Role of the Gut Microbiome in Vascular and Brain Health: An overview of the extra-intestinal impact of the gut microbiome

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1. Introduction

The human gut microbiome, a thriving collection of living organisms residing within the intestinal tract, exists in close physiological partnership with its host. It contributes to mucosal barrier integrity, immune regulation, and metabolic processes that the body cannot perform independently. This tight relationship means that disruption of the normalcy of the gut microbiome, or 'dysbiosis', carries significant consequences that stretch beyond the influence of the gastrointestinal tract [1]. Mounting research implicates dysbiosis in the pathogenesis of many diseases, which has led to renewed interest in the mechanisms linking microbiome compositional change to tangible, physical harms.

This research article emphasizes two of these harms, hypertension and atherosclerosis, as both of them are major contributors to global mortality. This comes despite both conditions being largely preventable through public health education and pharmacological agents. This leaves considerable room for the introduction of alternative therapies, particularly gut microbiome modulation [2]. Associations of these conditions with novel gut microbiome species, including but not limited to *Bifidobacterium*, have motivated two projects summarized in this article.

We aim to combine previous evidence linking gut dysbiosis to hypertension and atherosclerosis with new information these projects will unveil, identify their strengths and possible research gaps, and outline the methodologies taken in the two ongoing projects designed to address the weaknesses of information in the field currently. As both projects are still ongoing, this article will provide an overview of their rationale, necessity, and design.

2. Literature review

2.1 Importance of the gut microbiome and gut dysbiosis

It is now understood that the role of the gut microbiome extends beyond simply digestion and absorption: not only does it contribute to mucosal barrier integrity, it also plays a part in extra-intestinal tasks such as immunological defense and de novo synthesis of various metabolites and vitamins, showing an increasingly intertwined relationship with human physiology [1]. Because of this, the deviation of gut microbiota composition from the norm, or 'dysbiosis', is considered a potential cause of intestinal, circulatory, inflammatory and infectious disease, be it intestinal or extra-intestinal [3]. Literature shows that dysbiosis affects around 40% of Hong Kong Chinese adults [4], and it is estimated that it also reaches 11% of the global population, although no comprehensive quantification has been conducted worldwide. Given its potential in providing safe, alternative treatment strategies for patients with chronic yet controllable diseases, it is therefore reasonable to suggest that establishing the mechanistic

pathways between gut dysbiosis and said extra-intestinal diseases is a top priority in medical research.

In sections 2.2 and 2.3, we explore two chronic diseases that may have extensive links to the balance and imbalance of the gut microbiome.

2.2 Hypertension

Hypertension affects nearly 40% of the global population [5]. It is the leading risk factor of cardiovascular disease and death worldwide, yet less than 20% of affected individuals seem to be capable of achieving adequate control over it [6,7]. This comes despite readily available pharmacological options and an abundance of health education carried out on the subject.

This gap between treatment and outcome has led to renewed interest in gut microbiome modulation as a means of regulating blood pressure, given the strong link between the two [8]. Studies have shown that fecal microbiota transplantation, or FMT, can lead to the transmission of hypertension, suggesting a plausible mechanism of causation between the gut microbiome and vascular health [9]. Despite this, there remains a research gap in concretely narrowing down the mechanisms causing this phenomenon. If successful, this could generate viable probiotic-based therapies as a new and safe form of intervention available to the general public on the open market.

2.3 Atherosclerosis

As the underlying cause of almost half of all deaths among Western populations, atherosclerosis remains one of the trickiest diseases to prevent [10]. Due to its multifactorial etiology, asymptomatic progression, and various manifestations (the most common of which are peripheral artery disease, stroke or transient ischemic attacks, and ischemic heart disease) [11], it has become a problem of increasing prevalence, especially if compounded with an aging population, a rise in metabolic diseases, and the ever-expanding influence of diabetes. Although less evidence is available to show any mechanistic relation between atherosclerosis and the gut microbiome, studies have reported various associations between specific types of microbiota and carotid intima media thickness (IMT), a recognized marker of subclinical atherosclerosis [24].

Unlike hypertension, no causal link has been established between atherosclerosis and the gut microbiome. However, studies have shown that dietary compounds containing species such as *Akkermansia muciniphila* and *Bifidobacterium* have been able to slow IMT progression in mice models [22]. A recent Japanese trial has also proposed *Bacteroides* species as a potential anti-inflammatory probiotic for suppression of arteriosclerosis in both mouse and human cohorts [23]. There is a correlation but lacking causality, necessitating this domain of study in order to

explore potential avenues in reducing the prevalence of atherosclerosis by gut microbiome modulation, be it by lowering the level of cholesterol or other metabolites.

2.4 *Bifidobacterium*

Bifidobacterium is one of the most promising species offering mechanistic linkage between gut dysbiosis and vascular health deterioration (thus disease). Several Bifidobacterium species have established themselves as known producers of short-chain fatty acids (SCFAs) such as acetate, proprionate and butyrate, all of which have known causal relationships with reduced vascular inflammation, improved blood vessel wall function and relieved oxidative stress [12,13,14]. This, by extension, means that *Bifidobacterium* has a propensity to align its metabolites with factors that reduce the occurrence of hypertension. Perhaps more importantly, *Bifidobacterium*-increasing dietary interventions have also been associated with a potential correlation to reduced IMT in animal models, indicating a potential causal relationship between the two.

In previous research conducted by HKU Stroke, shotgun metagenomic sequencing of study participants' stool microbiota identified an inverse relationship between systolic blood pressure and three Bifidobacterium species [15], namely *B. adolescentis, B. bifidum* and *B. longus*. *B. adolescentis*-mediated T cell elevation, which in turn leads to increased anti-inflammatory cytokine secretion, has been proposed as a possible mechanism leading to this decrease in blood pressure [13]. Moreover, its role in the production of gamma-aminobutyric acid (GABA), a neurotransmitter with cardioprotective properties, has also come to the forefront as another link to this relationship [16], and GABA-rich supplements have also been reported to reduce hypertension in borderline hypertensive individuals [17]. Aside from these findings, *B. longum* has been shown to reduce the occurrence of hypertension and aortic lesions in hypertensive rats by promoting gut symbiosis [18].

These results show that Bifidobacterium is not just a promising candidate as a mere probiotic, but also a regulator for blood pressure and atherosclerotic risk. More work will be done to firmly establish its role in vascular health.

2.5 The problem, the research gap, and how it is addressed

Hypertension and atherosclerosis are not simply prevalent health problems. The World Health Organization estimates that cardiovascular diseases, including hypertension, are projected to cost low- to middle-income countries approximately $3.7 trillion USD, indicating a high economic burden worldwide [21]. This has led to greater economic inequality in these regions: failing to prevent these diseases can lead to increased, persistent economic costs [2]. These costs are incurred on hospital visits, medication purchases, and forgone income due to illness.

Two major gaps still define research in using gut microbiome modulation as a regulator of both hypertension and atherosclerosis, hence limiting its short-term potential. First, the linkage between the gut microbiome and the two diseases still lacks some degree of mechanistic clarity: while its relationship with hypertension is well-founded due to secondary findings from FMT studies, atherosclerosis research still remains, unfortunately, relatively correlative at this juncture.

If we narrow it down to *Bifidobacterium*, that gap is further compounded. The current proposed mechanisms show high plausibility; however, most evidence in these studies was derived from animal models or, at best, single-marker human studies. This absence of a multi-biomarker human cohort designed to study the efficacy of *Bifidobacterium* will be resolved by our trial of its use on Hong Kong Chinese.

Two projects address these gaps. One uses data from a pre-existing cohort observing Hong Kong Chinese individuals over a span of five years. It will find potential metabolomic markers [20] that correlate with vascular or brain health. The other hopes to observe any changes in blood pressure upon administration of a *Bifidobacterium*-based probiotic in a predominantly Hong Kong Chinese cohort. They will shed light on potential mechanisms linking gut microbiome and vascular health, and inform the use of probiotics or gut microbiome modulation as a viable treatment option for vascular diseases.

3. Methodology

3.1 Five-year cohort study

This study was designed as a comprehensive assessment of risk factors (lifestyle, psychosocial status, and environmental) and whether they contribute to variations in gut microbiome composition. These risk factors may have an effect on vascular and brain health.

Beginning in 2018, approximately six hundred individuals were recruited from the Employees' Union of the University of Hong Kong, as well as other HKU Stroke events. This resulted in a comprehensive community-dwelling cohort with broad representation across gender and age. Participants with disease, pharmacological or environmental exposures that perturb gut microbiome composition that may serve as confounders were excluded.

Throughout this study, participants were administered questionnaires by trained research personnel, allowing extensive analysis into the effects of socioeconomic and environmental factors across various demographics. Validated psychometric tools were also used to assess

mental function, psychological state, and sleep quality. A one-week food diary was also taken to record dietary intake as well as any changes in dietary habits.

For physical measurement, standard anthropometric measures were collected in tandem with markers of vascular health, with particular emphasis on carotid IMT and arterial stiffness. Vascular markers were collected using ultrasound. Physical activity and sleep quality were also assessed using ActiGraph GT9x wearable devices.

Biological samples were also collected: drawn blood for future analysis of biomarkers and genetic testing, spot urine for assessment of sodium level and stool samples for gut microbiome analysis. Eligible participants were also invited to undergo magnetic resonance imaging (MRI) of the brain to study their brain structure and function, as well as transient elastography for assessment of liver stiffness and steatosis.

Statistical analyses were performed using SPSS, STATA, and dedicated gut microbiome analysis software. Group proportions were compared using the chi-squared test, and group differences in means using the t-test. Only results with a p-value of <0.05 were considered statistically significant.

All subjects recruited into the study were re-invited to participate in a substudy five years after their baseline assessment, excluding those that had experienced a malignant cardiovascular or cerebrovascular event. Subjects underwent the same research assessment protocol they had completed five years prior, along with notable additions such as calf circumference measurement and the sit-to-stand test (30-second chair stand test). This provided us with data to evaluate changes in gut microbiota over a five-year period, lifestyle and environmental changes that may have resulted in said variation, as well as identify potential novel gut microbiota species that may exert an effect on vascular and brain aging.

3.2 *Bifidobacterium*-based probiotics in reducing blood pressure

The objective of this study, slated to begin in September 2026, is to assess whether administration of a Bifidobacterium-based probiotic would lead to a decrease in systolic blood pressure. The study targets untreated Hong Kong Chinese individuals with hypertension, and will analyze observable changes after a period of ten weeks. It is designed as a single-arm feasibility study to determine whether the usage of the probiotic would warrant progression to a randomized controlled trial with a larger cohort, which would yield results to support its use as an intervention for high blood pressure.

No blinding or placebo arm is employed in this study as its objective is to simply establish feasibility rather than efficacy. This will be rectified by the use of a placebo arm in any future randomized controlled trial.

As classified by ACC/AHA guidelines, 30 community-dwelling, middle-aged Hong Kong Chinese individuals (15 male, 15 female) with systolic blood pressure ≥130mmHg will be recruited. The recruited participants are ensured not to have taken any prior antihypertensive medication, nor have previous history of cardiovascular or cerebrovascular disease. To assess individuals with unaffected gut microbiota, participants will be excluded if they had any prior history of gastrointestinal disorders, or had travelled to any tropical region within the previous six months. Written consent will be obtained from all participants prior to formal recruitment.

The research period, spanning ten weeks, will be made up of one screening visit (at week -1) and two follow-up visits (at weeks 5 and 10). Measurements used in the study include questionnaires administered by our team (on past medical and drug history, vaccination history, and travel history), three clinic blood pressure readings, a 24-hour ambulatory blood pressure monitoring session, and the collection of fecal and blood samples. To facilitate collection of blood samples, participants will be instructed to fast overnight before their first and last visits.

Only participants who are able to provide the necessary data and samples by the end of week -1 will be eligible to receive the *Bifidobacterium* granules used in the trial, which they will mix in water and consume, at an amount of twenty billion cfu daily starting at week 0. Adherence will be measured by self-report from participating individuals.

For clinic blood pressure measurement, three consecutive measurements will be taken using machinery with the participant seated [19]. For 24-hour ambulatory blood pressure measurement, calibrated ambulatory blood pressure monitoring devices will be individually fitted onto the non-dominant arm of the participant for recording purposes. All equipment will be handled by trained personnel from HKU Stroke for purpose of reproducibility.

For assessment of gut microbiota and blood biomarkers, stool GM sequencing will be performed in order to compare different gut microbiome profiles before and after the administration of *Bifidobacterium*, allowing for metagenomic assembly, as well as community and functional profiling of individual gut microbiomes. Blood biomarkers will also be quantified to allow for a better understanding of blood pressure-modulating mechanisms of these metabolites, and to re-confirm their antihypertensive tendencies.

In terms of data treatment and statistical analysis, demographic characteristics obtained from questionnaires will be summarized using descriptive statistics, while paired t-tests will be applied to investigate commonalities between blood pressure and gut microbiome composition changes.

To tie respective associations between blood pressure and related metabolites, linear regression analysis will be conducted. Only data with a p-value <0.05 will be considered statistically significant and used to support or decry rationale for any future trials.

4. Expected outcomes and conclusion

The first study looked into associations between the gut microbiome and risk factors related to vascular and brain health. Most significantly, it covered surrogate markers used as indicators of vascular health, such as carotid IMT, ankle-brachial index, arterial stiffness and atherosclerosis in the carotid artery. Given that these markers are often used to assess, monitor, and diagnose subclinical atherosclerosis, more information regarding the mechanisms in gut microbiome alteration leading to atherosclerosis will be obtained from further analysis of the data obtained in this study. For example, a correlation analysis can be conducted on the changes in gut microbiome composition and carotid IMT thickness, respectively, to detect if any novel gut bacterial species would play a role in this condition, allowing us to assess the possibility of using said species in a probiotic or gut microbiome modulation therapy to reverse or slow arterial plaque build-up or intima media thickening. These possibilities are currently being explored and will be gradually fleshed out upon the continuation of my work with the HKU Stroke team.

The second study is expected to further contribute to the current work being done on Bifidobacterium and its potential antihypertensive effects in middle-aged individuals, while continuing to investigate potential mechanisms behind gut microbiome modulation through probiotics and their effects on vascular health. This may provide further support for the use of probiotics as a form of alternative intervention for hypertensive individuals. Given the comprehensive study design and rigorous data analysis in the project, we expect to be able to gain valuable insights into the mechanisms and benefits of using probiotics for blood pressure control, which may in turn inform medical practices in a clinical setting, as well as improve personalized medicine for hypertensive patients.

Given the importance of the gut microbiome in human physiology and the relative ease of administering probiotics (compared with other pharmacological agents or therapies), the study of gut microbiome modulation and its relationship with certain pathological conditions remains an important field of investigation. It seems reasonable to suggest that further analysis may yield higher mechanistic clarity as to how certain conditions come about, thus opening the door to the usage of probiotic formulas or fecal microbiota transplantation in delaying the onset, or slowing the progression of asymptomatic, yet potentially fatal diseases. The high prevalence of hypertension and atherosclerosis worldwide makes this a crucial global problem that needs to be alleviated, if not solved. It is hoped that this research work will be able to provide some form of relief to the health and economic burden of these diseases, by providing a more universally accepted alternative to the prevention and treatment of the two conditions.

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