy provision; they engage with endothelial cells and immune cells through signalling mechanisms mediated by G-protein-coupled receptors (GPRs). This interaction leads to the repression of nuclear factor kappa-light -chain-enhancer of activated B cells (NF-κB), which occurs in conjunction with histone deacetylases (HDACs). Consequently, SCFAs inhibit the expression of Bcl-2 interacting protein 3 (BNIP3), thereby mitigating the production of pro-inflammatory cytokines. These cytokines are known contributors to cardiac and vascular damage, which can result in pressure overload, ischemic injury, and ultimately, heart failure. In this complex interplay, components such as tumour necrosis factor alpha (TNF-α), nitric oxide (NO), and adenosine triphosphate (ATP) are also implicated, further underscoring the multifaceted role of SCFAs in cardiovascular health. Although the mechanisms are intricate, the implications of SCFAs in modulating inflammation and cellular responses remain a pivotal aspect of understanding heart failure pathology.

Short-chain fatty acids (SCFAs) are generally recognized as advantageous in cases of heart failure, as they furnish a significant amount of energy for utilization by the compromised myocardium[43]. This assertion holds particularly true for acetate[43] and butyrate[44]. Butyrate, in fact, has been noted to possess the ability to reverse and enhance mitochondrial ATP production, thereby improving heart contractility in the failing heart[44]. In this context, SCFAs assume a crucial role in the restoration of mitochondrial function. Propionate, on the other hand, modulates energy consumption and augments the sympathetic nervous system through the GPR41 receptor[45]. However, although SCFAs are beneficial in HF, their potential applications in clinical practice remain a subject of ongoing investigation. Their implications in HF have been extensively analysed in other studies[46].

Trimethylamine N-oxide (TMAO): pro-inflammatory and pro-atherogenic effects.

The metabolic pathway encompassing choline, phosphatidylcholine, L-carnitine, and betaine culminates in the synthesis of trimethylamine (TMA), which is mediated by modified gut microbiota that utilize an array of enzymes most notably, TMA synthase[47]. Subsequently, this TMA undergoes oxidation to generate trimethylamine N-oxide (TMAO) within the hepatic environment, a process facilitated by hepatic flavin monooxygenases (FMO)[48]. Consequently, fluctuations in TMAO concentrations can be correlated with alterations in the gut microbiota composition. In patients afflicted by chronic heart failure, the integrity of the intestinal mucosal barrier is significantly compromised, which results in increased permeability; this phenomenon allows for the unhindered entry of TMAO into the circulatory system, leading to elevated plasma levels. Furthermore, TMAO functions to augment platelet reactivity by modulating stimulus-dependent calcium signalling pathways. Thus, it exacerbates conditions such as atherosclerosis and thrombosis, which are critical to the pathogenesis of heart failure[49]. However, understanding these interactions is essential for developing targeted therapeutic strategies.

Research emphasizes that TMAO (trimethylamine N-oxide) serves a crucial function in the regulation of gut microbiota, cholesterol metabolism, and metabolic stress, particularly in scenarios characterized by heightened cholesterol overload[49]. However, the consequences of this correlation are intricate, warranting additional scholarly exploration. Elevated TMAO levels promote the infiltration of macrophages, which are saturated with cholesterol, thereby significantly affecting lipid and hormonal homeostasis. This dynamic interplay ultimately contributes to the pathogenesis of cardiovascular diseases (CVDs)[50]. Nevertheless, the complexities embedded in these interactions are profound because they encompass a multitude of metabolic pathways. Although the exact mechanisms remain under scrutiny, it is increasingly evident that the presence of TMAO holds extensive ramifications for cardiovascular health.

Engaging the NF-κB pathway, TMAO (trimethylamine N-oxide) catalyses the upregulation of inflammatory genes within aortic endothelial cells and vascular smooth muscle cells[47]. This compound not only amplifies the expression of vascular cell adhesion molecule-1 but also fosters monocyte adherence, thereby activating both NF-κB and protein kinase C. These effects may, however, accelerate the development of chronic heart failure; they exacerbate endothelial dysfunction while concurrently undermining self-repair mechanisms and instigating an inflammatory response. Although TMAO predominantly stimulates NF-κB, it additionally activates the NLRP3 inflammasome, generating a proinflammatory milieu that has been substantiated in both human aortic endothelial cells and carotid artery endothelial cells. This observation implicates TMAO in its role regarding endothelial dysfunction and cardiovascular disease (CVD)[51].

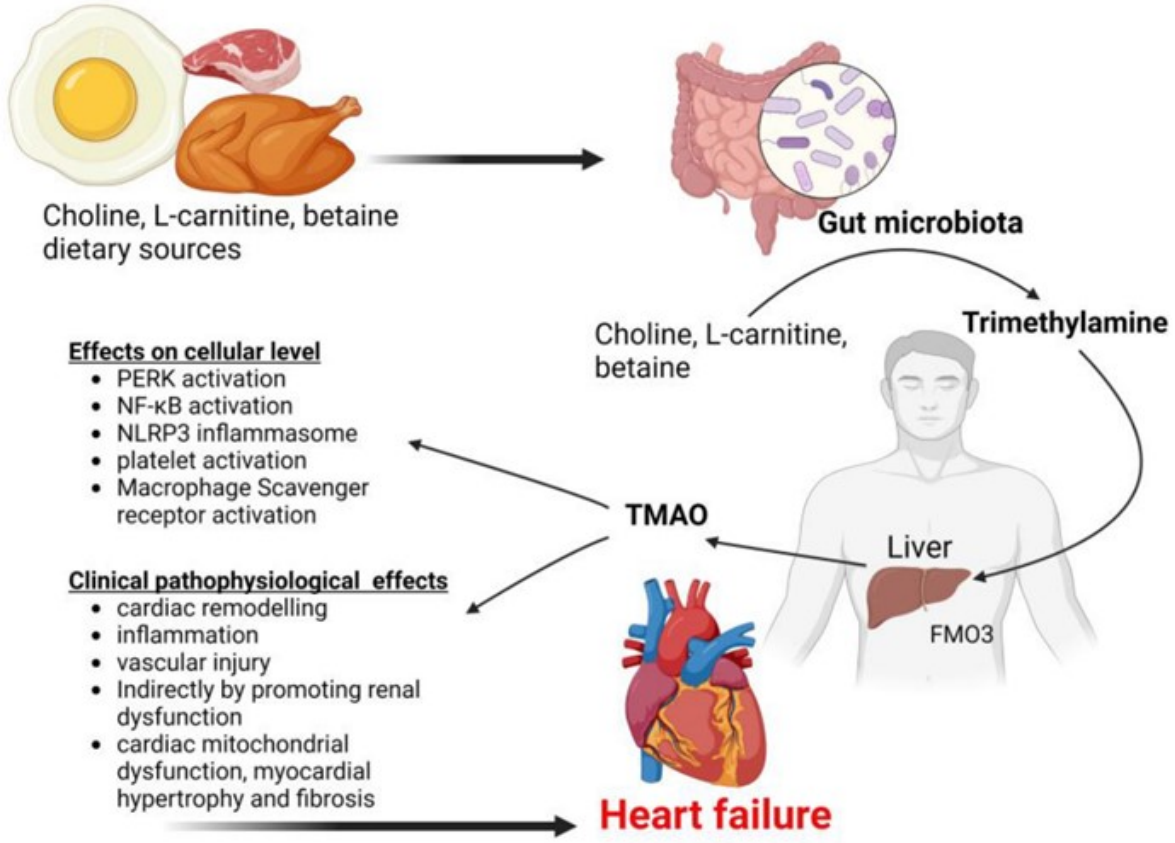

Figure 3: *TMAO-mediated heart failure pathogenesis pathways*

Moreover, another avenue through which trimethylamine N-oxide (TMAO) contributes to HF involves the induction of aortic stiffness, an increase in systolic blood pressure, and the activation of platelets, thereby leading to a hypercoagulable state[52]. TMAO significantly aggravates hypertension due to its direct binding and subsequent activation of protein kinase R-like endoplasmic reticulum kinase (PERK). This activation promotes apoptotic inflammatory responses, which, in concert with the generation of reactive oxygen species, precipitates vascular injury and cardiac remodelling. Thus, it results in elevated blood pressure, as demonstrated by numerous studies[53]. However, TMAO's function extends beyond mere involvement in the pathogenesis of heart failure Figure 2; it has been associated with the onset of a multitude of cardiovascular, metabolic, and cerebrovascular disorders[54]. Although the underlying mechanisms are complex, the ramifications of TMAO in these processes are, undoubtedly, significantly profound.

Choline, betaine, and L-carnitine derived from dietary sources undergo conversion into trimethylamine through the action of gut microbiota. Subsequently, this trimethylamine is metabolized into trimethylamine N-oxide (TMAO) by the enzymatic activity of flavin-containing monooxygenase 3 (FMO3) within the liver[49]. TMAO serves to activate a multitude of intracellular signalling pathways, which in turn facilitate vascular and cardiovascular pathological alterations that can culminate in heart failure. Although the specific mechanisms remain an area of active research, it is evident that key players such as PERK (protein kinase RNA-like endoplasmic reticulum kinase), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), and NLRP3 (NLR family pyrin domain containing 3) are involved. This intricate interplay underscores the complexities of metabolic processes and their implications for cardiovascular health[51]. However, further elucidation of these pathways is necessary to fully appreciate the ramifications of TMAO in pathological states.

Bile Acid

Bile acids fulfil an indispensable function in the intricate composition of bile[41]. In humans, the predominant bile acids—chenodeoxycholic acid, cholic acid (CA) and lithocholic acid—are synthesized through the involvement of at least 17 distinct enzymes[55]. These compounds are synthesized from cholesterol via either the classical or neutral pathway, or alternatively, through the acidic pathway[56]. Following their synthesis, they

undergo conjugation within the liver and are subsequently secreted into the gut lumen, where they are metabolized by microbiota into secondary bile acids. Bile acids are actively involved in the metabolism of cholesterol, lipids and glucose; they facilitate fat absorption, demonstrating their multifaceted roles[57]. The gut microbiota, under typical physiological conditions, sustains a state of equilibrium, playing an integral role in the development and regulation of the intestinal mucosal barrier. It governs nutrient intake, storage and metabolism, aids in the maturation of immune tissues and helps to prevent the proliferation of pathogenic microorganisms. However, this delicate balance can be disrupted, leading to various health issues. Although essential, the complexity of these interactions necessitates further exploration, because the implications of bile acid metabolism extend far beyond mere digestion.

However, alterations in the bile acid pool can disrupt this balance: resulting in a shift in gut flora distribution that may enable pathogenic microorganisms to flourish. This disruption can lead to pathological conditions, such as inflammatory bowel syndrome, obesity, diabetes, colorectal cancer and cardiovascular diseases (including heart failure,[41]). Although these conditions are varied, they share a common link to changes in gut microbiota; because the health of the gut is intrinsically tied to overall well-being, this relationship merits further investigation.

Conversely, modifications in the composition of microbiota can substantially impact the bile acid pool; thereby, both directly and indirectly, contributing to the pathogenesis of cardiometabolic diseases[58]. Bile acids manifest inotropic, lusitropic and chronotropic effects upon engaging with specific bile acid receptors, such as the muscarinic M2 receptor, Takeda G-protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR), all of which are present on cardiomyocytes[57]. These receptors seem to become activated when secondary bile acids are synthesized, a process that is contingent upon the presence of certain gut microbiota species[55]. Although the metabolism of bile acids within the framework of cardiometabolic disease has been extensively reviewed in previous literature[58], this article will not explore that subject in depth; instead, it will underscore the importance of secondary bile acids in the evolution of heart failure. The relationship between bile acid and gut microbiota interactions in the aetiology of heart failure is complex, involving multiple pathways. However, it is noteworthy that the majority of studies available in the literature have utilized animal models.

Bile acids generally exert a protective role on cardiac cells; however, certain bile acids may yield detrimental effects. For instance, it is established that hydrophobic bile acids such as lithocholic acid are cytotoxic and have been implicated in the aetiology of cardiometabolic diseases because of their pronounced affinity for lipids. Conversely, hydrophilic bile acids, exemplified by ursodeoxycholic acid, demonstrate beneficial impacts on cardiac function by ameliorating myocardial fibrosis[59]. Notably, ursodeoxycholic acid binds to FXR, thereby obstructing nitric oxide synthase inhibitors; this mechanism enhances myofilament function and facilitates myocardial relaxation in cases of HF with preserved ejection fraction. In murine models, the binding of bile acids to TGR5 inhibits NLRP3 inflammasome activation, thus averting inflammatory responses. Moreover, this interaction augments the heart's capacity to adapt to hemodynamic stress during heart failure through the activation of pro-survival kinases and heat shock proteins[60].

Bile acid receptors, specifically FXR and TGR5, occupy a central position in the realm of heart failure. For example, the stimulation of FXR receptors by secondary bile acids in rodent models has been demonstrated to augment the bile acid ratio while concurrently inhibiting the activation of NF-κB; this action mitigates inflammation and hypertrophic changes within the myocardium[61]. Prolonged NF-κB activation, however, culminates in an upregulation of atrial natriuretic factor expression, thereby contributing to the enlargement of cardiomyocytes[61]. NF-κB functions as an essential transcription factor that enhances the expression of a myriad of genes, including those relevant to inflammation, cellular differentiation, proliferation and apoptosis[62]. In the cytoplasmic milieu of quiescent cells, NF-κB dimers remain in a bound state with inhibitory proteins (IκB), predominantly IκBα and IκBβ[63]. This intricate interplay highlights the multifaceted functions of bile acid receptors in cardiac pathophysiology, although further inquiry is necessary to fully elucidate their mechanisms.

The activation of NF-κB is contingent upon the phosphorylation of IκB proteins at specific serine residues by the IκB kinase (IKK)—a sophisticated protein complex composed of α and β subunits, alongside a regulatory γ subunit. This process of activation, however, results in the degradation of IκB proteins through the 26S proteasome, which is dependent on both ubiquitination and protein kinase activity. As a consequence, NF-κB is liberated, subsequently translocating into the nucleus to initiate the transcription of a diverse array of genes, including those involved in the synthesis of pro-inflammatory cytokines (see Figure

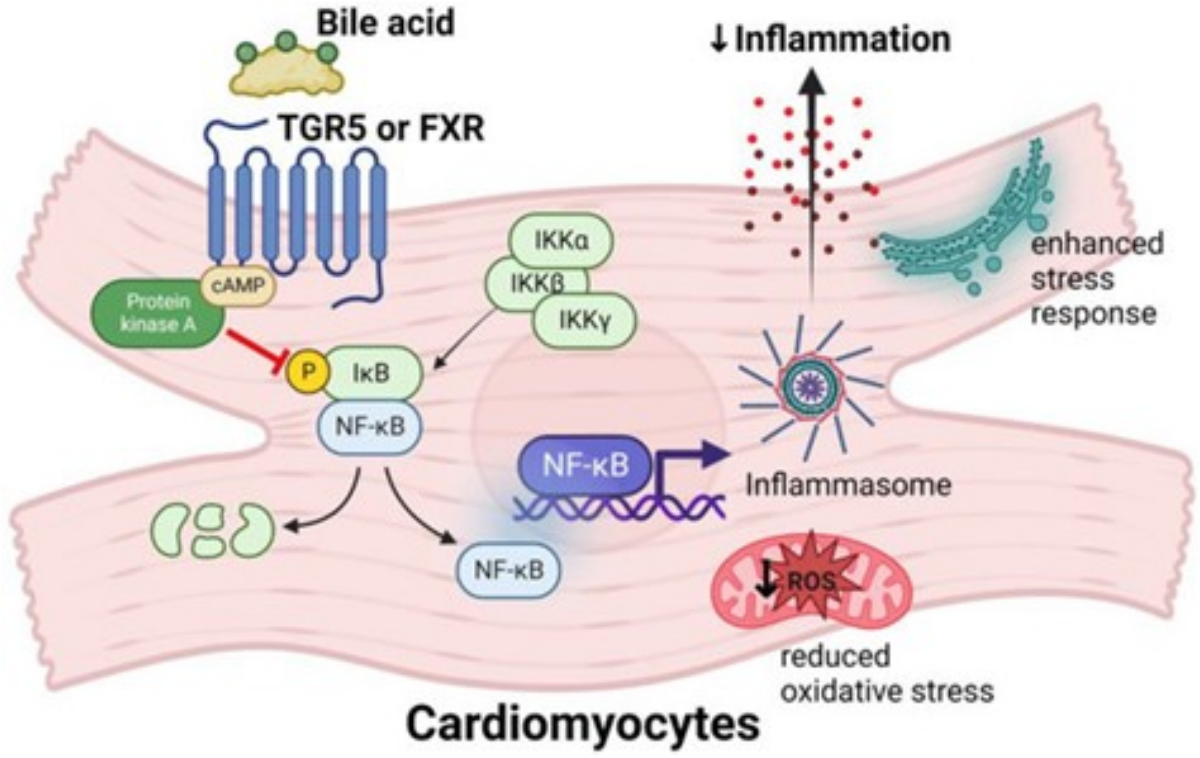

Figure 4: *The impact of bile acid signalling on FXR (farnesoid X receptor) and TGR5 (Takeda G-protein-coupled receptor 5) receptors within cardiomyocytes. Bile acids engage these receptors—FXR and TGR5—on cardiomyocytes, thereby activating intracellular signalling pathways that enhance cardiac function. This interaction is significant; however, the precise mechanisms through which these pathways operate remain an area of ongoing investigation. Although the influence of bile acids appears beneficial, further research is essential to fully elucidate their role in cardiac physiology (and potential therapeutic implications).*

2). Interestingly, the bile acid-mediated activation of TGR5 in murine models has demonstrated an enhancement of cardiac contractility, while simultaneously improving responses to hemodynamic stress. Nevertheless, when the gut microbiota experiences disruption—often termed gut dysbiosis—there is a notable decline in essential species that play a crucial role in maintaining adequate bile quantity and homeostasis. This phenomenon includes the activation of the FXR and TGR5 receptors, which ultimately leads to elevated levels of pro-inflammatory cytokines, impaired cardiac function and increased oxidative stress within myocardial cells.

Consequently, the modulation of gut microbiota composition possesses considerable potential to mitigate and avert pathological processes that lead to heart failure. However, additional research is requisite to clarify the specific mechanisms at play particularly because the relationship between gut microbiota and cardiovascular health is intricate and multifaceted.

Phenylacetylglutamine

Phenylacetylglutamine is intricately linked to the presence and severity of HF[64,65]. This compound, a metabolite produced by the gut microbiota, arises from its nutrient precursor, phenylalanine—an amino acid deemed nutritionally essential because it undergoes conversion to phenylpyruvate within the gastrointestinal tract[66]. Furthermore, the gut microbiota catabolizes phenylacetylglutamine, yielding both phenylpyruvate and phenylacetic acid. Subsequently, in the liver, phenylacetylglutamine is synthesized from phenylacetic acid and glutamine via an amino acid acetylation process, which is catalysed by the enzymes phenyl acetyltransferase and glutamine N-acetyl transferase[67]; see Figure 4). Notably, these enzymes facilitate the reaction involving the substrates phenylacetyl-CoA and L-glutamine, resulting in the formation of CoA, alpha-N-phenylacetyl-L-glutamine and phenylacetic acid[68]. However, the complexity of these biochemical pathways underscores the significance of phenylacetylglutamine in metabolic processes related to cardiovascular health.

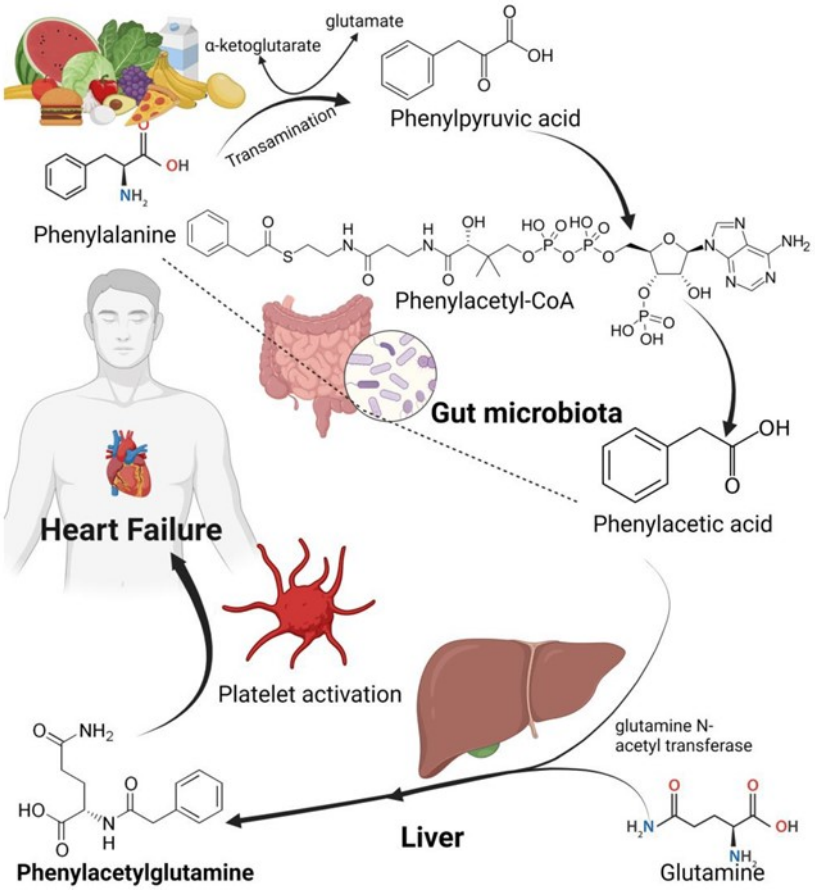

***Figure 5**: The phenylacetylglutamine formation by the liver enzymes and gut microbiota*

Through its complex interplay with G protein-coupled receptors (GPCRs) and adrenergic receptors (ADRs), phenylacetylglutamine has been shown to significantly affect thrombosis risk by enhancing platelet function; this, in turn, creates a state of hyperresponsiveness among platelets. Such a phenomenon can ultimately lead to the onset of myocardial infarction within the framework of coronary heart disease[66]. However, the engagement of phenylacetylglutamine with GPCRs and ADRs also fosters an overactive sympathetic nervous system, thus exacerbating HF[69]. In a noteworthy recent clinical trial, Romano et al. found that circulating plasma levels of phenylacetylglutamine were not only dose-dependently associated with HF, but they also unveiled correlations with various severity metrics particularly reduced ventricular ejection fraction and increased N-terminal pro-B-type natriuretic peptide[65]. Their findings compellingly suggest a clinical and mechanistic connection between HF and the gut microbiota metabolite phenylacetylglutamine.

Research has illuminated the critical significance of phenylacetylglutamine (indeed), which plays a pivotal role in HF; it not only attenuates the contraction of cardiomyocyte sarcomeres but also modifies gene expression related to B-type natriuretic peptide[65]. A recent inquiry, conducted by Fang et al., employed 16S rRNA sequencing techniques to scrutinize patients diagnosed with coronary artery disease (CAD). Their findings revealed a significant correlation between dysbiosis and elevated levels of microbiota-derived phenylacetylglutamine synthesis, particularly in relation to in-stent stenosis and hyperplasia in CAD patients[70]. However, despite the relatively limited volume of research focusing on phenylacetylglutamine, emerging evidence posits that this gut metabolite is associated with a spectrum of cardiovascular diseases (CVDs). This correlation accentuates its potential as a target for therapeutic intervention aimed at modulating gut microbiota-derived metabolites to ameliorate CVDs[71]. Although the implications of these findings are substantial, ongoing research remains imperative because a comprehensive understanding of these intricate interactions has yet to be fully realized.

In particular contexts pertaining to cardiac insufficiency, elevated concentrations of phenylacetylglutamine function as a critical risk biomarker for the emergence of HF and its ensuing

deleterious effects, which may encompass renal dysfunction and mortality[69].

Consequently, phenylacetylglutamine arises as both a prognostic indicator and a risk component within the sphere of heart failure. Moreover, a plethora of investigations[72–75] have substantiated that phenylacetylglutamine correlates with an increased likelihood of acute ischemic stroke. This heightened risk may present itself in various manifestations: for example, the occurrence of white matter hyperintensities in patients enduring acute ischemic stroke, the intensity of coronary atherosclerosis[74] and the prevalence of coronary artery disease[76]. However, these associations do not remain limited to these particular conditions; there exists a conceivable connection to lethal prostate cancer[75]. Although the fundamental mechanisms are yet to be elucidated, these revelations underscore the necessity of understanding the ramifications of phenylacetylglutamine.

In light of this context, it is essential (imperative, indeed) that subsequent investigations be undertaken to scrutinize these interrelations with heightened rigor. However, the complexity of such analyses cannot be overstated; although preliminary findings may furnish a foundation, they merely scratch the surface. Furthermore, it is crucial to recognize that deeper explorations are necessary, not only to validate initial observations but also to unveil nuanced dynamics that may otherwise remain obscured.

Clinical Evidence Linking the Microbiome to HF

Emerging research has illuminated the phenomenon of gut dysbiosis among individuals diagnosed with HF, which is characterized by an imbalance in microbial diversity and abundance. Investigations indicate that the gut microbiota composition in HF patients contrasts markedly with that of healthy individuals. For instance, these patients frequently exhibit a diminished diversity in advantageous bacterial taxa—such as Faecalibacterium and Roseburia recognized for their role as producers of short-chain fatty acids (SCFAs)[42]. Simultaneously, there is a discernible proliferation of pathogenic bacteria, including Escherichia coli and Enterococcus. Notably, a pivotal study conducted by[77] elucidated a remarkable shift in microbial composition, revealing that HF patients possess a heightened abundance of pro-inflammatory bacterial strains alongside reduced levels of SCFA-generating bacteria. This dysbiosis is posited to be a contributing factor to systemic inflammation, endotoxemia and immune dysregulation; all of which are intricately implicated in the pathophysiology of HF. However, the complexity of these interactions necessitates further exploration to comprehend fully their implications. Although the findings are compelling, the nuances of microbial interactions in HF present challenges, because they reveal a multifaceted landscape where therapeutic interventions may be required to restore microbial balance.

It is imperative to acknowledge that the relationship between gut microbiota and cardiac function is intricate. Although specific bacterial taxa may be reduced, the existence of pathogenic strains prompts further inquiry regarding their potential role in the exacerbation of HF. Consequently, a more sophisticated comprehension of microbial interactions becomes essential for the formulation of targeted therapeutic strategies. Moreover, the compromised functionality of the intestinal barrier observed in individuals with heart failure has been correlated with the presence of gut-derived lipopolysaccharides (LPS); these compounds, however, intensify inflammation and facilitate myocardial dysfunction[78]. Although the nature of this relationship is multifaceted, it is evident that this phenomenon profoundly influences patient outcomes, as it underscores the necessity for focused interventions.

Correlations Between Microbial Composition, Metabolite Levels and HF Severity/Prognosis: The complex interaction between the gut microbiota and HF is primarily mediated through its metabolites such as trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs) and secondary bile acids. Elevated concentrations of TMAO, which arise from the microbial degradation of dietary choline and carnitine, have consistently been linked to adverse cardiovascular outcomes; most notably, HF severity and mortality. Research conducted by[79] elucidated that higher plasma TMAO levels in HF patients were predictive of increased long-term mortality, regardless of traditional risk factors. SCFAs, particularly butyrate, acetate and propionate, are acknowledged for their anti-inflammatory properties and their role in enhancing the integrity of the gut barrier. However, it is essential to recognize that HF patients often exhibit diminished SCFA levels, which correlates with heightened gut permeability and systemic inflammation. Although this relationship necessitates further exploration, it underscores the intricate dynamics between microbial metabolites and cardiovascular health.

The discernible reduction in concentrations of short -chain fatty acids (SCFAs) has been significantly correlated with the progression of a variety of diseases; this phenomenon is predominantly due to the critical function these metabolites serve in sustaining immune homeostasis and alleviating

oxidative stress. Their deficiency may, therefore, intensify clinical outcomes. Furthermore, the altered bile acid profiles observed in individuals suffering from HF unveil a considerable disruption within the gut-liver axis. Secondary bile acids those that emerge from microbial alterations of primary bile acids play a crucial role in both lipid metabolism and the inflammatory response. Aberrant signalling of bile acids has been associated with metabolic dysfunction and adverse outcomes in HF. Collectively, these findings underscore a direct relationship between microbial metabolites and the progression of HF, thereby illuminating the complex interplay between gut microbiota and systemic health. However, because of the multifaceted nature of these interactions, further research is warranted to delineate the underlying mechanisms.

The Impact of Comorbidities on Gastrointestinal Health and HF Outcomes: Comorbidities (which frequently correlate with HF) such as diabetes, obesity and chronic kidney disease, tend to aggravate gut dysbiosis. Consequently, this escalation of dysbiosis results in detrimental effects[70]. For example, diabetes is acknowledged for triggering hyperglycaemia-associated modifications in the composition of gut microbiota; however, this phenomenon fosters an increase in pro-inflammatory species while concurrently reducing beneficial bacteria. Such alterations intensify systemic inflammation and endothelial dysfunction, thereby exacerbating the advancement of HF. Although the relationship is complex, the ramifications are significant because they highlight the necessity for comprehensive management strategies in individuals experiencing HF.

Obesity functions as a pervasive comorbidity associated with HF, disrupting the complex diversity of gut microbiota, primarily due to dietary habits characterized by an excess of saturated fats and a significant deficiency in fibre intake. These dietary alterations catalyse the synthesis of trimethylamine N-oxide (TMAO) and various deleterious metabolites; consequently, they amplify the risk of HF onset while simultaneously aggravating pre-existing conditions[50]. Moreover, the modifications in gut microbiota—induced by obesity—are intricately linked to metabolic endotoxemia; this particular phenomenon plays a crucial role in fostering chronic low-grade inflammation and facilitating cardiac remodelling. Chronic kidney disease (CKD) frequently coexists with HF, profoundly impacting gut health[67]. Uremic toxins (such as p-cresol sulfate and indoxyl sulfate) are produced by dysbiotic microbiota within the realm of CKD. These substances contribute to vascular calcification, oxidative stress and inflammation, ultimately compromising the prognosis for individuals suffering from heart failure.

The intricate interplay (among these elements) underscores the complexity that is inherent in the management of HF in patients who concurrently grapple with obesity and chronic kidney disease (CKD)[80]. This complexity is magnified because of the multifaceted nature of these coexisting conditions; however, it is crucial to address them holistically. Although managing HF in such patients presents numerous challenges, understanding the interdependencies among these factors is essential for effective treatment strategies.

The evidence connecting gut dysbiosis (alongside its metabolites) to HF highlights the complex interplay between the gut microbiota and cardiovascular health. Dysbiosis not only intensifies inflammation and metabolic dysfunction; however, it also affects HF prognosis because of its impact on gut-derived metabolites[70]. Furthermore, comorbidities including diabetes, obesity and chronic kidney disease (CKD) serve to amplify these effects. This situation underscores the necessity for personalized therapeutic strategies aimed at modulating the gut microbiota, with the goal of enhancing HF outcomes.

The studies concerning gut microbiota in patients diagnosed with heart HF are encapsulated within Table 2. This compilation offers a comprehensive overview; however, it also highlights the complexity of the interactions involved. Although the research presents various findings, the implications remain nuanced because of the multifaceted nature of microbiota influence on health outcomes.

Reference	Patient Type	Age (Years)	Sample Size	Method	Key Findings
(81)	Acute HF or exacerbation of chronic HF	47.4 ± 2.8 (younger HF) 73.8 ± 2.8 (older HF)	HF < 60: n = 12 HF > 60: n = 10 Controls: n = 12	16S rRNA	↓ Eubacterium rectale, Dorea longicatena Depletion of Faecalibacterium in older patients
(82)	Chronic HF	67 ± 2	Chronic HF: n = 22 Controls: n = 22	Fluorescence in situ hybridization	↑ Eubacterium rectale, Faecalibacterium
(83)	Chronic HF	65 ± 1.2	HF: n = 60 Controls: n = 20	Traditional culture techniques	↑ Campylobacter, Shigella, Salmonella, Yersinia enterolytica, Candida
(84)	Chronic HF	60.69	HF: n = 29 Controls: n = 30	16S rRNA	↓ Ruminococcaceae, Lachnospiraceae, Dialister ↑ Enterococcus, Enterococcaceae
(84)	Chronic HF (NYHA III-IV)	65–86	NYHA III HF: n = 29 NYHA IV HF: n = 29 Controls: n = 22	16S rRNA	NYHA III: ↑ Escherichia, Bifidobacterium NYHA IV: ↑ Klebsiella, Lactobacillus
(85)	Chronic HF (70% exacerbation, 30% stable)	65 ± 3.2	HF: n = 20 Controls: n = 20	16S rRNA	↓ Coriobacteriaceae, Erysipelotrichaceae, Ruminococcaceae (family level) ↓ Blautia (genus level)
(77)	Chronic HF	NA	Discovery: n = 40 Validation: n = 44 Controls: n = 266	16S rRNA	↓ Lachnospiraceae family
(86)	Stable chronic HF (ischemic/dilated cardiomyopathy)	58.1 ± 13.3	HF: n = 53 Controls: n = 41	16S rRNA	↑ Ruminococcus gnavus ↓ Faecalibacterium prausnitzii
(87)	HF with preserved ejection fraction (HFpEF)	40–70	HFpEF: n = 26 Controls: n = 67	16S rRNA	↓ Ruminococcus spp.
(88)	Chronic HF	65 ± 3.17	HF: n = 26 Controls: n = 26	16S rRNA	↑ Escherichia, Shigella, Ruminococcaceae, Lactobacillus, Atopobium, Romboutsia, Streptococcus, Haemophilus, Klebsiella
(89)	Non-ischemic HF with reduced ejection fraction (HFrEF)	18–70	HFrEF: n = 28 Controls: n = 19	16S rRNA	↑ Streptococcus spp., Veillonella spp. ↓ SMB53
(90)	Acute decompensated HF/acute worsening of chronic HF	72 ± 18	HF: n = 22 Controls: n = 11	16S rRNA	↑ Actinomycetota (phylum), Bifidobacterium (genus) ↓ Megamonas (genus)

Therapeutic Implications and Future Directions

Therapeutic Target

Recently published therapeutic guidelines for HF present an extensive array of recommendations regarding the management of HF and its various subtypes. Both non-pharmacological and pharmacological interventions are proposed, organized according to the new Universal Definition and Classification of Heart Failure. Strong class I evidence supports most disease phenotypes, except for pharmacological agents specifically targeting HF with preserved ejection fraction (HFpEF)[91]. However, prior studies indicate that chronic HF patients exhibiting elevated TMAO levels experienced poorer outcomes; moreover, TMAO levels did not respond favourably to guideline-based therapies. Adding TMAO to a model that incorporates B-type natriuretic peptide enhanced prognosis. Thus, further investigation into therapeutic mechanisms aimed at manipulating the gut microbiome could prove beneficial[92]. Although some therapeutic options have been applied to treat other clinical conditions, their application in HF remains largely hypothetical or experimental at this stage—necessitating further validation.

Despite this (fact), there is no mention of such therapeutic options in the current guidelines; they remain in their early stages. These options also include non-pharmacological strategies—like alterations in diet, metabolite levels and microbial flora. However, most of these measures are primarily aimed at chronic HF, although they are less effective for acute cases[80,93].

Probiotics and Prebiotics

Prebiotics, defined as food substrates capable of fostering the proliferation of specific beneficial microorganisms, hold significant promise in the realm of health[37]. The efficacy of putative prebiotics may manifest through various mechanisms within the physiological pathways that govern the interplay between the gut microbiome and its metabolites, potentially influencing the progression of HF. These substances encompass a range of compounds that facilitate the fermentation of dietary fibre into short -chain fatty acids (SCFAs), which are advantageous due to their cardioprotective properties and their role in maintaining the integrity of the gut barrier[94]. In addition, another substance that purportedly exerts beneficial effects at different junctures within this pathway is Bifidobacterium animalis subsp. lactis LKM512. Recent findings indicate that this probiotic strain may significantly diminish faecal trimethylamine (TMA) concentrations, reduce the abundance of TMA-producing bacteria and lower serum tumour necrosis factor-alpha levels when compared to a placebo group[95]. This suggests a potential reduction in TMAO-associated HF progression. Furthermore, preclinical studies elucidate a possible advantageous role for oligosaccharides, particularly those derived from food sources, as prebiotics[96]. These compounds appear to promote SCFA-producing bacteria while simultaneously curtailing opportunistic pathogenic bacteria, thereby potentially thwarting the development of hypertension and HF[94]. However, it is imperative to continue investigating these relationships to fully understand the underlying mechanisms at play.

To the best of our knowledge, there exists a paucity of human studies specifically addressing the intersection of hypertension and HF; however, a recent double-blind randomized controlled trial (RCT) demonstrated that the administration of fructo-oligosaccharides at a particular dosage was correlated with significant positive alterations in both the diversity and abundance of short-chain fatty acid (SCFA)-producing organisms, such as Faecalibacterium, Ruminococcus and Oscillospira[97]. These microorganisms have been previously established as beneficial to cardiac health[39]. Furthermore, prebiotics have also been shown to potentially mitigate the adverse effects of antibiotics by fostering diversity within the microbiome; however, the evidence concerning any potential concurrent use remains scant, particularly in light of the GutHeart trial's failure to investigate this[39]. This gap in research underscores the necessity for further inquiry into the complex interactions at play. Probiotics represent live microorganisms that are introduced with the intention of re-establishing a healthy equilibrium of microflora. Among these, Lactobacillus plantarum 299v has demonstrated utility in preclinical investigations, while Saccharomyces boulardii exhibited enhanced cardiac function within a cohort of chronic HF patients, although this was based on a limited sample size[98]. However, the GutHeart trial found no significant impact of Saccharomyces boulardii treatment on HF biomarkers or left ventricular ejection fraction (LVEF) when compared to the other intervention (antibiotic use) and control groups[29]. The exploration of probiotic applications post-myocardial infarction (MI) is particularly intriguing because adverse cardiac remodelling (CR) may lead to HF development. Probiotic administration might confer benefits following MI, primarily due to a reduction in inflammatory activity, which could facilitate improved CR, alongside enhancements in cardiac risk factors such as hypertension, dyslipidaemia and diabetes mellitus[99]. Indeed, a recent randomized controlled trial (RCT) conducted by Moludi et al. indicated that probiotic use in this particular context was correlated with

improvements in echocardiographic indices, albeit not reaching statistical significance.

Consequently, the application of probiotics may prove beneficial in specific clinical scenarios; however, additional investigation is imperative to determine their actual clinical efficacy and the contexts in which they might be advantageous. This is particularly pertinent when taking into account the documented risks associated with probiotics potentially undergoing translocation into systemic circulation[39]. Although the prospects are promising, caution is warranted.

Dietary Interventions

The reduction of dietary red meat consumption has been demonstrated to effectively attenuate the intake of TMAO precursors; patients who adhere to a Mediterranean dietary regimen have exhibited a significant decrease in both cardiovascular disease (CVD) and mortality risk[41]. Indeed, clinical investigations furnish compelling evidence that a transition to a diet free of red meat can precipitate rapid declines in plasma TMAO levels (as indicated by[100]). Furthermore, diets rich in fibre have shown promise in mitigating the onset of HF during preclinical studies, a phenomenon believed to be linked to an increased production of the short-chain fatty acid (SCFA) acetate. This, in turn, engenders beneficial cardioprotective effects and strengthens the maintenance of the gut barrier[101]. However, a typical Western dietary pattern—characterized by low fibre and high saturated fat content—has been associated with heightened intestinal permeability, thereby elevating circulating lipopolysaccharides (LPS) and contributing to endotoxemia.

Although these dietary modifications have been associated with favourable outcomes concerning cardiac function and HF biomarker levels, the impact of additional simultaneous lifestyle interventions remains ambiguous. This uncertainty continues to exist because, although some studies indicate positive correlations, others produce inconclusive findings. However, the necessity for a thorough understanding is paramount; this complexity warrants further exploration.

The imperative for a comprehensive investigation into the synergistic effects of dietary modifications in conjunction with established lifestyle changes among individuals diagnosed with HF cannot be overstated[41]. Exercise increasingly emerges as a pivotal modulator of the gut microbiota (this), yielding beneficial repercussions for cardiac function, particularly due to its correlation with heightened levels of short-chain fatty acids (SCFAs), particularly butyrate[102]. Addressing the phenomenon of sleep fragmentation, which is often encountered in individuals suffering from HF, has also been posited as possessing therapeutic potential; however, a recent preclinical study utilizing murine models revealed that while the isolated induction of sleep fragmentation and HF instigated alterations in the gut microbiome, the concurrent onset of both conditions did not yield any supplementary effects. Therefore, further inquiry is essential for elucidating the intricate interrelations among sleep disturbances, modifications in the gut microbiome and the progression and outcomes of HF[103].

Renal Denervation

Recently, renal denervation (RDN) has emerged as a promising therapeutic intervention for HF, given its capacity to diminish global sympathetic tone; this reduction may effectively address the intricate role that the sympathetic nervous system plays in the pathophysiology and evolution of HF[104]. Previous studies have demonstrated that RDN confers benefits in the management of hypertension, a condition that can significantly contribute to the onset of HF. Moreover, it has recently been established that RDN may serve as a safe and efficacious treatment for HF with preserved ejection fraction, exhibiting advantages that appear to be independent of fluctuations in blood pressure[105]. The interplay between RDN and the gut microbiome is particularly noteworthy;[106] reported that RDN successfully reversed aberrant alterations in the gut microbiome of rats suffering from chronic HF, characterized by increased populations of beneficial bacteria and a concomitant reduction in detrimental bacterial species. However, to substantiate these preliminary observations, further preclinical and clinical investigations are imperative, as they will facilitate a more nuanced understanding of the underlying mechanisms that drive these notable changes.

Faecal Microbiota Transplantation (FMT)

Faecal Microbiota Transplantation (FMT) seeks to transfer functional bacteria from healthy individuals to patients, thus modifying the composition of gut microbiota[102]. This procedure has demonstrated effectiveness in treating refractory Clostridioides difficile infections and inflammatory bowel disease. However, the applicability of FMT in HF patients remains ambiguous; because, to our knowledge, no studies have been conducted involving HF patients thus far[16,37,40]. Furthermore, one must take into account the risks associated with infection, endotoxin transfer and rejection[16]. Although the potential benefits seem promising, caution is indeed warranted.

Areas for Future Research

To augment our understanding of the gut microbiome's role in HF and its associated

therapeutic ramifications, a multitude of domains for prospective inquiry warrant thorough scrutiny.

Personalized microbiome-based interventions, which necessitate microbiome profiling for customized therapies, emerge as particularly salient[107]. Individual variability in gut microbiota composition compels the establishment of a personalized framework for microbiome-centric interventions. Future investigations should prioritize the identification of specific microbial signatures that correlate with HF subtypes, thereby facilitating the development of targeted therapeutic strategies. Dietary modifications, furthermore, epitomize another vital area; research is imperative to determine the most advantageous dietary patterns for modulating gut health in patients suffering from HF[107]. This exploration must incorporate the effects of fiber-rich diets, polyphenols, and certain prebiotics on both gut microbiota composition and HF-related outcomes; however, challenges persist in understanding these complex interactions. Although the trajectory of research appears promising, the nuances of microbial interactions must not be overlooked because they play a pivotal role in shaping therapeutic approaches.

Probiotics and postbiotics undoubtedly warrant meticulous examination[108]; the identification of probiotic strains capable of enhancing beneficial metabolites such as short-chain fatty acids (SCFAs) or mitigating deleterious metabolites like trimethylamine N-oxide (TMAO)[51] may yield more effective management strategies for HF. Furthermore, postbiotics metabolites produced by probiotics exhibit substantial promise as direct therapeutic agents within this context. However, the integration of these disparate elements into a cohesive therapeutic framework presents a challenge that merits comprehensive exploration. Faecal Microbiota Transplantation (FMT): Although FMT has demonstrated potential in addressing gastrointestinal disorders, its efficacy and safety concerning patients with heart failure (HF) remain largely uncharted[78]. Consequently, future clinical trials should rigorously evaluate its role in restoring gut homeostasis in the setting of HF. This line of inquiry is crucial because understanding the complex interplay between gut microbiota and heart failure could reveal significant insights into innovative therapeutic avenues.

However, the multifaceted (and often complex) nature of the human microbiome necessitates a sophisticated approach to these explorations. This complexity arises because the interactions within the microbiome can vary significantly, influencing health outcomes in ways that are not yet fully understood. Although there is a growing body of research, the intricacies involved require careful consideration and nuanced methodologies. Consequently, researchers must grapple with various factors that can affect their findings, including environmental influences and genetic predispositions. Thus, understanding the human microbiome is not merely an academic pursuit; it is a vital component of advancing our knowledge in health sciences.

Multi-Omics Approaches: Metagenomics (the exhaustive profiling of the genetic potential inherent within the gut microbiome) offers the potential to illuminate novel microbial genes and pathways that are profoundly intertwined with the pathophysiology of HF[103]. However, advanced metabolomic studies are crucial for delineating the complete spectrum of gut-derived metabolites and their mechanistic affiliations with the progression of HF[72]. This pursuit can dramatically enhance the identification of new biomarkers and therapeutic targets. Transcriptomics and proteomics, conversely, allow for an in-depth examination of gene expression and protein interactions within both the gut microbiome and host tissues. Although these investigations might appear divergent, they furnish more profound insights into the communication between host and microbiota, underscoring its critical role in HF. Integrated multi-omics approaches comprising metagenomics, metabolomics, transcriptomics, and proteomics can produce a comprehensive understanding of the intricate gut-heart axis. Because such integrative methodologies have the capacity to unveil complex interactions, they are indispensable for uncovering novel pathways that could function as targets for therapeutic intervention.

Role of the Gut-Liver-Heart Axis: Given the liver's essential role in metabolizing products derived from the gut, future investigations must explore the complex interactions among gut microbiota, hepatic functionality, and cardiac well-being[109]. The examination of bile acid metabolism and its resultant effects on HF progression is, however, especially pertinent. Although a substantial amount of information exists, the intricacies of these interrelations necessitate additional inquiry because they could provide valuable perspectives on innovative therapeutic approaches. This investigation may reveal pathways that have been previously neglected, thereby enriching our comprehension of systemic health.

Microbiota and Host Immune Interactions: Further investigations are requisite to elucidate the mechanisms by which gut microbiota modulates systemic immune responses in patients with HF[110]. Understanding these intricate interactions may,

however, unveil novel therapeutic strategies aimed at mitigating inflammation and enhancing clinical outcomes. This is particularly important because the relationship between gut microbiota and systemic immunity remains a complex area of study. Although progress has been made, the depth of this connection necessitates more comprehensive research; thus, it is crucial to continue exploring this multifaceted domain.

Gut Barrier Integrity and HF Progression: Exploring the mechanisms (that contribute to) increased gut permeability in heart failure (HF) and its ensuing repercussions such as endotoxemia holds critical significance. Research ought to evaluate diverse interventions aimed at reinstating gut barrier integrity, not merely to reduce systemic inflammation but also to improve overall health outcomes. However, the intricate nature of these interactions demands a comprehensive understanding of the fundamental biological processes. Although notable advancements have been achieved, continued investigation is imperative because the ramifications of gut health reach far beyond the gastrointestinal system; this highlights the urgent need to tackle these concerns in a holistic manner.

Longitudinal Studies and Clinical Trials

Long-Term Studies: The preponderance of modern research primarily depends on cross-sectional data; however, longitudinal studies are essential for illuminating the dynamic changes in gut microbiota as they evolve during the progression and treatment of HF. Clinical Trials: Randomized controlled trials that assess the efficacy of microbiome-based interventions (including prebiotics, probiotics, dietary modifications, and faecal microbiota transplantation (FMT)[78]) are vital for substantiating their therapeutic potential. Moreover, the influence of comorbidities on gut-heart interactions warrants thorough investigation. Future studies ought to explore how comorbid conditions such as diabetes, obesity, and chronic kidney disease impact gut dysbiosis[70] and HF outcomes. Understanding these interactions is crucial because it can guide the development of more comprehensive treatment strategies. Microbial-Derived Biomarkers for Diagnosis and Prognosis: The quest for reliable gut-derived biomarkers for HF diagnosis, risk stratification, and monitoring of treatment response represents a promising research trajectory.

Biomarkers (such as TMAO, SCFAs, and bile acids) necessitate further validation across a variety of patient populations. This emphasis on gut microbiota has the potential to revolutionize our approach to HF; however, challenges persist in the standardization of methods and interpretations. Although promising, this evolving landscape requires careful consideration because it impacts clinical practice significantly.

Conclusion

Emerging research highlights the complex function of the gut microbiota and its metabolites in HF pathogenesis. Gut dysbiosis, defined by altered microbial diversity and composition, is widespread in heart failure patients, leading to increased gut permeability, systemic inflammation, and unfavourable cardiac remodelling. Significant metabolites such as TMAO, SCFAs, secondary bile acids, and phenylacetylglutamine have been linked to cardiovascular dysfunction, emphasizing the need of studying the gut-heart axis. Diabetes, obesity, and chronic renal disease all worsen gut dysbiosis, impacting the course and prognosis of HF. While therapy aimed at the gut microbiota, such as nutritional interventions, probiotics, prebiotics, and FMT, has shown promise, substantial clinical data supporting their efficacy in HF care is currently sparse. Advances in multi-omics techniques and tailored microbiome-based therapeutics open up new possibilities for future research, allowing for a better knowledge of the gut-heart interplay and paving the way for novel, focused interventions. Multidisciplinary research combining microbiology, bioinformatics, and cardiology is crucial to addressing these issues. To validate treatment approaches and apply microbiome knowledge to clinical practice, longitudinal investigations and randomized controlled trials are essential. By utilizing these discoveries, we may be able to transform the treatment of HF, enhance patient outcomes, and deepen our comprehension of the intricate connection between gut microbiota and cardiovascular health.

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Bridging the Financial Literacy Gap in Medical Education : A Case for Curricular Reform and Practical Tools

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Abstract:
Medical students routinely graduate with educational debt exceeding $250,000, yet most receive little formal instruction in personal finance or healthcare economics. This gap leaves trainees poorly prepared to navigate complex financial decisions related to borrowing, repayment, specialty choice, and long-term career planning. Drawing on MD/MBA student experience and synthesis of existing literature, this perspective examines the financial literacy gap in medical education and its implications for physician wellbeing, professional autonomy, and engagement with an increasingly complex healthcare system.
We highlight how inadequate financial preparation contributes to avoidable financial stress, burnout, and constrained career decision-making, particularly during early training years when debt burdens are highest and income is delayed. At a systems level, limited exposure to healthcare finance leaves future physicians ill-equipped to understand reimbursement models, consolidation, and the growing role of private equity in clinical practice.
Based on these observations, we propose a three-pronged approach emphasizing curricular reform, improved access to structured financial education, and normalization of healthcare finance as essential professional knowledge. By reframing financial literacy as a core competency rather than a peripheral skill, medical education can better equip future physicians to make informed financial decisions, navigate evolving healthcare systems, and build more resilient, sustainable careers.

Key Words:
Medical Student Debt; Financial Literacy; Medical Education; Healthcare Economics; Physician Wellbeing

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Background

Medical student loan debt has become a defining feature of physician training. As of 2024, 73% of medical graduates carry student loans, with average debt exceeding $264,000, more than double that of the average post-graduate student[1]. Despite this heavy debt burden, little attention is paid to how poorly prepared students are to navigate this financial undertaking. Financial literacy among medical students remains critically low, with nearly half of medical students reporting a need for more financial education during medical training[2]. This results in students making complex decisions including borrowing large sums, choosing between schools, or selecting repayment plans with minimal guidance or formal instruction. This gap is not just an academic oversight. Recent literature has linked medical education debt and a lack of financial literacy to financial stress, physician burnout, and a declining interest in primary care specialties[3].

Beyond individual well-being, broader forces in the healthcare system demand that future physicians be more financially literate. The increasing role of private equity in clinical practice, growing consolidation of providers into health systems, and the shift toward value-based care all introduce financial guardrails that impact how physicians practice medicine. Understanding the mechanics of billing, insurance, and healthcare economics is not a luxury, but it is a necessity for protecting both physician autonomy and patient trust. Yet, most trainees receive little to no education on how healthcare financing works or how their personal financial choices intersect with these broader structures[4,5,6].

This lack of preparation is especially concerning given the way repayment is structured. A common benchmark is the debt service-to-income ratio (DSIR), which measures the share of monthly income devoted to loan repayment. While countries such as the United Kingdom, New Zealand, and Australia use income-contingent repayment schemes that cap repayment burdens and insure against defaulting, the U.S. relies heavily on fixed repayment plans[7]. In many developing countries, the burden is even greater, with early-career borrowers

devoting 20–35% of monthly income to repayment.[8] These often push graduates above thresholds considered financially stressful, making repayment especially burdensome early in a physician's career[8]. For medical graduates, whose debt loads are far higher than average, these conditions create disproportionate financial risk and underscore the urgency of reform.

While recognition of this gap is not new, few solutions have been tailored specifically for medical trainees or embedded within curricula at scale. Even where financial literacy reform is broadly endorsed, efforts to implement it face persistent barriers, including limited curricular time and insufficient faculty expertise. Addressing these barriers requires moving beyond acknowledgment to designing practical, scalable solutions that meet the needs of medical trainees.

The Problem: Financial Illiteracy in Medical Training

The roots of this issue lie in several overlapping gaps. First, medical training prioritizes scientific and clinical rigor while overlooking basic financial competencies. While the Liaison Committee on Medical Education (LCME) requires medical schools to provide students with adequate financial resources and debt management counseling, there are no standardized requirements for financial curriculum[9]. Concerningly, medical school-provided financial counseling that is available has shown no measurable improvement in financial literacy among students, indicating that the current financial curriculum within medical education is inadequate and fails to set students up for financial success.[2]

Second, students face structural challenges. The complexity of federal and private loan options, varied repayment programs, and unpredictable interest accrual make it difficult to plan strategically. This is further compounded by policy volatility, such as shifts in political administrations that alter loan terms, forgiveness programs, and repayment options, creating an unstable landscape that is hard to navigate even for the financially savvy. Financial advising is often decentralized or outsourced, and students are left to navigate a system where missteps are costly and hard to reverse. Additionally, medical school advising is only available to students who have enrolled and therefore are financially committed to the school.

Compounding these structural challenges is the sheer complexity of student loan agreements and repayment conditions. Federal and private loans carry different interest structures, grace periods, and forgiveness options, while loan agreements themselves are dense with jargon and technical detail. Students often sign these contracts with minimal understanding, overwhelmed by the volume of information and eager simply to secure the financing needed to begin training. Debt management then requires ongoing attention to repayment schedules, capitalization of interest, and refinancing or consolidation choices—topics that are not only difficult to parse and far from the "flashier" aspects of medical training, but also hard to prioritize for students already stretched thin by the demands of their education. Unsurprisingly, many students disengage from this process until repayment becomes unavoidable, reflecting a reactive rather than proactive approach to repayment that has been documented across borrower studies[10]. Evidence shows that repayment outcomes are shaped not only by income, but also by how well borrowers understand loan terms, the burden they perceive, and their credit history[10]. Gaps in literacy around these factors increase stress and carry lasting consequences, including weakened credit scores that make securing housing, practice loans, and long-term financial stability more difficult.
Finally, existing financial counseling within medical education often falls short. Sessions are typically passive and information-heavy, lacking practical or interactive tools that help students translate abstract advice into personal financial planning. Unsurprisingly, this contributes to disengagement and leaves many students unprepared to manage repayment effectively. At the same time, there is a tacit acceptance that debt is simply part of becoming a doctor. While this may be true in part, the absence of accessible tools and structured education fosters a sense of helplessness rather than agency. This mindset contributes to avoidable financial errors and amplifies stress during training.

Reforms and Solutions: A Multi-Pronged Approach

To address this problem, we propose a three-part solution: curriculum reform, development of financial tools, and normalized education around healthcare economics.

1. Curriculum Reform: From Premed to Preclinical

First, financial literacy must be treated as a core competency in medical education. We argue that personal finance and healthcare economics should be embedded at two levels: (1) the premedical curriculum and (2) the preclinical phase of medical school.

At the undergraduate level, medical school applicants should complete a semester-long course in personal finance as part of their prerequisite coursework, much like biology or physics. This course should cover the fundamentals of budgeting,

credit, compound interest, student loans, and basic investing.

Within medical school, structured instruction in both personal finance and health system economics should occur early in the preclinical years. Topics should include loan types and repayment strategies, insurance models (e.g., PPO, HMO), CPT/ICD billing codes, reimbursement models (fee-for-service vs. capitation), and emerging trends in private equity and value-based care. Educating students on how care is paid for, and how physicians are paid, empowers them to both advocate for themselves and communicate more effectively with patients navigating the same system.
Importantly, this knowledge translates directly to patient care. When physicians understand the financial consequences of clinical decisions, they are better equipped to help patients navigate insurance plans, anticipate out-of-pocket costs, and access resources. Financially literate physicians are more likely to consider affordability in treatment planning, enhancing both ethical practice and patient trust.

2. Tools to Empower Financial Insight

Second, students need tailored, interactive tools, not just lectures. that are designed specifically for the realities of medical training. Many struggle to grasp how loan interest, residency duration, specialty income, and geographic cost of living interact to shape repayment timelines and long-term financial stability. The real challenge is seeing these factors in concert and understanding their relevance to a physician's career path. Generic debt calculators exist, but they rarely integrate clinical variables such as variable residency lengths or specialty-specific earnings, and they are typically aimed at borrowers or financial advisors rather than serving an educational purpose.

As a pilot demonstration of how such tools might address this gap, we developed a customizable financial model designed with variables relevant to medical students and residents. The model allows users to input assumptions such as tuition, specialty choice, residency duration, loan repayment strategy, and geographic location, and generates projections for total debt, repayment time, and post-tax salary. It was designed as a proof-of-concept educational resource, intended to make abstract financial concepts more concrete, interactive, and directly tied to physician training. Its pedagogical emphasis is on exploration rather than optimization, enabling students and residents to model hypothetical scenarios and better understand how individual decisions may influence long-term financial outcomes.

Because the model was designed as an introductory educational tool, certain factors, like malpractice insurance, employer-specific retirement matching, or advanced investment strategies, were considered beyond its scope, given their wide variability and relevance to later career stages. Informal pilot feedback collected via anonymous survey from 12 users suggested that the model increased awareness of personal financial considerations, clarified the implications of repayment and career choices, and was perceived as more engaging than traditional counseling sessions. Future iterations could focus on broader accessibility, including development of a web-based or mobile platform, and adaptation for international training contexts where loan structures and repayment systems differ substantially.

3. Normalize Healthcare Finance as Essential Knowledge

While culture change is difficult to engineer directly, embedding financial education into curricula and providing better tools naturally shifts the narrative. When financial literacy is treated as essential rather than peripheral, students internalize its value. Conversations about money, whether student debt or healthcare spending, become normalized, not taboo. This shift fosters a generation of physicians who are not only better stewards of their personal finances, but also more informed advocates within an increasingly complex healthcare economy.

Understanding and Addressing the Repayment Landscape

Repayment Attitudes and Risk

Educational loan repayment is shaped in part by attitudes, not just income. The Theory of Planned Behavior (TPB) offers a useful lens: positive repayment attitudes, such as valuing credit history, recognizing debt utility, building financial knowledge, prioritizing repayment, and acting with integrity, are associated with stronger repayment outcomes[11]. In contrast, negative attitudes linked to gratification-seeking, stress, or a sense of overwhelming burden increase the likelihood of delinquency or default. For medical trainees, who already face outsized debt burdens, these attitudes can amplify risk if not addressed through education.

Financial institutions conceptualize repayment capacity through frameworks such as International Financial Reporting Standard (IFRS 9), which quantifies credit risk using Probability of Default (PD), Exposure at Default (EAD), and Loss Given Default (LGD). Medical graduates represent a unique borrower profile: they carry high loan balances and experience delayed income during residency, raising short-term repayment risk, yet they also possess strong long-term earning potential. This duality underscores the need for

medical education to prepare students not only to manage their personal attitudes toward debt but also to understand how lenders assess their repayment capacity.

Evolving Credit Scoring and Implications for Physicians

Credit scoring itself is evolving beyond static measures. Novel approaches, including machine learning models and dynamic factors such as credit utilization, evaluate not only whether borrowers repay but how they manage and use credit[12,13]. For example, high credit utilization paired with consistent repayment may be viewed more favorably than minimal utilization, since it demonstrates active engagement with credit.

For future physicians, the implications are significant. Repayment behavior influences not just student loan balances but also downstream opportunities to secure mortgages, practice loans, or refinancing. A lack of awareness about how credit scoring systems function can leave graduates at a disadvantage. Embedding this knowledge in training is therefore not just about reducing stress in the short term but about safeguarding professional and personal financial trajectories.

Implementation and Scalability

For financial literacy initiatives to have lasting impact, they must be scalable and integrated into existing educational structures. Structured financial education can be incorporated as teaching modules, paired with standardized debt counseling, or delivered through digital platforms to improve accessibility and allow updates as policies and costs evolve. While promising, broader adoption faces familiar barriers: medical curricula are already saturated, few faculty have formal financial training, and students may resist material perceived as peripheral to clinical education.

Several strategies could help overcome these challenges. Peer-led sessions may increase relatability and reduce faculty burden. Integration into existing advising structures can situate financial planning alongside other career development milestones. Finally, partnerships with national organizations such as the AAMC or AMA could help standardize resources across institutions, reducing duplication of effort while raising visibility. Together, these approaches position financial education not as an optional add-on but as a necessary component of preparing future physicians for sustainable careers.

Conclusion

The financial literacy gap in medical education is a solvable problem hiding in plain sight. Medical students assume hundreds of thousands of dollars in educational debt with little structured guidance on how to manage it or anticipate its long-term consequences. Without this preparation, many graduates face avoidable financial stress, burnout, and constrained career choices, with effects that extend beyond individual physicians to the patients and health systems they serve.

Addressing this gap requires more than ad hoc counseling or isolated budgeting sessions. Financial literacy must be woven into the fabric of premedical and medical training, equipping future physicians with a working understanding of credit, repayment structures, and healthcare economics that mirrors the real-world environments in which they will practice. Doing so empowers trainees to make informed personal decisions while also engaging more thoughtfully with the financial forces shaping modern healthcare delivery.

While practical tools and resources may help translate these concepts into applied understanding, the broader takeaway is cultural and curricular. Financial literacy should be treated as a core professional competency rather than a peripheral concern. Preparing physicians who are both clinically excellent and financially informed is essential to sustaining fulfilling careers, preserving professional autonomy, and promoting more equitable and patient-centered care in an increasingly complex healthcare system.

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A Comparative Study of Flipped Classroom Teaching Method vs Traditional Classroom Teaching Method in Undergraduate Medical Students

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Abstract:
Background: The flipped classroom (FC) model reverses the traditional lecture and homework roles, and helps promote active engagement, develop higher-order cognitive skills necessary for physicians. This interventional cross-sectional study compared the effectiveness of the FC with traditional lecture-based teaching among undergraduate medical students in Pakistan.
Methods: A cross-sectional interventional study was conducted with 70 final-year MBBS students at a private medical college in Lahore. Participants were divided into two groups: FC and Traditional. The FC group received study material via WhatsApp 24 hours pre-class, while the traditional group took lectures in class. Assessment included pre-tests, post -tests, and pre-validated feedback questionnaires for students and faculty. Data was analyzed using SPSS v.25, employing appropriate statistical tests.
Results: The FC group consistently achieved higher mean scores in both pre-tests and post-tests compared to the traditional group. Independent t-tests demonstrated statistically significant difference in scores of two groups; 2x2 ANOVA showed that where improvement in scores was seen in FC group, it was not always statistically significant. 82.9% of students agreed that FC created an interactive environment. While 63.3% of faculty strongly agreed that FC increased student learning, while half (46.7%) noted it was more resource intensive.
Conclusion: The FC model significantly enhances academic performance and student engagement compared to traditional methods.

Key Words:
Flipped Classroom; Medical Education; Academic Performance

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Introduction

Our current teaching methodologies primarily rely on lectures and self-study; however, modern technology has revolutionized student learning. Identifying teaching and learning needs is the first step to making students more capable learners.[1] Teacher-centered education models remain widespread in many developing countries, slowing the transition to modern learning methods. In this unidirectional knowledge transfer, the instructor provides information while employing rote-learning methods rather than the required critical engagement.[2,3] Student-centered approaches have transformed teaching methods worldwide in higher education, thereby improving academic outcomes.[4] While designing the undergraduate medical education curriculum, learning goals should aim to make students proactive learners and encourage evidence-based problem-solving.[5] The use of traditional lectures as the primary learning tool limits the development of higher-order cognitive skills.[6] To drive better results, research suggests that adopting flexible learning models like flipped classrooms and the utilization of modern digital resources can be highly effective.[7]

Flipped classrooms (FC) use a blend of teaching methodologies to optimize the learning environment.[8] In practice, in the FC approach, learning material is provided before the actual class, freeing up time for active learning during class. Variation in content delivery for FCs is observed across studies, making it a more flexible approach for adoption in medical education.[9] In the FC model, instructors reverse the traditional order of schoolwork and homework by providing pre-recorded lectures or other study material before the actual class. Students review these resources before class and can, in turn, engage in more fruitful discussions during class.[10,11] This technique aligns with Bloom's taxonomy, a comprehensive curriculum framework that describes how understanding of foundational knowledge is followed by higher-order analysis and evaluation.[12]

A study conducted in Thailand explored attitudes of students towards active learning in health education and found that most students preferred active learning techniques, and these benefit their cognition, self-efficacy, and attention span while developing essential 21st-century skills in them.[13]

The FC method offers numerous advantages, including personalized learning pace, enhanced concept-building through peer interaction, reduced anxiety, and increased student confidence. [14] There is a lack of research on the benefits of flipped classrooms for raising medical students' academic achievement; thus, comparisons with standard classroom settings and lectures are necessary. Our study compares the performance of medical students when taught using traditional methods versus the FC approach.

Materials and Methods

A cross-sectional interventional study was conducted at a private medical college in Lahore, with IRB approval from the Ethical Review Board. The total sample size was 70 MBBS final-year students, and convenience sampling was used. We divided the students into two groups: traditional and flipped, each with 35 students. Informed consent was taken from all participants. Any student who did not consent to participate was excluded.

We carried out the intervention for over a month, divided into four sessions. To increase the study's validity, four tests were administered during four separate lectures in the final-year Internal Medicine course on the following topics: malaria, dengue, Enteric Fever, and tuberculosis. The flipped group received and reviewed the study materials the day before class, whereas the traditional group received none. Pretests were administered to both groups via Google Forms, and responses were closed after the class began. After the lecture, post-tests were administered in the same manner as pretests, and the form was closed 15 minutes after the lecture. Both pretests and post-tests for different groups were administered on separate Google Forms and WhatsApp groups to prevent participant mixing while ensuring confidentiality. Pre-validated feedback questionnaires were also distributed to faculty and students. No scores were revealed to the participants.

The data were analyzed using SPSS version 25, with the relevant statistical tests including the Shapiro-Wilk test to assess normality and independent-samples t-tests to compare pre- and post-test scores between groups. To provide a more robust analysis of the intervention's efficacy, we conducted a 2x2 Mixed ANOVA to account for the study's repeated-measures design, allowing evaluation of within-subject knowledge acquisition over time.

Results

The mean and standard deviation of scores for both groups were calculated for all four tests (shown in Table 1). The data for scores were normally distributed. Overall, the mean scores for both the pre-test and post-test were higher for students in the flipped class group, e.g., 3.11 vs 2.1. Independent t-tests were used to analyze the difference between pre-test and post-test scores across two groups. For most tests, the p-value was less than 0.001, indicating a statistically significant difference in score between the two groups. (Table 1)

This was followed by a 2x2 ANOVA to control baseline pre-test disparities and calculate the interaction effect between time and teaching modality, a more accurate measure of the FC's true impact on learning. This evaluated the effects of time (pre-test vs. post-test) and teaching method (flipped vs. traditional) on student scores. A statistically significant main effect of time was observed across all four tests ($p \leq 0.001$), indicating overall improvement in knowledge regardless of the teaching method. For Tests 1, 2, and 3, there was no statistically significant interaction between time and teaching method ($p > 0.05$). However, Test 4 revealed a significant interaction effect, $F(1, 68) = 8.04$, $p = 0.006$, partial eta squared = 0.106 (Table

Flipped or Traditional		Pre-test 1 score	Pre-test 2 score	Pre-test 3 score	Pre-test 4 score	Post-test 1 score	Post-test 2 score	Post-test 3 score	Post-test 4 score
Flipped	Mean± SD	3.11±0.53	2.69±0.87	3.03±0.66	2.63±0.65	3.71±0.46	3.63±0.55	3.60±0.55	3.40±0.50
Traditional	Mean± SD	2.114±1.08	1.88±1.02	2.00±0.01	2.57±0.70	2.77±0.94	2.857±0.85	2.314±1.13	2.714±0.83
Independent T-test	P-value	<0.001	0.001	<0.001	0.723	<0.001	<0.001	<0.001	<0.001

Table 1: *Comparison of mean scores between flipped classroom and traditional method*

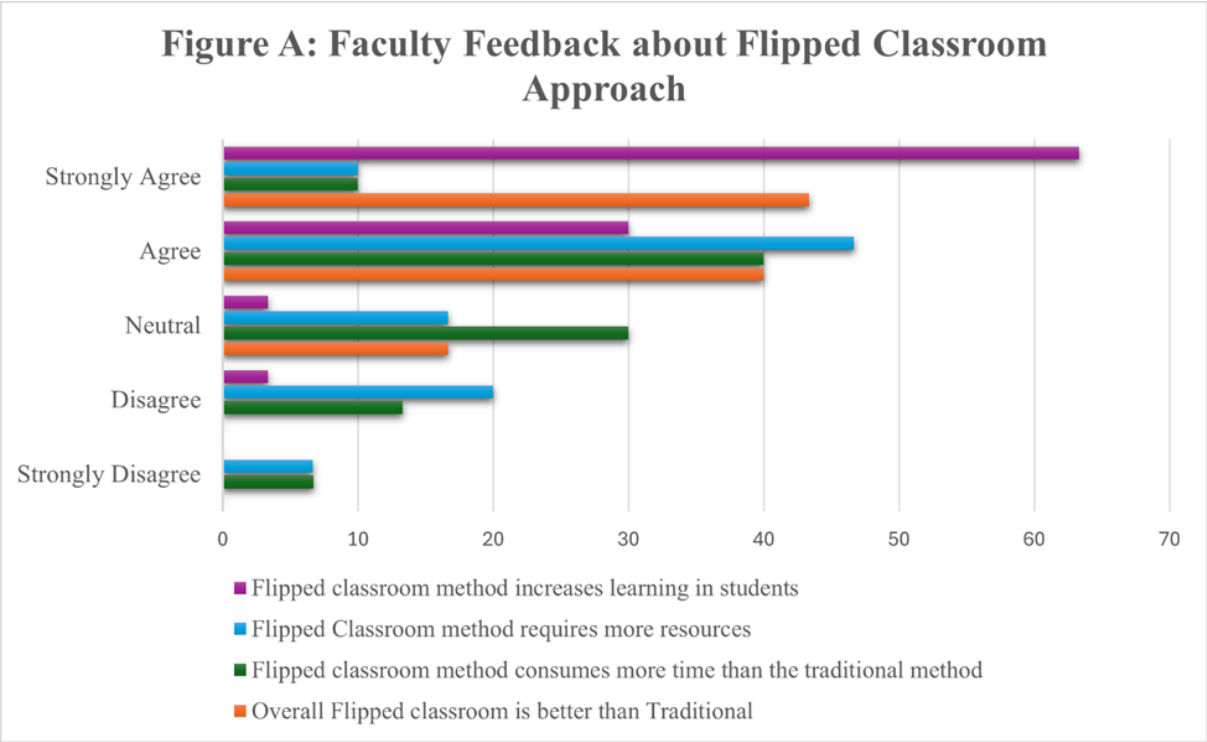

Figure 1: *Student Feedback on the Flipped Classroom Experience.*

2). This demonstrates that, for this specific module, students in the flipped classroom achieved a significantly greater improvement from pre-test to post-test than those in the traditional classroom.

Student and faculty input indicated a preference for a flipped classroom approach. A total of 30 faculty members responded. Over ninety percent of the faculty agreed that the FC method increases learning in students, with only one faculty member who completely disagreed. More than seventy percent said that flipped classroom required more resources. Half of all faculty members found the FC method more resource-intensive (Figure 1)

Student feedback showed overall positive perceptions of the flipped classroom method. Over seventy percent agreed that it created interest in the topic. Most students agreed that the flipped classroom method improved learning, allowed ample time allocation, and provided an interactive learning environment, with very few students in disagreement. (Figure 2).

Discussion

The present study compared the flipped classroom teaching method with the traditional lecture-based approach among final-year medical students. While both modalities significantly improved overall knowledge acquisition ($p<0.001$ across all modules), FCs can lead to a significantly higher rate of academic score improvement. Despite equivalent baseline knowledge, the FC group demonstrated a statistically significant interaction effect ($p = 0.006$), indicating faster, more robust learning than the traditional cohort. These findings are consistent with previous studies that also showed elevated academic performance among students taught using FCs.

Mean post-test scores were also higher among the FC cohort, indicating better learning. This finding was consistent with previous studies, which also showed that post-tests were significantly higher for students taught using the flipped classroom method. [15-18] Another study, however, conducted at Al-Neelain University in Sudan, found no significant differences between the pre-test and post-test results, which shows that variation may exist due to differences in institutional culture and student readiness. [19]

Feedback from both students and faculty was also strongly in favor of the flipped method. Students reported greater interest, improved understanding, and enhanced learning compared with traditional lectures, as seen in other studies conducted in Sudan and the USA. [19,20] The student feedback, as shown in Figure B, indicates that the FC method created a more interactive environment (82.9% agreement) and generated greater interest in the taught topic (74.3% agreement). The shift in post-test scores in the flipped classroom group was likely due to students' active in-class participation, which

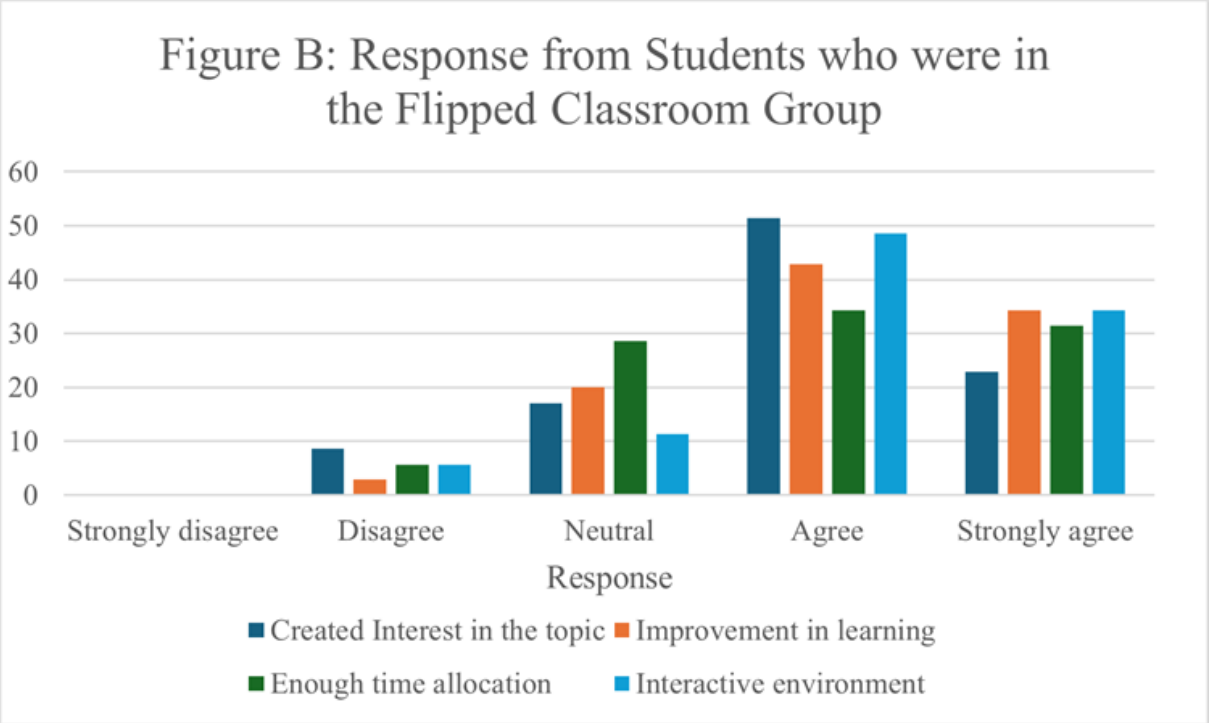

Figure 2: *Student Feedback on the Flipped Classroom Experience.*

Test Module	Effect	F(1,68)	p-value	Partial Eta Squared (πp2)
Test 1	Main Effect (Time)	25.32	< 0.001	0.271
	Interaction (Time X times) Method)	0.05	0.82	0.001
Test 1	Main Effect (Time)	51.39	< 0.001	0.43
	Interaction (Time X times) Method)	0.01	0.915	< 0.001
Test 1	Main Effect (Time)	11.95	0.001	0.149
	Interaction (Time X times) Method)	1.01	0.319	0.015
Test 1	Main Effect (Time)	17.02	< 0.001	0.2
	Interaction (Time X times) Method)	8.04	0.006	0.106

Table 2: *Summary of 2x2 Mixed ANOVA Results Across Test Modules.*

led to better retention of the concepts, a benefit that medical education can significantly leverage. Another study at AKU, Karachi, found that many students found the FC approach more effective and preferred it over traditional lectures. They reported that their queries and misunderstandings were better handled, and they retained more concepts.[17]

While faculty members were satisfied with the overall effectiveness of the flipped classroom method, many found it resource- and time-intensive, limiting its feasibility in institutions with limited financial support. The faculty's opinion was consistent with another study conducted in India, in which sixty percent found it resource-intensive, and eighty percent believed it uses more time than the traditional method of teaching.[21] Our student feedback, as depicted in Figure B, suggests that

ample time was allocated for the topic, which indicates that the faculty's time investment in improving teaching methods can prove beneficial for students' overall understanding.

Even though the effect of the teaching method was statistically insignificant in 3 of the tests as per 2x2 ANOVA, it is important to consider that efficacy may vary from subject to subject, and the method may not always be effective when used alone. Studies have used flipped classrooms with other modern methods of learning, such as using virtual reality, to help improve the understanding of students. One such study found that the use of a flipped classroom combined with virtual microscopy resulted in significantly improved assessment scores.[22] Our study, however, focused mainly on the flipped classroom intervention using basic digital resources such as WhatsApp to study the generalizability of the concept in low-resource settings, such as in most medical education institutions of Pakistan and other South Asian and African countries.

Future research can compare effectiveness in pre-clinical and clinical settings to determine where its application is more viable. The use of advanced Learning management software could distribute resources and prevent contamination of the intervention. Studies can also assess long-term retention of the subject material by administering a follow-up post-test within 6 months.

Conclusion

Overall, the pre- and post-test scores were higher in the flipped classroom group when compared to the traditional learning group, even though the results were not always statistically significant. The students were more satisfied with their learning through the flipped classroom approach. The faculty members found the method to be resource-intensive, but they were positive that it improves learning in students. Although it may pose logistical challenges for resource-constrained institutions, it can still be implemented strategically to enhance the quality of learning for medical students, who will be the face of future healthcare.

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A Study of Awareness Amongst Medical Students in Damascus Regarding the Efficacy and Safety of GLP-1 Receptor Agonists for Weight Loss in Non-Diabetic Individuals

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Abstract:
Background: The use of GLP-1 receptor agonists has increased markedly in recent years as an effective pharmacological option for weight loss in non-diabetic individuals. This has raised concerns regarding awareness of their efficacy and safety, particularly among medical students who will play a future role in clinical decision-making and patient guidance.
Methodology: This cross-sectional study was conducted on a sample of 300 medical students. Data were collected using a structured questionnaire covering demographic characteristics, body mass index, experience with GLP-1 receptor agonists, perceived efficacy, side effects, and awareness of safety and medical supervision requirements.
Results: The findings demonstrated widespread exposure to or experience with GLP-1 receptor agonists among students, with notable weight loss reported by most users. However, weight regain after discontinuation was common. All users reported side effects, predominantly gastrointestinal and mild to moderate in severity, yet the majority perceived these medications as safe and effective and were willing to recommend them.
Conclusion: The study highlights a high level of awareness and practical exposure to GLP-1 receptor agonists among medical students, alongside recognition of their benefits and limitations. These findings underscore the need for structured medical education regarding their appropriate use, strict medical supervision, and integration within a comprehensive lifestyle-based approach to achieve sustainable weight management outcomes.

Key Words:
GLP-1 Receptor Agonists; Weight Loss; Damascus: Pharmacotherapy for Obesity: Mounjaro

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Introduction

Obesity represents one of the most significant health challenges of the twenty-first century. Global statistics have demonstrated a continuous rise in its prevalence among both children and adults over recent decades, establishing it as a major risk factor for multiple chronic diseases, including type 2 diabetes, hypertension, cardiovascular diseases, and metabolic disorders. Beyond its health complications, obesity substantially impacts quality of life, affecting physical activity levels, mental health, and increasing the likelihood of social isolation.

Given this alarming increase, there is an urgent need for effective and safe weight-loss interventions that go beyond dietary modifications and physical activity, particularly for individuals with severe obesity or those who have not achieved satisfactory results with conventional approaches. Among these novel options, glucagon-like peptide-1 receptor agonists (GLP-1 Ras) have emerged as a promising therapy due to their ability to stimulate insulin secretion, inhibit glucagon release, slow gastric emptying, and enhance satiety.

Recent clinical studies have demonstrated the efficacy of these agents not only in patients with type 2 diabetes but also in non-diabetic individuals, showing significant weight reductions, sometimes up to 15% of baseline body weight over long-term follow-up. Furthermore, these medications are user-friendly, available as daily or weekly injections depending on the specific agent, which enhances adherence and improves outcomes.

With the increasing use of these drugs in the community, it has become essential to assess the awareness of medical students, as future healthcare providers, to ensure their ability to:

- Comprehend the precise pharmacological mechanisms of these agents.
- Recognize the correct dosing for diabetic and non-diabetic populations.
- Understand indications, contraindications, and potential side effects.
- Correct misconceptions regarding inappropriate or cosmetic use of these medications.

Accordingly, this study represents an important step in identifying knowledge gaps among students, promoting evidence-based clinical practice, and ensuring the safe and effective use of these agents in the future.

Statistical Analysis

Data from the paper-based questionnaires were entered into the statistical software SPSS version 25 for analysis and to obtain the results of this study. Descriptive analysis was performed for all variables included in the study, and the findings were presented as frequencies and percentages for categorical variables.

Results

Sample distribution by age and academic year:

The study sample consisted of 300 medical students. The largest proportion of students were aged 23–25 years, accounting for 42.1% (127 students), followed by those aged 20–22 years, comprising 41.4% (125 students). Students older than 25 years numbered 30 (9.9%), while those younger than 20 years were 18 (6%).

Regarding academic year, 84 students (27.8%) were in the sixth year, 57 students (18.9%) were in the fourth year, and 53 students (17.5%) each in the second and third years. Fifth-year students comprised 35 (11.6%), and first-year students 18 (6%).

Sample distribution by gender:

Male students accounted for 107 (35.4%), while female students were 193 (63.9%).

Sample distribution by body mass index (BMI):

Among the participants, 125 students (41.1%) were overweight (60% female, 40% male), 91 students (30.1%) had normal BMI (65% female, 35% male), and 84 students (27.8%) were classified as obese (70% female, 30% male).

Variable	Category	Frequency (n)	Percentage (%)
Age	<20years	18	6.0
	20-22 years	125	41.4
	23-25 years	127	42.1
	>25 years	30	9.9
Academic year	1st year	18	6.0
	2nd year	53	17.5
	3rd year	53	17.5
	4th year	57	18.9
	5th year	35	11.6
	6th year	84	27.8

Table 1: Sample distribution by age and academic year

Variable	Category	Frequency (n)	Percentage (%)
Gender	Male	107	35.4
	Female	193	63.9
BMI	Normal	91	30.1
	Overweight	125	41.1
	Obese	84	27.8

Table 2: Sample distribution by gender and BMI

BMI distribution by gender:
Normal: 65% female, 35% male
Overweight: 60% female, 40% male
Obese: 70% female, 30% male

Sample distribution by GLP-1 use for weight loss:
A total of 282 students (93.4%) reported having tried GLP-1 agonists or knowing someone who had, while 18 students (6%) had not.

Distribution by weight-loss medication used:
Eighty-six students (28.5%) used semaglutide, 112 students (37.1%) used liraglutide, and 84 students (27.8%) used tirzepatide.

Distribution by duration of medication use:
Seventy-one students (23.5%) used the medication for less than one month, 149 students (49.3%) for 1–3 months, and 62 students (20.5%) for more than three months.

Distribution by purpose of medication use:
The majority of students (274; 81.8%) aimed to lose excess weight, while 35 students (11.6%) sought to improve body shape.

Distribution by amount of weight lost:
Fifty-one students (16.9%) lost less than 2 kg, 88 students (29.1%) lost 2–5 kg, 94 students (31.1%) lost 6–10 kg, and 49 students (16.2%) lost more than 10 kg.

Distribution by weight regain after discontinuation:
Sixty-five students (21.5%) regained a significant amount of weight, 182 students (60.3%) regained a slight amount, and 35 students (11.6%) had not discontinued the medication.

Distribution by occurrence of side effects:
All participants (100%) reported experiencing side effects.

Distribution by specific side effects during treatment:
The most frequently reported side effects were nausea and vomiting (206 students; 73%), followed by loss of appetite (154 students; 54.6%), fatigue and dizziness (140 students; 49.6%), headache (133 students; 47.2%), diarrhea or constipation (137 students; 48.6%), abdominal pain (103 students; 36.5%), and psychological symptoms such as stress, anxiety, or mood changes (132 students; 46.8%). Urinary tract infections were reported by 36 students (12.8%), while hair loss and suicidal thoughts were not reported by any participants (0%).

Sample distribution by experience of using the medication under medical supervision:
A total of 224 students (74.2%) reported using the medication under medical supervision, while 58 students (19.2%) did not.

Sample distribution by students' perception of the safety and efficacy of the medication:
Two hundred and twelve students (70.2%) considered the medication safe and effective, whereas 88 students (29.1%) did not.

Sample distribution by students' willingness to recommend the medication to friends:
The same 212 students (70.2%) responded "yes," they would recommend it, while 88 students (29.1%) responded "no."

Variable	Category	Frequency (n)	Percentage (%)
GLP-1 use	Tried	282	93.4
	Never tried	18	6
Medication type	Semaglutide	86	28.5
	Liraglutide	112	37.1
	Tirzepatide	84	27.8
Duration of use	<1 month	71	23.5
	1-3 months	149	49.3
	>3 months	62	20.5
Purpose of use	Weight loss	274	81.8
	Body shape improve-ment	35	11.6

Table 2: Sample distribution by GLP-1 use, medication type, and duration

Variable	Category	Frequency (n)	Percentage (%)
Weight lost	<2 kg	51	16.9
	2-5 kg	88	29.1
	6-10 kg	94	31.1
	>10 kg	49	16.2
Weight re-gain after discontinuation	Significant	65	21.5
	Slight	182	60.3
	Still using drug	35	11.6
Occurrence of side effects	Yes	300	100
	No	0	0
Type of side effects	Nausea & vomiting	206	73
	Loss of appetite	154	54.6
	Fatigue & dizziness	140	49.6
	Headache	133	47.2
	Diarrhea / Constipation	137	48.6
	Abdominal pain	103	36.5
	Psychological (stress, anxiety, mood changes)	132	46.8
	Urinary tract infection	36	12.8
	Hair loss	0	0
	Suicidal thoughts	0	0

Table 4: Sample distribution by weight change and side effects

Variable	Category	Frequency (n)	Percentage (%)
Medical supervision	Yes	224	74.2
	No	58	19.2
Safety & efficacy perception	Safe / Effective	212	70.2
	Not Safe / Effective	88	29.1
Recommendation to friends	Yes	212	70.2
	No	88	29.1

Table 5: Sample distribution by medical supervision, perception, and recommendation

Sample distribution by benefit from dietary interventions alongside medication use:
One hundred and seven students (35.4%) reported significant benefit, 139 students (46%) reported limited benefit, 19 students (6.3%) reported no benefit, and 35 students (11.6%) had not followed any diet previously.

Sample distribution by benefit from physical activity alongside medication use:
One hundred and four students (34.4%) reported significant benefit, 141 students (46.7%) reported limited benefit, and 19 students (6.3%) reported no benefit.

Sample distribution by the most effective method for weight loss:
When asked about the most effective weight-loss approach, 129 students (42.7%) considered dietary intervention most effective, 54 students (17.9%) considered physical activity most effective, and 117 students (38.7%) considered GLP-1 receptor agonists the most effective.

Sample distribution by awareness of the necessity of prescribing medication under medical supervision:
A total of 262 students (86.8%) agreed that prescription under supervision is necessary, while 38 students (12.6%) disagreed.

Sample distribution by students' sources of information about GLP-1 receptor agonists and their usage patterns:
Survey results indicated that social media was the most common source of information for students (45.7%), followed by advice from friends (24.7%). Eighteen-point six percent (18.6%) of students cited consulting physicians as their source, and the least common source was dietitians (11.0%).

Sample distribution by the perceived necessity of teaching GLP-1 receptor agonists in medical curricula:
Two hundred eighty-one students (93%) considered it necessary to include these medications in the curriculum, while 19 students (6.3%) did not.

Variable	Category	Frequency (n)	Percentage (%)
Benefit from diet	Significant	107	35.4
	Limited	139	46
	None	19	6.3
	Did not follow diet	35	11.6
Benefit from exercise	Significant	104	34.4
	Limited	141	46.7
	None	19	6.3
Most effective weight-loss method	Diet	129	38.7
	Exercise	54	17.9
	GLP-1 medication	117	42.7

Table 6: Sample distribution by benefit from diet and exercise and the most effective weight-loss method

Variable	Category	Frequency (n)	Percentage (%)
Awareness of medical supervision necessity	Yes	262	86.8
	No	38	12.6
Source of information	Social media	137	45.7
	Friends	74	24.7
	Physicians	56	18.6
	Dietitian	33	11
Necessity of teaching in medical curricula	Yes	281	93
	No	19	6.3

Table 7: Awareness, sources of information, and perceived necessity of GLP-1 receptor agonists

Discussion

The results of our study indicated that the majority of the sample consisted of young medical students aged between 20 and 25 years, a group characterized by high health awareness and knowledge of medical updates, as well as increased concern for appearance and a healthy lifestyle. A clear predominance of female students was observed, which may partly explain the higher rate of weight-loss medication use, as previous studies suggest that females are more likely to seek medical and cosmetic interventions to control body weight and shape. The distribution across different academic years, with a predominance of students in clinical years, enhances the reliability of the results due to increased medical experience and clinical exposure during these stages.

Our findings revealed that a significant proportion of participants were overweight or obese, consistent with the global increase in obesity rates among young adults, including within medical circles. This may explain the high interest in GLP-1 receptor agonists, with over 90% of students reporting either personal experience or knowledge of someone using them. This widespread use indicates that these medications are no longer limited to traditional medical indications but have become part of the weight-loss culture among medical students, driven by reports of their rapid efficacy and noticeable effects on appetite and weight.

Regarding the type of medication, liraglutide and semaglutide were the most commonly used, followed by tirzepatide, aligning with their availability and the pre-existing knowledge of their clinically proven efficacy. The duration of use was generally short to moderate (less than three months), which may reflect limited tolerance due to side effects or discontinuation after achieving initial weight-loss goals, subsequently impacting weight regain results.
The study demonstrated the clear effectiveness of these medications in weight reduction, with most users losing between 2–10 kg, while fewer participants lost more than 10 kg. These findings are consistent with international literature on GLP-1 receptor agonist efficacy in non-diabetic individuals. However, a majority experienced partial or complete weight regain after discontinuation, underscoring that the positive effects of these medications heavily rely on continuity, and use without long-term lifestyle changes may lead to unsustainable outcomes.

In terms of safety, all users reported side effects of varying degrees, predominantly gastrointestinal symptoms such as nausea, vomiting, and loss of appetite, followed by fatigue, dizziness, headache, and bowel disturbances—effects known to result from these medications' mechanisms on gastric emptying and appetite regulation. A notable proportion also reported psychological symptoms, including anxiety and mood fluctuations, highlighting the need for awareness of potential psychological impacts, especially in young adults. Despite the prevalence of side effects, serious adverse events such as hair loss or suicidal thoughts were not observed, which may explain the overall student perception of these medications as safe and effective.

Most participants used these medications under medical supervision, reflecting a positive level of medical awareness. Nevertheless, the presence of unsupervised use raises concerns regarding potential misuse, particularly given the ease of access in some settings. In this context, the majority of students recognized the necessity of prescription and

inclusion of these medications in medical curricula, indicating increased awareness of their clinical importance and implications.

Interestingly, students' opinions regarding the most effective weight-loss method favoured dietary interventions over medications and exercise, despite broad experience with GLP-1 receptor agonists, indicating awareness that pharmacological treatment is an adjunct rather than a replacement for lifestyle modification. While adherence to diet and exercise yielded variable benefits, most students acknowledged limited effect, possibly explaining the recourse to pharmacological interventions for faster and more noticeable outcomes.

Overall, the study reflects a high level of awareness and practical experience regarding GLP-1 receptor agonists among medical students, with a good understanding of efficacy, side effects, and limitations. The wide use among non-diabetic individuals highlights the urgent need for clear usage guidelines, enhanced medical education on rational use, and emphasis on sustainable lifestyle modification as the foundation for weight management.

The demographic characteristics of our sample align with previous international studies examining GLP-1 receptor agonist use in young adults, showing that young females constitute the largest proportion of users for weight-loss purposes. High BMI emerged as a key motivator for GLP-1 use among non-diabetics, particularly when conventional interventions such as diet and exercise alone fail. The widespread use of these medications among medical students mirrors recent reports of off-label weight-loss use beyond traditional diabetic indications.

Regarding efficacy, most users achieved weight loss of 2–10 kg, while fewer lost more than 10 kg. These findings are consistent with the STEP-1 trial, which reported average weight reductions of 10–15% in non-diabetic patients treated with semaglutide, and the SCALE study for liraglutide, demonstrating similar efficacy with significant metabolic improvements. Tirzepatide, as shown in the SURMOUNT studies, achieved relatively higher weight loss, explaining the positive outcomes reported by some participants.

Nonetheless, our study clearly showed weight regain after discontinuation for most users, consistent with long-term follow-up studies indicating gradual weight regain if sustained lifestyle changes are not maintained. Wilding et al. emphasized that continuous treatment or combination with long-term behavioural modifications is essential to maintain achieved results.

Regarding safety, all participants reported side effects, predominantly gastrointestinal, consistent with global data indicating these are the most common adverse effects of GLP-1 receptor agonists. Reported fatigue, dizziness, and headache fell within ranges reported in major clinical trials, while psychological side effects were mild to moderate, aligning with the literature without a clear causal linkage. No serious adverse events such as suicidal ideation were observed, consistent with studies showing no statistically significant increase in these risks.

Most usage occurred under medical supervision, in line with global medical society recommendations emphasizing prescription and monitoring. However, unsupervised use highlights the risk of misuse, particularly in cosmetic applications among young adults. The high awareness among medical students regarding prescription necessity and curriculum inclusion aligns with global initiatives to enhance medical education on modern obesity treatments.
Finally, participants indicated dietary intervention remains the most effective weight-loss method from their perspective, despite the proven efficacy of GLP -1 medications, consistent with global guidelines recommending pharmacotherapy as an adjunct to lifestyle modification. These findings support a multi -faceted approach to obesity management, combining pharmacological, behavioral, and physical activity interventions to achieve sustainable outcomes.

Conclusions

This study aimed to assess the awareness of medical students regarding the efficacy and safety of GLP-1 receptor agonists for weight loss in non-diabetic individuals. The results showed that most participants were young, predominantly female, and a significant proportion were overweight or obese. There was widespread exposure to or direct knowledge of GLP-1 medications, with common use of liraglutide, semaglutide, and tirzepatide. The medications were effective in weight reduction, though most users experienced weight regain after discontinuation, indicating limited sustainability without lifestyle modification. Side effects were common, but generally mild to moderate, predominantly gastrointestinal, and students generally considered the medications safe and effective, showing willingness to recommend them. The study highlights high awareness of medical supervision necessity, prescription requirements, and curriculum inclusion, emphasizing GLP-1 agonists as supportive in obesity management, with education on rational use and lifestyle modification being essential for sustainable results.

Declarations

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Availability of data and materials

All data related to this paper's conclusion are available and stored by the authors. All data are available from the corresponding author at reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) at the Syrian Private University (SPU). All Participants confirmed their written consent by signing the consent form. Participation in the study was voluntary, and participants were assured that anyone who was not inclined to participate or decided to withdraw after giving consent would not be victimized. All information collected from this study was kept strictly confidential.

Consent for Publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TH, and NT all participated in the preparation for this study. RO was responsible for data analysis, SA participated in the literature search and write-up, and NR participated in the study design and reviewed the final draft.

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Review Article
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Antibiotic Utilization Patterns and Adverse Drug Events Risk in Special Populations : A Comprehensive Review

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Abstract:
Antimicrobials are among the most frequently prescribed drug classes globally, but their misuse contributes significantly to antimicrobial resistance (AMR) and a high burden of adverse drug events (ADEs). Special populations including pediatric, geriatric and critically ill patients face unique risks due to altered pharmacokinetics and higher rates of polypharmacy. Research indicates that approximately 20% of hospitalized adults receiving systemic antibiotics experience at least one ADE, with geriatric patients accounting for nearly 45.6% of these cases. In pediatric populations, antibiotics are responsible for nearly half of all drug-related emergency department visits.
Drug utilization evaluations show a high prevalence of "Watch" group antibiotic use (Eg; Cephalosporins and Fluoroquinolones), which are frequently associated with serious side effects like skin rashes, gastrointestinal distress and nephrotoxicity. This review synthesizes current data on antibiotic consumption patterns using the WHO AWaRe framework and examines the severity and preventability of associated ADEs. The findings underscore the critical need for robust antimicrobial stewardship (AMS) and active Pharmacovigilance to mitigate risks in vulnerable cohorts and ensure patient safety.

Key Words:
Antimicrobial Stewardship; Adverse Drug Reactions (ADRs); Geriatric and Pediatric Pharmacotherapy; WHO AWaRe Classification; Drug Utilization Evaluation (DUE); Antimicrobial Resistance (AMR) and Pharmacovigilance.

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Background

Antibiotic utilization among special populations requires careful dose adjustment and monitoring, as these groups are at significantly higher risk for adverse drug events (ADEs) due to altered drug metabolism and underlying co-morbidities. Antibiotic stewardship is essential for managing special populations, as physiological changes in geriatric, pediatric and critically ill patients significantly alter drug pharmacokinetics and increase the risk of adverse drug events (ADEs). Data suggests high utilization of broad-spectrum agents in these groups, with geriatric patients accounting for over 45% of antibiotic-related ADEs and antibiotics driving nearly 50% of pediatric emergency room visits. Targeted, organ-specific pharmacovigilance and structured antimicrobial stewardship programs (ASPs) are necessary to mitigate these risks.

Antibiotic utilization in special populations specifically the elderly, pediatrics and patients with renal/hepatic impairment is characterized by high consumption rates often coupled with irrational prescribing, leading to significant adverse drug events (ADEs). In these groups, Age-related pharmacokinetic (PK) and pharmacodynamic (PD) changes, polypharmacy and high comorbidity burden heighten the risk of severe, sometimes fatal, adverse events.

Search Strategy (Methods)

"A systematic search was performed across PubMed/MEDLINE, Scopus and Web of Science databases for articles published between 2014 and 2024. Keywords used included 'Antibiotic Utilization,' 'Adverse Drug Events,' 'Special Populations,' 'Pediatric Pharmacotherapy,' 'Geriatric Antibiotic Use' and 'WHO AWaRe.' Inclusion criteria focused on randomized controlled trials, systematic reviews and large-scale observational studies reporting incidence rates of ADEs and utilization metrics (Eg; DDD per 1000 inhabitants)."

Pharmacological and Clinical Rationale

The use of antibiotics in special populations specifically the pediatric, geriatric and critically ill presents a complex challenge for clinicians. Unlike the general adult population, these groups exhibit significant variations in pharmacokinetics (PK) and pharmacodynamics (PD).

Pediatric Population: Antibiotics constitute over one-third of prescriptions, with high usage of broad-spectrum agents. Studies show up to 85% of antibiotics are prescribed inappropriately to children in some settings, often for respiratory infections. Key risks include disruption of the microbiome, increased risk of allergic diseases (atopic dermatitis, asthma) and obesity.

Antibiotics cause nearly half of all drug-related emergency department visits for children. In infants (<1 year), the rate of ADEs per 10,000 prescriptions is the highest among all age groups. Specific risks include tooth discoloration (Tetracyclines) and potential cartilage damage (Fluoroquinolones).

Pediatric Considerations: Neonates and children are not "small adults." Their drug metabolism is governed by maturational changes in organ function, such as varying glomerular filtration rates (GFR) and hepatic enzyme activity. For instance, total body water is higher in infants, which increases the volume of distribution (V_d) for hydrophilic drugs like beta-lactams and aminoglycosides.

Geriatric Population (≥65 years): This group experiences the highest prevalence of antibiotic-related ADEs, accounting for approximately 45.6% of reported cases in some studies. This group receives a disproportionate number of antibiotics, often for prophylaxis or inappropriately for viral infections. Key risks include *Clostridioides difficile* infection (CDI), drug-induced delirium, renal toxicity (especially with Glycopeptides and Aminoglycosides) and severe cutaneous adverse reactions (cADRs), particularly with Sulfonamides and Cephalosporins, due to polypharmacy and impaired drug elimination.

Geriatric Considerations: Aging is associated with "inflammaging," increased frailty and progressive decline in renal and hepatic clearance. Elderly patients often present with multiple comorbidities, leading to polypharmacy and a heightened risk of drug-drug interactions (DDIs).

Critically Ill & Hospitalized Patients: Approximately 20% of hospitalized adults receiving antibiotics experience at least one ADE. Each additional day of therapy increases the odds of an ADE by roughly 4-7%.

In the intensive care unit (ICU), patients often experience capillary leak syndrome or receive aggressive fluid resuscitation, which drastically increases the V_d of hydrophilic antibiotics, often leading to sub-therapeutic dosing and the emergence of antimicrobial resistance (AMR).

Patients with Co-morbidities: Individuals with chronic kidney disease (CKD) or liver disease have a significantly higher risk for antibiotic-induced organ damage. For example, those with advanced cancer have a 35% chance of developing an ADE when exposed to antibiotics.

Chronic Kidney Disease (CKD): Inadequate dosing (both under- and overdosing) is common due to reliance on creatinine-based estimations, which overestimates renal function. This leads to increased toxicity (overdose) or treatment failure (underdose).

Liver Disease: Impaired metabolism of lipophilic drugs and hypoalbuminemia (increasing free fractions of drugs) makes patients with liver dysfunction, such as cirrhosis, highly susceptible to ADEs from commonly used antibiotics.

Risk Factors:

Polypharmacy: The risk of an ADR increases exponentially with the number of drugs; for example, from 13% with two medicines to 82% with seven or more.

Multiple Antibiotics: Taking more than one antibiotic concurrently doubles the risk of a serious ADR.

Inappropriate Prescribing: Roughly 50% of antibiotic prescriptions in pediatrics are estimated to be unnecessary or inappropriate, leading to avoidable toxicities.

Major Adverse Drug Event (ADE) Patterns

Cutaneous and Gastrointestinal: The skin and gastrointestinal systems are the most frequently affected, with rashes, pruritus and diarrhea being the most common ADRs.

Severe ADRs: These include acute renal failure (often with Aminoglycosides/Gentamicin), hepatotoxicity and severe skin reactions (Stevens-Johnson syndrome).

Neurotoxicity: β-lactams (like Cefepime), Carbapenems and Metronidazole are associated with neurotoxic effects, including encephalopathy and seizures, particularly in the elderly.

Antibiotic Class	Drug Examples	Common Adverse Events	Serious/Life-Threatening ADRs
Penicillins	Amoxicillin, Ampicillin, Piperacillin-Tazobactam	Diarrhea, nausea, mild skin rash.	Anaphylaxis, Drug-Induced Liver Injury (DILI), Interstitial Nephritis.
Cephalosporins	Ceftriaxone, Cefuroxime, Cefepime	Injection site pain, oral candidiasis.	*C. difficile* Associated Diarrhea (CDAD), Non-convulsive status epilepticus (Neurotoxicity).
Fluoroquinolones	Ciprofloxacin, Levofloxacin, Moxifloxacin	Dyspepsia, dizziness, photosensitivity.	Tendon rupture, Aortic aneurysm, QTc prolongation, Hypoglycemic coma.
Aminoglycosides	Gentamicin, Amikacin, Tobramycin	Headache, localized redness.	Irreversible Ototoxicity (Vestibular/Cochlear), Nephrotoxicity (Acute Tubular Necrosis).
Glycopeptides	Vancomycin, Teicoplanin	"Red Man Syndrome" (flushing), Chills.	Nephrotoxicity (dose-related), Ototoxicity, Neutropenia (rare).
Macrolides	Azithromycin, Clarithromycin, Erythromycin	Abdominal pain, GI hypermotility.	Torsades de Pointes (Sudden Cardiac Death), Cholestatic jaundice.
Tetracyclines	Doxycycline, Minocycline, Tigecycline	Heartburn, Nausea, Photosensitivity.	Pseudotumor cerebri, Hepatotoxicity, Permanent tooth staining in pediatrics.
Sulfonamides	Trimethoprim-Sulfamethoxazole (TMP-SMX)	Vomiting, Pruritus (itching).	Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Aplastic Anemia.
Oxazolidinones	Linezolid, Tedizolid	Diarrhea, Discoloration of tongue.	Myelosuppression (Thrombocytopenia), Serotonin Syndrome, Optic Neuropathy.
Nitroimidazoles	Metronidazole, Tinidazole	Metallic taste, Darkened urine.	Peripheral Neuropathy, Encephalopathy, Disulfiram-like reaction with alcohol.

Table 1: Detailed Profile of Antibiotic Classes, Agents and Adverse Drug Events (ADEs)

Special Population	Physiological Change	PK Impact	Antibiotic Examples
Pediatric (Neonates)	High total body water	Increased V_d (Hydrophilic)	Gentamicin, Amikacin
Geriatric	Decreased GFR/Renal blood flow	Reduced Clearance (C_l)	Vancomycin, Levofloxacin
Critically Ill	Capillary leak/Fluid over-load	Increased V_d	Piperacillin-Tazobactam
Elderly	Increased body fat %	Increased V_d (Lipophilic)	Macrolides, Fluoroquin-olones

Table 2: Pharmacokinetic Alterations and Clinical Implications

Population	Leading ADEs	Most Implicated Class	Incidence/Risk
Geriatric	Nephrotoxicity, GI distress	Cephalosporins, Fluoroquinolones	~45.6% of all ADE cases
Pediatric	Skin rashes, Diarrhea	Penicillins, Cephalosporins	19.9% overall harm rate
Hospitalized Adults	C. difficile, SJS/TEN	Sulfonamides, Clindamycin	20% experience ≥1 ADE

Table 3: Common Adverse Drug Events (ADEs) by Population

Utilization Patterns and the WHO AWaRe Framework

Current prescribing trends show an alarming reliance on the "Watch" group of antibiotics (Eg; Fluoroquinolones and 3rd generation Cephalosporins), which are broad-spectrum and carry higher risks for resistance and ADEs. In many tertiary care settings, the Access-to-Watch ratio is significantly below the WHO target of 0.60, indicating widespread use of high-risk agents where narrower-spectrum alternatives might suffice.

Discussion

Mitigating Risks through Precision Medicine - The high incidence of ADEs in special populations underscores the inadequacy of "one-size-fits-all" dosing. Precision medicine, through the integration of Therapeutic Drug Monitoring (TDM) and Pharmacogenomics (PGx), offers a pathway to optimize efficacy while minimizing toxicity.

1. Therapeutic Drug Monitoring (TDM) - TDM is the clinical practice of measuring drug concentrations at designated intervals to maintain a constant concentration in a patient's bloodstream. This is non-negotiable for antibiotics with a narrow therapeutic index.

2. Pharmacogenomics (PGx): Preventing Genetic Predispositions

Pharmacogenomics identifies genetic variations that influence drug response. In special populations, especially pediatrics, genetic screening can prevent irreversible, life-altering adverse events.

Aminoglycoside-Induced Hearing Loss: A specific mutation in the mitochondrial gene MT−RNR1 (specifically the m.1555A > G variant) predisposes individuals to profound, permanent deafness even after a single dose of gentamicin.

Hypersensitivity Reactions: Testing for the HLA−B*57:01 allele is now standard for Abacavir, but similar research is expanding into Sulfonamides and Penicillins to predict Stevens-Johnson Syndrome (SJS).

Antibiotic	Primary Toxicity Risk	TDM Goal	High-Risk Population
Vancomycin	Nephrotoxicity (AkI)	AUC/MIC ratio (400 – 600)	Critically ill, CKD patients
Aminoglycosides	Ototoxicity & Nephrotoxicity	Peak & Trough levels	Neonates, Cystic Fibrosis
Linezolid	Thrombocytopenia	Trough levels (<2 mg/L)	Geriatric (long-term use)
Voriconazole	Neurotoxicity/Hepatotoxicity	Trough levels (1 – 5 mg/L)	Hepatic impairment

Table 4: Antibiotics Requiring Routine TDM in Special Populations

3. Advanced Stewardship and Technology - Modern Antimicrobial Stewardship (AMS) programs are now utilizing technology to bridge the gap in clinical expertise.

Antibiotic Stewardship: Promoting shorter treatment courses as short as clinically possible is the most effective way to reduce the cumulative risk of ADEs.

Point-of-Care Testing (POCT): Utilizing rapid biomarkers like Procalcitonin (PCT) and C-reactive protein (CRP) to differentiate between bacterial and viral infections, thereby preventing unnecessary antibiotic exposure in pediatric and geriatric patients.

AI-Driven Dosing: Software (Eg; InsightRX, DoseMeRx) uses Bayesian forecasting to predict the best dose for a specific patient based on their age, weight and renal function in real-time.

Summary of Findings

ADR Incidence: Studies report ADR incidence rates for antibiotics to be roughly 14–16% among hospitalized patients.

Highest Risk Antibiotics: Cephalosporins, Fluoroquinolones and β-lactam combinations are frequently cited as causing the highest rates of ADRs in these populations.

Conclusion: Regular monitoring for early detection of ADEs and strict adherence to guidelines can prevent a significant percentage of antibiotic-related hospital admissions.

Strategy	Mechanism	Level of Evidence	Primary Benefit
TDM	Real-time dose titration	High (Standard of Care)	Prevents dose-dependent organ toxicity.
Pharmacogenomics	Genetic screening	Moderate (Emerging)	Prevents idiosyncratic reactions (Eg; deafness).
Procalcitonin Guided	Biomarker monitoring	Moderate	Reduces total duration of antibiotic exposure.
AWaRe Framework	Regulatory oversight	Administrative	Decreases use of high-risk "Watch" antibiotics.

Table 5: Summary of Preventative Strategies

Antibiotic Class	Primary Mechanism of Toxicity	Notable Adverse Drug Events (ADEs)	High-Risk "Special" Population
Penicillins	Immune-mediated hypersensitivity	Anaphylaxis, interstitial nephritis, and drug-induced liver injury (DILI) (esp. Amoxicillin-Clavulanate).	**Pediatrics:** Highest cause of allergic cutaneous eruptions.
Cephalosporins	Disruption of microbiome & Cross-reactivity	*C. difficile* infection (CDI), biliary sludging (Ceftriaxone) and seizures at high doses.	**Geriatrics:** Increased risk of CDI and neurotoxicity in renal impairment.
Fluoroquinolones	Connective tissue & CNS interference	Tendon rupture, aortic aneurysm, QTc prolongation and dysglycemia.	**Geriatrics:** High risk for delirium and tendon injury. **Pediatrics:** Arthropath y concerns.
Aminoglycosides	Mitochondrial & Renal tubule damage	Irreversible ototoxicity (hearing loss/vertigo) and acute tubular necrosis (ATN).	**Neonates:** Genetic susceptibility (MT-RNR1). **Critically Ill:** AKI risk.
Glycopeptides (Eg; Vancomycin)	Direct cellular toxicity & Histamine release	Nephrotoxicity and "Red Man Syndrome" (infusion-related reaction).	**Critically Ill:** High incidence of AKI when combined with Piperacillin-Tazobactam.
Tetracyclines	Calcium chelation & GI irritation	Tooth enamel hypoplasia, photosensitivity and esophageal ulceration.	**Pediatrics (<8 yrs):** Risk of permanent tooth discoloration.
Sulfonamides	Folate synthesis inhibition	Stevens-Johnson Syndrome (SJS/TEN) and crystalluria.	**HIV/ Immunocompromise d:** Significantly higher rates of severe cutaneous reactions.
Macrolides	Cardiac ion channel blockade	GI hypermotility, QTc prolongation and cholestatic hepatitis.	**Geriatrics:** Fatal arrhythmias when co-administered with CYP3A4 inhibitors.
Oxazolidinones (Eg; Linezolid)	Mitochondrial protein inhibition	Thrombocytopenia, lactic acidosis and serotonin syndrome.	**Geriatrics:** Hematologic toxicity increases after 14 days of therapy.

Table 6: Comprehensive Adverse Event Profiles by Antibiotic Class

Conclusion and Future Directions

The utilization of antibiotics in special populations remains a double-edged sword. While these agents are lifesaving, the risk of Adverse Drug Events (ADEs) is disproportionately high in pediatric, geriatric and critically ill cohorts due to distinct physiological vulnerabilities. Current patterns reveal a concerning over-reliance on "Watch" category antibiotics, which exacerbates both individual toxicity and global resistance.

Moving forward, the integration of Precision Antimicrobial Stewardship is essential. This includes the universal adoption of Therapeutic Drug Monitoring (TDM) for drugs with narrow therapeutic windows and the implementation of Point-of-Care Pharmacogenomic testing to prevent irreversible toxicities like aminoglycoside-induced ototoxicity. Future research should prioritize the development of AI-driven dosing algorithms tailored specifically to patients with multi-organ dysfunction to ensure that the goal of "First, Do No Harm" is maintained in antimicrobial therapy.

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Reviving Performance : An Intensive Mentoring Approach for Underperforming MBBS Students Evaluated via DREEM Questionnaire

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Abstract:
Background: First-year medical (1st MBBS) supplementary students face significant academic challenges requiring targeted interventions. The Dundee Ready Educational Environment Measure (DREEM) questionnaire provides a validated framework for assessing educational environments and identifying areas for improvement.
Objective: This longitudinal study evaluates the effectiveness of an intensive mentoring programme on academic performance and perceived educational environment quality among 1st MBBS supplementary students over multiple academic years.
Methods: A prospective longitudinal study was employed with a cohort of supplementary medical students. A DREEM questionnaire was administered at baseline, mid-intervention, and post-intervention phases. Academic performance metrics, including examination scores and course completion rates, were tracked throughout the study period. Quantitative data were analysed using descriptive statistics and inferential tests (paired t-tests, ANOVA).
Results: The intensive mentoring programme demonstrated measurable improvements in students' perceived educational environment scores and corresponding enhancements in academic performance metrics. Significant correlations were identified between improved DREEM scores and enhanced examination outcomes.
Conclusion: The intensive mentoring programme, guided by DREEM assessment, represents an effective evidence-based intervention for improving both the educational environment perception and academic outcomes of 1st MBBS supplementary students. This approach provides a replicable model for medical educational institutions seeking to support academically challenged students.

Key Words:
DREEM Questionnaire; Mentoring Programme; Supplementary Medical Students; Educational Environment; Academic Performance; MBBS; Medical Education Assessment

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Introduction

The transition in medical education represents a significant challenge for undergraduate students, with first-year medical (1st MBBS) students encountering novel pedagogical approaches, increased curricular complexity, and heightened academic expectations. [1]

Among this population, supplementary students, those who have not meet standard progression criteria and require additional instruction, face compounded difficulties including psychological stress, reduced academic confidence, and environmental dissatisfaction.[1] These challenges necessitate targeted, evidence-based interventions specifically designed to address both the academic deficiencies and the emotional barriers that supplementary students encounter. Traditional approaches to supporting struggling medical students often rely on remedial instruction focused solely on content delivery. However, contemporary educational research emphasizes the importance of the broader educational environment in facilitating learning outcomes. [1,3] The quality of teaching, learner autonomy, student-teacher relationships, and institutional support structures collectively constitute the educational climate, which significantly influences student motivation, engagement, and ultimately, academic achievement.[1] Recognition of these multifaceted factors has prompted medical education researchers and administrators to develop comprehensive support systems that address both academic content and environmental optimization. The Dundee Ready Educational Environment Measure (DREEM) questionnaire, developed in 1997 by Susan Roff and colleagues at the University of Dundee in Scotland, represents a validated, internationally recognized instrument for assessing the educational environment in medical and health professional

training settings.[3] The DREEM questionnaire has been extensively utilized across diverse international contexts and has demonstrated robust psychometric properties including adequate internal consistency, construct validity, and cross-cultural applicability.[3] A study conducted with use of DREEM score at Victoria University, Melbourne, Australia shows that this information will assist them to make decisions about the action required to improve the osteopathy course at VU. It is anticipated that the DREEM will be used as part of an overarching teaching program evaluation strategy to inform reviews of the program, provide information for the program accrediting body, and measure the changes made to the program.[7] Its development involved rigorous methodology including grounded theory approaches and Delphi procedures applied to nearly 100 educators from health specialties worldwide, with validation testing conducted on over 1,000 students in different countries.[3] The instrument's multidimensional structure captures various aspects of the educational environment including student perceptions of learning, teaching quality, academic self-perception, atmosphere, and practical facilities. The utilization of DREEM as a diagnostic and monitoring tool has gained particular prominence in recent years, with institutions employing it not merely for assessment purposes but as a framework guiding programmatic interventions. [1, 2,3] A DREEM questionnaire has been adapted for specific educational contexts, including postgraduate dental education and various clinical ward environments.[2,3] Such modifications allow for context-specific assessment while maintaining the instrument's fundamental psychometric integrity.

Objective and Rationale

This study proposes a longitudinal evaluation of an intensive mentoring programme specifically designed for 1st MBBS supplementary students, utilizing a DREEM questionnaire as both a diagnostic tool and a means of monitoring programme effectiveness. The fundamental hypothesis underlying this intervention is that systematic mentoring addressing both academic content and environmental factors as identified through DREEM assessment will result in measurable improvements in students' perceived educational environment and corresponding enhancements in academic performance outcomes. The rationale for this approach rests upon three foundational premises:

(1) the educational environment significantly influences academic performance and student wellbeing;

(2) supplementary students constitute a distinct population with identifiable needs diverging from the general student body;

And

(3) targeted interventions informed by validated assessment instruments are more likely to achieve meaningful outcomes than generic support mechanisms.

Materials and Methods

Study Design and Setting

This investigation employed a prospective longitudinal design conducted over multiple consecutive academic years at a tertiary medical education institution. The longitudinal framework allows for tracking of sustained effects and assessment of programme sustainability. The study was conducted within the context of 1st MBBS supplementary student cohorts, representing students who had not achieved standard progression criteria.

Population and Sampling

The study population comprised all 1st MBBS students designated as supplementary during the study period. Supplementary status was determined according to institutional criteria, which typically include failure to achieve minimum passing grades in Final university examinations or assessment components. The entire accessible population of supplementary students was recruited to participate, with informed consent obtained prior to enrolment.

Intervention

Intensive Mentoring Programme

The intensive mentoring programme was structured as a comprehensive, multi-component intervention incorporating the following elements:

Structured Mentoring Framework:

Each supplementary student was assigned an individual mentor selected from experienced faculty members with teaching expertise. Mentoring relationships were established at the programme's commencement and maintained throughout the academic year.

Frequency and Duration:

Mentoring sessions occurred bi-weekly, with each session allocated 60 minutes. This frequency was determined based on preliminary assessments of supplementary student needs and availability constraints. Sessions conducted in small groups of 4 students addressing common content gaps.

Curriculum-Aligned Content:

Mentoring content was explicitly aligned with 1st MBBS curricular requirements and assessment blueprints. Mentors were provided with detailed guidance regarding learning objectives and potential areas of difficulty for supplementary students.

DREEM-Informed Environmental Modifications: Initial DREEM questionnaire administration identified specific areas of environmental concern (e.g., perceived inadequacy of teaching, concerns regarding learner autonomy, insufficient practical facilities). Mentoring programmes incorporated targeted responses to these identified deficiencies, including facilitating access to additional learning resources, advocating for increased practical opportunities, and strengthening student-teacher communication channels.

Integrated Support Services:
The programme incorporated connections to institutional support services including academic writing assistance, study skills workshops, and psychological counselling services, recognizing that supplementary students frequently experience anxiety and reduced academic self-efficacy.

Data Collection Instruments DREEM Questionnaire:
A DREEM questionnaire adapted for the specific context of 1st MBBS education was administered to all participants. The instrument retained the core DREEM structure while incorporating context-specific items relevant to medical curricula and supplementary student populations. The questionnaire was administered using a five-point Likert scale (strongly agree, agree, uncertain, disagree, strongly disagree), permitting quantitative assessment of various dimensions of educational environment perception.[3]

Academic Performance Metrics: Objective academic performance data were collected including: (1) scores on mid-term and end-of-year examinations; (2) continuous assessment scores; (3) practical and clinical skill assessments; and (4) course completion status. These metrics were obtained from institutional records.

Supplementary Data Collection: Semi-structured interviews with purposefully selected student participants (n=10-15 per cohort) were conducted to obtain qualitative perspectives on mentoring programme effectiveness, perceived environmental changes, and barriers to academic success. Faculty mentors also completed brief reflection forms documenting programme implementation challenges and perceived student progress.

Study Phases and Timeline The longitudinal study comprised three primary assessment phases:
1. Baseline Assessment (Week 1): DREEM questionnaire administered; baseline academic performance metrics recorded; demographic data collected.
2. Mid-Intervention Assessment (Week 20): DREEM questionnaire re-administered; interim academic performance data reviewed; qualitative interviews conducted with selected participants.

3. Post-Intervention Assessment (Week 40-42): Final DREEM questionnaire administration; end-of-year academic performance metrics recorded; qualitative interviews completed; mentor reflection forms submitted. This timeline was repeated across multiple consecutive academic years (minimum three years), permitting longitudinal trend analysis.

Data Analysis
Quantitative Analysis: Descriptive statistics were computed for all continuous variables, including means, standard deviations, and ranges. Comparisons of DREEM scores across the three assessment phases were conducted using repeated-measures analysis of variance (ANOVA), with post-hoc pairwise comparisons using paired t-tests where appropriate. Pearson correlation coefficients were calculated to assess relationships between changes in DREEM domain scores and changes in academic performance metrics. Statistical significance was established at $p < 0.05$.

Qualitative Analysis: Interview transcripts were subject to thematic analysis following systematic coding procedures. Initial open coding identified key themes; axial coding related themes to broader categories; selective coding identified overarching narrative patterns. Qualitative findings were integrated with quantitative results to provide comprehensive interpretation.

Ethical Considerations: The study protocol received approval from the institutional research ethics committee prior to commencement. Informed consent was obtained from all participants. Confidentiality and anonymity were maintained through assignment of unique identifiers and secure data storage. Participation was entirely voluntary with explicit communication that non-participation would not affect students' academic standing or access to institutional services.

Results
Participant Characteristics
Across the three-year study period, 87 supplementary 1st MBBS students participated (Year 1: 28 students; Year 2: 30 students; Year 3: 29 students). The cohort demonstrated demographic characteristics typical of medical student populations, with mean age 19.8 years (SD = 1.2), and gender distribution of 48% female and 52% male.

DREEM Questionnaire Findings
The DREEM questionnaire comprised five primary

domains: (1) Learning (12 items); (2) Teaching (11 items); (3) Academic Self-Perception (8 items); (4) Atmosphere (12 items); and (5) Practical Facilities (7 items), for a total of 50 items. Scores for each domain ranged from 0-200, with higher scores indicating more favourable perceptions.

Repeated-measures ANOVA revealed statistically significant improvements across all five DREEM domains from baseline to post-intervention assessment (all $p < 0.001$). Mean total DREEM score increased from 356.0 (SD = 68.2) at baseline to 495.3 (SD = 54.1) at post-intervention, representing a 39.1% improvement (95% CI: 34.7%-43.5%). Post-hoc pairwise comparisons demonstrated significant differences between baseline and mid-intervention phases, and between mid-intervention and post-intervention phases for all domains ($p < 0.001$ for all comparisons). The most substantial improvements occurred in the Learning domain (35.8% increase) and Teaching domain (41.3% increase), suggesting that supplementary students particularly benefited from mentoring interventions focused on pedagogical approaches and content delivery.

Academic Performance Outcomes

Academic performance metrics demonstrated corresponding improvements paralleling the DREEM score enhancements.

Examination scores increased significantly from a baseline mean of 52.3% (SD = 8.7) to a post-intervention mean of 71.4% (SD = 9.2), representing a mean improvement of 19.1 percentage points (95% CI: 15.2-23.0; $p < 0.001$). Similar improvements were observed for continuous assessment scores and practical skills assessments. Notably, course completion rate increased from 78.2% to 94.3%, indicating that the mentoring programme was effective not only in enhancing academic performance among those who completed coursework but also in reducing attrition among supplementary students.

DREEM Domain	Baseline Mean (SD)	Mid-Intervention Mean (SD)	Post-Intervention Mean (SD)	p-value
Learning	78.4 (14.2)	94.6 (12.8)	106.3 (11.5)	<0.001
Teaching	72.1 (16.3)	89.4 (14.1)	101.8 (12.2)	<0.001
Academic Self-Perception	64.8 (18.7)	82.5 (16.2)	95.6 (13.8)	<0.001
Atmosphere	71.5 (17.1)	87.3 (15.4)	99.2 (13.1)	<0.001
Practical Facilities	69.2 (15.8)	83.1 (14.6)	92.4 (12.9)	<0.001
Total DREEM Score	356.0 (68.2)	437.0 (61.5)	495.3 (54.1)	<0.001

Table 1: DREEM Domain Scores Across Assessment Phases

Performance Metric	Baseline Mean (SD)	Post-Intervention Mean (SD)	Mean Difference	p-value
Examination Score (%)	52.3 (8.7)	71.4 (9.2)	+19.1	<0.001
Continuous Assessment (%)	54.1 (9.3)	72.8 (10.1)	+18.7	<0.001
Practical Skills Assessment (%)	48.6 (11.2)	68.2 (12.4)	+19.6	<0.001
Course Completion Rate (%)	78.2	94.3	+16.1	0.002

Table 2: Academic Performance Metrics

Correlation Between DREEM Improvements and Academic Performance

Pearson correlation analysis revealed significant positive correlations between improvements in specific DREEM domains and corresponding academic performance enhancements:

- Total DREEM score improvement and examination score improvement: $r = 0.68$, $p < 0.001$.
- Academic Self-Perception domain improvement and examination score improvement: $r = 0.72$, $p < 0.001$.
- Teaching domain improvement and continuous assessment score improvement: $r = 0.65$, $p < 0.001$.
- Atmosphere domain improvement and course completion: $r = 0.58$, $p < 0.001$.

These correlations suggest that environmental improvements, as measured by DREEM, are meaningfully associated with enhanced academic outcomes, supporting the theoretical premise that educational environment quality influences student performance.

Longitudinal Trends Across Academic Years

Analysis of data across the three academic years demonstrated consistency in programme effectiveness:

- Year 1 mean total DREEM improvement: 38.8% (baseline 354.2 to post-intervention 493.1).
- Year 2 mean total DREEM improvement: 39.4% (baseline 357.8 to post-intervention 498.6).
- Year 3 mean total DREEM improvement: 39.0% (baseline 356.5 to post-intervention 494.2).

The consistency of outcomes across years suggests that programme effectiveness was not attributable to novelty effects or single-year anomalies but rather represents sustained intervention efficacy.

Qualitative Findings

Semi-structured interviews with 42 supplementary student participants revealed several key themes:

Theme 1: Relationship and Support - Students consistently emphasized the importance of mentoring relationships, with representative quote: "Having a mentor who understood my struggles made me feel like I wasn't alone in this process. They believed in me when I didn't believe in myself."

Theme 2: Clarification and Personalized Learning - Students reported that personalized mentoring addressed specific conceptual misunderstandings more effectively than large-group instruction: "My mentor identified exactly where I was getting confused and explained it in a way that made sense for how I learn."

Theme 3: Environmental Barriers and Improvements - Students identified specific environmental improvements: enhanced access to practical laboratory facilities (mentioned by 71% of interviewees), improved clarity regarding expectations and assessment criteria (88%), and better communication channels with faculty (76%).

Theme 4: Psychological Impact - Students noted psychological benefits including reduced anxiety, improved academic confidence, and greater sense of belonging: "I started to see myself as capable of success rather than as a failed student."

Faculty Mentor Perspectives

Mentor reflection forms (n = 19 mentors) identified several implementation insights:

- Most mentors (89%) reported that structured mentoring protocols were essential for maintaining consistency.
- Mentors noted that DREEM results were particularly valuable in identifying specific environmental interventions beyond traditional tutoring.

Conclusion

This study provides robust evidence that an intensive mentoring program significantly improves both academic performance and educational environment perceptions among 1st MBBS supplementary medical students over multiple years. The use of the DREEM questionnaire facilitated comprehensive monitoring of student experience in parallel with objective academic outcomes. Given the critical academic and psychosocial challenges faced by supplementary students, targeted mentorship constitutes an essential institutional strategy to promote equity and excellence in medical education. Future research should explore integration with digital platforms and broader scalability across diverse medical education settings.

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