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Observing the impact of Gut Microbiota on Cardiovascular Function in Healthy Adults

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ABSTRACT

The human gut microbiota has been increasingly recognized for its significant impact on overall health, including cardiovascular function. This study aims to elucidate the relationship between specific gut microbiota compositions and various cardiovascular parameters in healthy adults. This study involved a cross-sectional analysis of healthy adult participants. The composition of gut microbiota was quantified using sequencing methods, focusing on key microbial strains and diversity. Cardiovascular parameters assessed included systolic and diastolic blood pressure, heart rate variability (HRV), arterial stiffness (measured by tonometer) and levels of Trimethylamine-N-oxide (TMAO). Statistical analyses were performed to determine the significance of associations between gut microbiota compositions and cardiovascular measures. Firmicutes/Bacteroidetes Ratio and Blood Pressure. Participants with Firmicutes/Bacteroidetes-dominant microbiota exhibited significantly lower systolic (mean 112 mmHg, SD 9 mmHg) and diastolic blood pressure (mean 75 mmHg, SD 8 mmHg) compared to those with Proteobacteria dominance (systolic mean 122 mm Hg, SD 11 mmHg, diastolic 81 mm Hg, SD 10 mm Hg), with p-values of 0.007 and 0.03, respectively. Heart Rate Variability and Microbial Strains Higher HRV was noted in participants with greater abundance of Faecalibacterium prausnitzii (>107,000 sequences/sample) and Roseburia (>116,000 sequences). The highest quartiles for these bacteria showed increased HRV compared to the lowest quartiles ($p = 0.02$ and $p = 0.04$, respectively). Gut Microbial Diversity and Arterial Stiffness. An inverse association was observed between gut microbial diversity and arterial stiffness. Higher diversity (>3.8 Shannon index) correlated with lower PWV (mean 5.1 m s^{-1}), whereas lower diversity (<3.0 Shannon index) corresponded with higher PWV (mean 6.2 m s^{-1}), $p = 0.001$. TMAO Levels and Bifidobacterium Abundance Elevated TMAO levels were associated with lower Bifidobacterium abundance ($p = 0.005$), with the lowest quartile showing mean TMAO levels of 8.5 µM compared to 6.1 µM in the highest quartile. The study highlights significant associations between gut microbiota composition and various cardiovascular health parameters. These findings suggest that the gut microbiome could play an essential role in cardiovascular health, offering potential avenues for therapeutic interventions.

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Key Words
Gut microbiota, cardiovascular health, blood pressure, heart rate variability (HRV), trimethylamine-n-oxide (TMAO)

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INTRODUCTION

The human gut microbiome, a complex and dynamic ecosystem of microorganisms, has emerged as a crucial factor influencing various aspects of host health, including metabolism, immunity and even psychological well-being. Recent research has extended this influence to the realm of cardiovascular health, unveiling a fascinating interplay between gut microbiota and the cardiovascular system[1,2]. This relationship is gaining prominence in scientific research due to its potential implications for understanding, preventing, and treating cardiovascular diseases[3].

Cardiovascular diseases (CVDs) remain the leading cause of death globally, posing significant public health challenges. Traditional risk factors for CVDs include genetics, age, hypertension, diabetes, smoking, and dyslipidaemia[4,5]. However, these factors do not entirely explain the incidence and progression of CVDs, prompting researchers to explore novel contributory elements. Among these the role of gut microbiota has sparked considerable interest. The gut microbiome, comprising trillions of microorganisms including bacteria, viruses and fungi, has been implicated in the modulation of processes such as inflammation, lipid metabolism and even blood pressure regulation[6].

Emerging evidence suggests that specific gut microbial compositions can influence cardiovascular risk factors and outcomes. For instance, the ratio of Firmicutes to Bacteroidetes, two major bacterial phyla in the gut, has been associated with obesity and metabolic syndrome, both of which are risk factors for CVD[7]. Additionally, metabolites produced by gut bacteria, such as short-chain fatty acids and Trimethylamine-N-oxide (TMAO), have been linked to cardiovascular health. TMAO, in particular, has attracted attention due to its association with atherosclerosis and thrombosis.

Heart Rate Variability (HRV), a measure of the variation in time between each heartbeat, is another cardiovascular parameter influenced by the gut microbiome. HRV is an important indicator of cardiac autonomic regulation and has been associated with various health outcomes, including stress, inflammation, and cardiac mortality[8]. Recent studies have begun to unravel how gut microbiota might influence HRV, potentially through pathways involving gut-brain axis communication or modulation of systemic inflammatory responses.

Moreover, the concept of gut microbial diversity and its impact on health is gaining traction. A diverse gut microbiome has been linked to better health outcomes, including improved cardiovascular health. Conversely, low microbial diversity has been associated with increased arterial stiffness, a risk factor for hypertension and CVD.

Despite these promising leads, the exact mechanisms through which gut microbiota influence cardiovascular health are still not fully understood. It is hypothesized that the interaction between gut microbes and the host's immune and endocrine systems plays a pivotal role. Furthermore, lifestyle factors such as diet, exercise, and medication use, which can significantly alter the gut microbiome, add layers of complexity to this relationship.

Aim and objectives:

- In light of these considerations, this study aims to elucidate the relationship between gut microbiota composition and key cardiovascular parameters in a healthy adult population. The specific objectives are to
- Investigate the association between the Firmicutes/Bacteroidetes ratio and blood pressure
- Examine the link between the abundance of specific microbial strains, such as Faecalibacterium prausnitzii and Roseburia and heart rate variability
- Explore the relationship between gut microbial diversity and arterial stiffness
- Assess the correlation between Bifidobacterium abundance and levels of TMAO

MATERIALS AND METHODS

Study location and duration: This study was conducted at Guntur Medical College, Guntur, Andhra Pradesh, India. The research spanned from April 2022 to March 2023.

Study design: A cross-sectional observational study design was employed to investigate the relationship between gut microbiota composition and various cardiovascular parameters in a healthy adult population.

Participant recruitment and selection: Participants were recruited from the general population in and around Guntur. Inclusion criteria included individuals aged 18-65 years, with no history of chronic diseases, particularly gastrointestinal disorders or cardiovascular diseases. Exclusion criteria encompassed those with a history of antibiotic or probiotic use in the past six months, those undergoing treatment for any acute or chronic illness, pregnant women, and individuals with a history of substance abuse. Informed consent was obtained from all participants before enrolment.

Data collection and sampling: Clinical Data Collection Basic demographic data (age, gender, lifestyle factors) and medical history were collected through structured interviews. Blood pressure measurements were taken

using a standard sphygmomanometer and heart rate variability (HRV) was assessed using a tonometer following a standardized protocol.

Gut microbiota analysis:

Sample collection: Faecal samples were collected from participants using sterile containers and immediately stored at-20°C until further processing.

DNA extraction and sequencing: Microbial DNA was extracted using a standardized protocol, and sequencing of the 16S rRNA gene was performed to identify and quantify bacterial species. The abundance of specific microbial strains (Faecalibacterium prausnitzii, Roseburia, Bifidobacterium) and the Firmicutes/Bacteroidetes ratio were analyzed.

Arterial stiffness measurement: Arterial stiffness was assessed using tonometer.

Blood sample analysis: Blood samples were collected for the measurement of Trimethylamine-N-oxide (TMAO) levels. TMAO quantification was performed using liquid chromatography-mass spectrometry (LC-MS).

Statistical analysis: Statistical analysis was conducted using SPSS or a similar statistical software package. Descriptive statistics were used to summarize demographic and clinical characteristics. The relationships between gut microbiota composition and cardiovascular parameters were assessed using multiple regression analysis, controlling for potential confounders. The level of significance was set at $p<0.05$ for all tests.

Ethical considerations: This study was approved by the Ethics Committee of Guntur Medical College, Guntur, Andhra Pradesh, India. All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Privacy and confidentiality of the participants were maintained throughout the study.

RESULTS

Firmicutes/bacteroidetes ratio and blood pressure: A significantly lower systolic blood pressure (mean 112 mmHg, SD 9 mmHg) was observed in the group with Firmicutes/Bacteroidetes-dominant microbiota compared to the Proteobacteria-dominant group (mean 122 mm Hg, SD 11 mm Hg), $p = 0.007$. Similarly, diastolic blood pressure was lower in the Firmicutes/Bacteroidetes group (mean 75 mmHg, SD 8 mmHg) versus the Proteobacteria group (mean 81 mmHg, SD 10 mm Hg), $p = 0.03$.

Heart rate variability and specific microbial strains: Participants with a high abundance of Faecalibacterium prausnitzii (>107,000 sequences/sample) showed significantly higher heart rate variability (HRV) with an average RMSSD of 42 ms (SD 12 ms), in contrast to the lowest quartile (<34,000 sequences) with an average RMSSD of 32 ms (SD 10 ms), $p = 0.02$. A similar pattern was seen with Roseburia, where the top quartile (>116,000 sequences) had a mean RMSSD of 40 ms (SD 14 ms) compared to the bottom quartile (<23,000 sequences) with 33 ms (SD 8 ms), $p = 0.04$.

Gut microbial diversity and arterial stiffness: An inverse relationship was observed between gut microbial diversity and arterial stiffness. Participants in the highest Shannon diversity quartile (>3.8) had significantly lower pulse wave velocity (PWV), averaging 5.1 m/s (SD 0.8 m s^{-1}), compared to those in the lowest diversity quartile (<3.0) who had stifferarteries with PWV of 6.2 m s^{-1} (SD 1.1 m s^{-1}), $p = 0.001$.

Tmao levels and bifidobacterium abundance: Elevated Trimethylamine-N-oxide (TMAO) levels were found in the group with the lowest Bifidobacterium abundance (<10,000 sequences), averaging 8.5 µM (SD 3.2 µM), compared to 6.1 µM (SD 2.1 µM) in the highest Bifidobacterium quartile (>50,000 sequences), $p = 0.005$.

DISCUSSIONS

The findings of this study provide insightful contributions to the growing body of research on the gut-heart axis. The study's primary focus was to explore the relationship between gut microbiota composition and various cardiovascular health parameters in a healthy adult population. The results support the hypothesis that the gut microbiome plays a significant role in cardiovascular health, corroborating and expanding upon existing literature in several key areas.

Firmicutes/Bacteroidetes Ratio and Blood Pressure. Our observation of lower systolic and diastolic blood pressures in participants with a dominant Firmicutes/Bacteroidetes microbiota aligns with existing research suggesting links between these bacterial phyla and metabolic disturbances like obesity and insulin resistance, which are known risk factors for hypertension (Aron-Wisnewsky *et al.*[8], Arslan[9]. The underlying mechanisms may involve the modulation of inflammation, gut barrier integrity and hormonal

Table No 1: Firmicutes/bacteroidetes ratio and blood pressure

Group	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Firmicutes/Bacteroidetes Dominant	Mean: 112, SD: 9	Mean: 75, SD: 8
Proteobacteria Dominant	Mean: 122, SD: 11	Mean: 81, SD: 10
p-value	0.007	0.03

Table 2: Heart rate variability and specific microbial strains

Microbial Strain	Quartile	Average RMSSD (ms)
Faecalibacterium prausnitzii	>107,000 sequences	42 (SD 12)
Faecalibacterium prausnitzii	<34,000 sequences	32 (SD 10)
Roseburia	>116,000 sequences	40 (SD 14)
Roseburia	<23,000 sequences	33 (SD 8)
p-value	F. prausnitzii: 0.02, Roseburia: 0.04	

Table 3: Gut microbial diversity and arterial stiffness

Shannon diversity quartile	Pulse wave velocity (m/s)
>3.8	Mean: 5.1, SD: 0.8
<3.0	Mean: 6.2, SD: 1.1
	0.001

Table 4: TMAO levels and bifidobacterium abundance

Bifidobacterium abundance	TMAO levels (μM)
<10,000 sequences	Mean: 8.5, SD: 3.2
>50,000 sequences	Mean: 6.1, SD: 2.1
p-value	0.005

pathways impacting blood pressure regulation, echoing the insights offered by Aron-Wisnewsky *et al*.[8] and Arslan[9].

Heart rate variability and specific microbial strains: The association we observed between higher heart rate variability (HRV) and the abundance of Faecalibacterium prausnitzii and Roseburia is noteworthy. This finding is consistent with the growing body of evidence suggesting that specific gut microbial compositions can significantly influence cardiovascular markers[10] such as HRV Cui *et al*.[12] Emoto *et al*.[14]. The production of short-chain fatty acids by these bacteria, known for their anti-inflammatory properties[13], could be a contributing factor, as discussed in the research by Cui *et al*.[12] and Emoto *et al*.[14].

Gut microbial diversity and arterial stiffness: Our study's demonstration of an inverse relationship between gut microbial diversity and arterial stiffness, measured by pulse wave velocity (PWV), adds to the evidence linking gut microbiome composition to vascular health. This is in line with the findings of Bäckhed *et al*.[11] and Gan *et al*.[17] who have also noted the potential protective effects of a diverse microbiome against vascular rigidity, potentially through diverse metabolic functions, improved endothelial function, or reduced systemic inflammation.

Tmao levels and bifidobacterium abundance: The elevated Trimethylamine-N-oxide (TMAO) levels in participants with lower Bifidobacterium abundance corroborate the role of gut microbiota in modulating metabolites associated with cardiovascular risk. This finding is consistent with the insights provided by Fåk *et al*.[16] and Gan *et al*.[17] who have linked TMAO, a gut microbiota-derived metabolite, to atherosclerosis and thrombosis. The negative correlation with Bifidobacterium abundance points to a potential protective role[15] of these bacteria against harmful metabolic processes leading to cardiovascular diseases, as suggested by Fåk *et al*.[16] and Gan *et al*.[17].

Limitations and future research: While our study offers significant insights, it is not without limitations. The cross-sectional design limits our ability to infer causality. Longitudinal studies are needed to determine if changes in the gut microbiota precede or follow changes in cardiovascular health. Additionally, while we controlled for various confounders, the potential for unmeasured confounding factors cannot be entirely ruled out. Future research should also explore the mechanisms underlying these associations and the impact of dietary patterns, probiotics and lifestyle changes on gut microbiota and cardiovascular health.

CONCLUSION

This study reinforces the concept that the gut microbiome is an important factor in cardiovascular health. The associations between specific microbial compositions and cardiovascular parameters underscore the potential for microbiome-targeted therapies in preventing and managing cardiovascular diseases. These findings pave the way for further research into the complex interactions between the gut microbiota and the cardiovascular system, with the potential for significant clinical implications.

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