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Review
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Is there a link between the gut microbiome and arterial hypertension?

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Abstract

The human microbiota consists of a variety of bacterial species which populate the mucosal surfaces and contribute a great deal to the education of our immune system. In terms of metabolism, the microbiota plays an important role by decomposing nutrients that we consume in our food and degrading environmental toxicants and environmental chemicals and drugs. Changing the state of eubiosis to dysbiosis represents an area of extreme interest nowadays, as researchers try to understand the pathophysiology behind it fully. Blood pressure can be influenced by changes in ratios of gut microbiota categories, short-chain fatty acids, specific kidney and blood vessel receptors, gut metabolites trimethylamine (TMA), and trimethylamine N-oxide (TMAO). This minireview aims to reveal some of the major aspects that support the hypothesis that gut microbiota contributes to the regulation of blood pressure. The purpose of all research is to discover the possibility of future personalized microbiome targeted therapy in order to lower the prevalence and incidence of some of the most common afflictions of our time, especially arterial hypertension.

Keywords: microbiota, microbiome, blood pressure, hypertension, TMAO, short chain fatty acids, Olfr 78.

Introduction

The microbiota represents a multitude of bacterial species which can be found on mucosal surfaces. Its widest category, the gut microbiota, is believed to be in correlation with a considerable variety of afflictions and susceptibility to diseases. The microbiome, which is now considered our hidden organ, received excessive attention in recent years. There are between 3 and 10 microorganisms for every human cell; therefore, humans are nowadays considered holobionts [1].

However, the attention over the microbiota is focused mainly on the gut because of its digestive functions and connections to the brain. It is a continuous

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strive for research in this area in order to accurately identify how this micro-world influences our lives and our well-being [1].

The main aim of progressive studies regarding microbial populations within the human gut consists of the possibility of developing future personalized microbiome-related risk stratification, diagnosis, and treatment for specific ailments. Recent research suggests that dysbiosis can be linked to a variety of afflictions related to cardiology, endocrinology, psychiatry, or even neurology [2]. Affecting the state of eubiosis is of extreme interest as some of the above-mentioned disorders, such as essential hypertension, might benefit from correction of dysbiosis, with a huge impact on the general health of individuals [3].

Hypertension is the leading risk factor for cardiovascular disease and a global public health concern. Therefore, the human microbiome is both a provocative and a beneficial concept to be studied since aberrant gut microbial communities were linked to blood pressure changes of the host [3].

Adult microbiota is made up predominantly of 4 major phyla: *Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria* [4]. Gut microbiota can be affected not only by diet and environment but also by genetic heritage [5]. It is also suggested to influence and be influenced by type 2 diabetes mellitus, aging, glucose intolerance [6–7], obesity [6–7], and nonalcoholic fatty liver disease [8].

Hypertension is one of the most frequent primary diagnoses in the United States [9]. According to the 2018 European Society of Cardiology (ESC)/ European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension, high blood pressure (BP) can be defined as repeated office systolic blood pressure (SBP) measurements over 140 mmHg and/or diastolic BP (DBP) over 90 mmHg or as repeatedly ambulatory BP measurement as a 24h-average SBP over 130 mmHg and/or DBP over 80 mmHg, as a day time average SBP over 135 mmHg and/or DBP over 85 mmHg, as a nighttime average SBP over 120 mmHg and/or DBP over 70 mmHg or as home BP measurement SBP over 135 mmHg and/or DBP over 85 mmHg [10].

Is gut dysbiosis a cause of hypertension?

The relationship between BP and microbiome has been intensely investigated so far. Growing evidence suggests that changes in the ratio of the microbiota *Firmicutes/Bacteroidetes* categories could be considered an indicator for some health imbalances [11, 12].

Massive gut colonization with *Firmicutes* and *Bacteroidetes* species proved to be in correlation with high blood pressure. The use of antibiotics, besides expected adverse effects (shrinking gut microbiota), can also cause BP variations, which can be influenced by the microorganisms' genotype. Compounds of bacterial fermentation can lead to BP adjustments through variations of energy consumption, ion transport at renal and gastrointestinal levels, and consequently salt sensitivity. Furthermore, antibiotic administration can modify blood pressure by changing the gut microbiota [13].

A cohort study of 48 hypertensive and 32 normotensive Brazilian individuals showed that hypertensive patients also had dysbiosis (intestinal microbiota with reduced biodiversity). The *Firmicutes/Bacteroidetes* (F/B) ratio in the category of hypertensive patients was found to be higher than the normotensive group, through a lowering proportion of Bacteroidetes. The F/B ratio was also used as an indicator of obesogenic microbiota, its raised values being linked to high fat and low fiber Western diet and inflammatory status of the patient [14]. In an F/B perturbed ratio, fewer short-chain fatty acids (SCFAs) (main butyrate) producers were reported, such as constituents of *Lachnospiraceae* and *Ruminococcaceae* families, like *Roseburia* and *Faecalibacterium* [14–17].

As thoroughly communicated by Million *et al.* in 2018, butyrate could embody the most useful indicator of healthy anaerobic gut microbiota [18]. Thus, oxidative stress-sensitive butyrate-producing commensal bacteria could develop into a novel target of therapy. This way, the preservation of immunity generated by microbiota can be preserved, and several serious local and systemic disruptions can be avoided. It should be mentioned that *Roseburia*, one of the main butyrate-producing bacteria that seem to be underrepresented in patients suffering from hypertension, also produces conjugated linoleic acid. This acid was proven to possess anti-inflammatory properties and also possible blood pressure lowering effects [14, 19–22].

Microbiota is influenced by a variety of factors ranging from diet, physical activity to genetics and epigenetics. SCFAs produced by the gut microbiota include the favorable SCFAs (acetate, butyrate and propionate) and non-favorable (lactate). SCFAs act on surface cell receptors, such as G protein-coupled receptors (GPR) 43 and 41, olfactory receptor-78 (Olfr-78), exerting relaxing effects on resistance arteries [23], thus regulating blood pressure [24]. Olfr-78 can be found in kidneys and vascular resistance beds, including also renal afferent arteriole. These are receptors for SCFAs, in particular propionate and acetate. Propionate can modify BP in a manner dependent on the presence/absence of either Olfr-78 or GPR 41. Also, propionate can influence renin release through mechanisms dependent on Olfr-78. The identification of Olfr-78 as an SCFA receptor, along with its localization, led to the possibility that Olfr-78 may be triggered by gut microbiota-derived SCFAs, with the purpose to control BP [25–28].

Important contributions in hypertension have gut metabolites trimethylamine (TMA) and trimeth-

ylamine N-oxide (TMAO). TMA results from gut bacteria's metabolism, choline and L-carnitine (red meat, saltwater fish, eggs, dairy) and can be transformed into TMAO by specific enzymes. Plasma TMA levels were linked to higher blood pressure values. TMAO displays an important role in hypertension as it can influence lipid and glucose metabolism and also inflammation. TMAO upregulates inflammatory gene expression and phenomena in endothelial cells and vascular smooth muscles [29]. Some studies suggested that high concentrations of TMAO are correlated with a high risk for atherosclerosis, serious adverse cardiovascular events. Also, they influenced the metabolism of steroids and bile acid, aggravating vascular dysfunction. TMAO is thought to raise blood pressure through lengthening the hypertensive effect in an angiotensin II-induced hypertensive model [30].

A study involving 205 overweight and obese pregnant women showed a correlation between BP and gut microbiome composition (inversely association with butyrate-producing bacteria). SCFAs produced by the gut microbiota seem to affect BP by acting on olfactory receptors in blood vessels and kidneys [25, 26].

Associated with high BP are suggested to be Lactobacillus (*L. salivarius*), *Akkermansia muciniphila* (mucin degrader) [17], *Bifidobacterium*, unclassified *Enterobacteriaceae*, *B. plebeius* (found in patients with elevated BP) [16] and *Eggerthella* (associated with dyslipidemia) [31]. Some research suggests that some *Lactobacillus* species as probiotics can have hypotensive effects [32], but they are also identified in high numbers in inflammatory afflictions, obesity [33], coronary heart disease [34], and heart failure [35]. *L. salivarius* could be linked to atherosclerosis, as abundant populations of it were found in the gut microbiome of patients suffering from atherosclerotic heart disease [36], making us wonder if this microorganism can be used as an indicator of heart-related conditions [14].

Concerning urinary metabolites, in the INTERMAP study that included 4630 participants, urinary hippurate was inversely associated with BP values, while urinary alanine was directly associated with BP [37, 38].

An interesting study including 653 patients with no history of stroke or myocardial infarction assessed the link between periodontal microbiota and hypertension. It revealed a direct relationship between the amount of subgingival periodontal bacteria and SBP, DBP, and hypertension prevalence. Bacteria that can cause periodontitis, like *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola*, were associated with elevated BP levels [39].

Some interesting conclusions can be drawn from the CARDIA study regarding the relationship between bacteria and hypertension. *Catabacter* and *Robinsoniella* were positively associated with hypertension and systolic blood pressure, while *Akkermansia*, associated with normal BP values, may reflect better gut epithelial integrity while also being linked to inflammation, diabetes, and obesity. *Sporobacter* and *Ruminococcus*, which are members of the *Ruminococcaceae* family within the phylum *Firmicutes*, were associated with normotension [40].

Regarding microbiome and blood pressure, there is also a vicious cycle among all these phenomena: diet, salt, and gut microbiota can all influence epigenetics [41–44]. Salt increases oxidative stress [45, 46], and oxidative stress influences epigenetics [47].

Moreover, the monoamine-containing enterochromaffin cells can be found in the mucosa and submucosa of the stomach and small intestine [13, 48]. The gut microbiota can affect the production of serotonin, dopamine, and norepinephrine, thus determining human behavior through the brain-gut microbiome axis [49, 50] and renal function through the so-called gastrorenal reflex [51, 52].

The acute stress response in cases with lack or severe fading of gut microbiome showed increased anxiety-like behavior and alterations of dopamine turnover in the central nervous system's structures [13, 53].

Additionally, norepinephrine releases as a stress reaction response and can be exacerbated when there are plenty of virulence-related factors of gram-negative bacteria [54].

The search for solutions

Gut microbiota dysbiosis was proved to be associated with high blood pressure. Low levels of *acetate* and *butyrate*-producing microorganisms were correlated with a diminished gut microbial abundance and variety. Nevertheless, a solution was developed. Treatment with oral minocycline (an anti-inflammatory antibiotic) revealed promising results. Besides rebuilding gut microbiota and decreasing the *Firmicutes/Bacteroidetes* ratio, minocycline led to lower BP values [55, 56], lower levels of glycated hemoglobin (HbA1C) and weight loss [57, 58].

A handful of clinical trials aimed to assess the effect of probiotics use on BP modulation. A meta-analysis of nine randomized control trials displayed a considerable lowering of both systolic and diastolic blood pressure levels for patients who received 109 to 1012 colony-forming units (CFU) of probiotics daily for 3 to 9 weeks. The adjustment of BP was higher in those patients with higher BP before the treatment, who underwent probiotic supplementation for more than 8 weeks, with daily doses of more than 1011 CFU [59].

An unfit gut microbiota configuration and activity at young ages can affect the function of the immune system and general health. Probiotics can be seen as a method of prevention for chronic immune-mediated conditions. Epigenetic mechanisms

generated by probiotics through SCFA formation could be the solution for unraveling the vast beneficial effects of probiotics on general health [60].

Conclusion

The effects of the gut microbiome on blood pressure embody the results of various factors, ranging from individual genetic susceptibility and epigenetics to lifestyle and medication. Much evidence remains to be gathered and much research to be done. However, one thing is for sure: the faster the discovery of most of the intrinsic and extrinsic influences of the gut microbiome over blood pressure values, the better one can use targeted therapy in order to provide the best patient care there can possibly be.

Conflict of interest

The author confirms that there are no conflicts of interest.

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