The gut microbiome and hypertension

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Purpose of review
The mammalian mucosal surfaces are densely inhabited by a diverse microbial ecosystem termed the microbiota. Among these highly heterogeneous populations, the largest and richest is the gut microbiota, recently suggested to affect various physiological traits and susceptibility to disease. Novel metagenomic and metabolomic approaches, which have been developed in the past decade, have enabled the elucidation of the contribution of the microbiota to metabolic, immunologic, neurologic and endocrine homeostasis.

Recent findings
Dysbiosis, the alteration in the gut microbiota composition and function, has been lately associated with the pathogenesis of multifactorial diseases such as obesity, diabetes and cardiovascular disorders. Recent studies have also suggested associations between dysbiosis and essential hypertension, a common chronic medical condition affecting 20% or more of the adult population worldwide, which is considered a major causative factor for heart disease, stroke, chronic renal failure, blindness and dementia.

Summary
In this review, we discuss the accumulating research pointing to possible interplays between the gut microbiome and hypertension and highlight future prospects by which utilization of microbiome-related techniques may be incorporated into the diagnosis and therapeutic arsenal of hypertension management.

Keywords
dysbiosis, hypertension, microbiome

INTRODUCTION

The microbiome is a diverse microbial ecosystem that has coevolved with the host, which plays a part in the modulation of multiple physiological processes [1]. Seminal studies [1,2] pointed toward possible microbiome effects on metabolic homeostasis including obesity, glucose intolerance [3,4], type 2 diabetes mellitus [5–7], aging [8] and nonalcoholic fatty liver disease [9].

Hypertension is a common human condition, historically defined by a sustained elevation of systolic blood pressure (SBP) above 140 mmHg or diastolic BP (DBP) above 90 mmHg. Essential hypertension (~90% of patients) is a heterogeneous disorder [10] typically emerging in middle or old age, a cumulative result of complex gene–gene and gene–environment interactions. It has no single identifiable or curable cause, with risk factors including advanced age, non-Hispanic black ethnicity, obesity and the metabolic syndrome, low birth weight [11], prolonged and excessive alcohol intake, consumption of salt-rich diet and vitamin deficiency [12–14]. In contrast to essential hypertension, secondary hypertension often arises at younger age, in individuals with no family history of hypertension (unless tied to a monogenic disorder), and has an identifiable cause, such as chronic kidney disease, narrowing of a renal artery or an endocrine disorder, including the use of oral contraceptive agents [15,16]. Untreated hypertension [17] has grave long-term prognosis, although a minority of affected patients have no tangible sequelae. Complications of untreated hypertension, largely mediated by atherosclerosis and arteriosclerosis, include cardiac, renal, cerebrovascular and retinal damage. To date, hypertension remains the largest single contributor to the global burden of disease and mortality, resulting in millions of deaths each year by stroke and coronary heart disease [18], as well as

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KEY POINTS

- Hypertension may be directly or indirectly linked to compositional or functional gut microbiome alterations, or both.
- Understanding the nature of hypertension-related microbial aberrations may enable future development of personalized microbiome-based diagnostics for individuals at risk.
- Deciphering whether microbiome–hypertension associations are causal may enable the designing of rational microbiome modifications as a means of reducing the risk of hypertension or altering its clinical course.

heart failure, peripheral vascular disease, chronic kidney disease, cognitive dysfunction and dementia [19]. Despite much progress in prevention, detection, treatment and control of hypertension, it remains a critical public health problem.

The homeostatic maintenance of BP is a complex process, governed by the kidneys, and regulated by genetic, environmental and endocrine factors. Recent studies suggest that the microbiome participates in BP regulation and the pathogenesis of hypertension [20▪,21▪,22▪▪,23–25], mainly through secretion of a variety of microbial-derived bioactive metabolites [26–28] such as short-chain fatty acids (SCFAs) [29,30]. In this review, we portray the interplay between the gut microbiome and hypertension. In addition, we discuss future directions toward potential incorporation of microbiome-centered techniques in striving toward the development of personally tailored curative treatment for this common and cureless disorder.

ANIMAL STUDIES ASSESSING THE MICROBIOME ROLES IN HYPERTENSION

Experiments in animal models put forward possible associations between features of essential hypertension and alterations in the gut microbiome. A time-honored animal model for the study of hypertension utilizes the Dahl-R (salt resistant) and Dahl-S (salt sensitive) rats [21▪,31], derived from the Sprague-Dawley strain. While R rats do not develop an elevated BP after being fed with high salt diet (8% NaCl), S rats respond to high salt diet by a significant increase in BP. Although gene variants are present in Dahl-S vs. R rats, they do not relate to phenotype in other salt-sensitive rat models and are not more common in the Dahl than in the Sprague-Dawley strain [32]. The microbiota of S rats was found to be distinct from that of R rats, with bacteria of the phylum *Bacteroidetes* and the family *Veillonellaceae* found to be more abundant in the former as compared to the latter strain [21▪]. However, microbiome depletion in S rats by antibiotic administration did not significantly affect their hypertensive responses to the high salt diet, suggesting that the gut microbiome does not directly mediate the hypertensive phenotype in this model. In addition, fecal microbiome transplantation from S to R rats did not transfer the hypertensive phenotype into the R rats. Surprisingly, reverse fecal microbiome transplantation from R to S rats exacerbated the transplanted S rats' hypertensive responses, an effect that was associated with significantly elevated plasma levels of the fatty acids acetate and heptanoate, leading to the hypothesis that the different microbial composition altered plasma SCFA levels that, in turn, may affect BP regulation [33].

The microbiome composition was further examined in an additional rodent model of hypertension, the spontaneously hypertensive rats (SHRs), which features elevated BP levels and increased response to high salt diet, as compared to normotensive Wistar Kyoto (WKY) control rats [22▪▪,34]. Fecal microbiota analysis revealed profound differences in the bacterial composition between the SHR and WKY rats, with the former featuring reduced taxa richness and compositional alterations as compared to WKY rats. At the phylum level, the *Firmicutes* to *Bacteroidetes* ratio was fivefold higher in the SHR rats as compared to WKY rats. *Actinobacteria* population was reduced in the SHR compared with WKY rats, and a similar reduction was also observed for *Bifidobacterium* at the genus level. Pattern recognition using Linear Discriminant Analysis Effect Size (LEfSe) analysis, a biomarker discovery and explanation tool for high-dimensional data, revealed that *Coprococcus* and *Pseudobutyrivibrio*, which are butyrate-producing bacteria, accumulated more in WKY rats, whereas *Streptococcus* and *Turicibacter,* lactate-producing bacteria, accumulated more in SHR rats.

Microbiome compositional alterations were also inspected in a pharmacological hypertension rat model, in which angiotensin II (Ang II) is constantly infused into the rats to induce hypertension. As compared to control groups, Ang II-treated rats presented a reduction in microbial species richness and an increased *Firmicutes*/*Bacteroidetes* ratio [22▪▪]. To deplete the majority of microbiota members, the rats were treated for 4 weeks with the antibiotic minocycline. This resulted in significantly reduced *Firmicutes*/*Bacteroidetes* ratio and mean arterial pressure in the Ang II–infused rats. By using LEfSe analysis, Ang II–infused rats were suggested to host less acetate-producing and butyrate-producing

genera, whereas oral administration of minocycline resulted in an increase in the acetate-producing to butyrate-producing bacteria ratio.

A common culprit in human hypertension is obstructive sleep apnea (OSA) in which 50% of patients present with hypertension. OSA is a disorder characterized by apneic episodes leading to transient hypoxia, hypercapnia and excessing negative intrathoracic pressure as the patient breathes against a closed airway [35]. In the Sleep Heart Health Study [36], a linear relationship was shown between mean SBP and DBP and OSA severity. Moreover, the prevalence of hypertension was linked with the presence and severity of OSA [37,38]. A study by Durgan *et al*. [20▪] suggested that gut dysbiosis contributes to OSA-associated hypertension. In this study, rats were implanted with an endotracheal obstruction device and were fed with high-fat diet, to mimic the human condition in which OSA is often accompanied by obesity and other features of the metabolic syndrome. The combined intervention caused hypertension that did not appear in control groups treated with endotracheal obstruction device or high-fat diet alone. Administration of antibiotics prevented elevation in BP, suggesting a potential role of the microbiota in mediating hypertension in this model. Analysis of microbiome composition in rats featuring OSA-induced hypertension revealed a reduced relative abundance of three main taxa in comparison with sham rats fed high-fat diet: *Clostridiaceae, Dehalobacterium* and *Holdemania*. In a search for a causative relation between the microbial composition and hypertension in this model, fecal microbiome was transferred from OSA induced-hypertensive or from control rats into untreated rats, followed by induction of OSA in recipient rats under normal diet conditions. Although recipient rats implanted with microbiota from control donors did not exhibit change in BP, rats receiving microbiota from OSA-induced hypertensive donors exhibited increased BP 7 and 14 days following OSA induction. A detailed microbiome analysis of the OSA-microbiome implanted rats showed an increase in the relative abundance of bacteria from the family *Coriobacteriaceae*, which contains lactate-producing genera, and an about four-fold decrease in the relative abundance of the *Eubacterium*, known to convert lactate to butyrate. Collectively, these results suggest that apnea-induced hypertension is associated with a decrease in bacteria involved in butyrate production and an increase in bacteria involved with lactate production. Moreover, it appears that in rat models, hypertension is associated with gut dysbiosis, akin to observations in other features of the metabolic syndrome [1–5]. Hypertension-associated dysbiosis is characterized by decreased SCFA production [21▪], change in the *Firmicute/Bacteroidetes* ratio [20▪,21▪,22▪▪] and decreased bacterial richness [20▪,21▪,22▪▪]. In some of the studies, a causal role of the microbiome was demonstrated by antibiotic treatment or fecal transfer experiments [20▪,22▪▪,39]. Other microbiome mechanisms of potential contribution to hypertension, such as its modulatory effect on the immune response, were suggested but not sufficiently studied. Interestingly, toll-like receptor (TLRs) activation was shown to contribute to elevated arterial pressure and vascular dysfunction. In the SHR model, induction of low-grade inflammation was suggested to play a role in the augmented vascular contractility displayed in these rats [40–42]. Future studies utilizing immune perturbed animal models such as TLR-deficient mice might shed light on potential involvement of the microbiome-immune axis in BP regulation.

HUMAN STUDIES ASSESSING THE MICROBIOME ROLES IN HYPERTENSION

The potential role of the microbiome in regulating human BP and causing hypertension has been scarcely studied to date. Hinting that gut dysbiosis is associated with hypertension in humans, gut microbiome composition analysis of 10 patients with normal SBP (119 ± 2 mmHg) and seven patients with elevated SBP (144 ± 9 mm Hg) revealed a decreased bacterial richness and altered bacterial compositions, as demonstrated by weighted UniFrac analysis in hypertensive individuals compared with normotensive controls [22▪▪]. Specific differences between bacterial composition of hypertensive and control patients were not specified in this study. In a different study, an interesting association was noted between levels of subgingival periodontal bacterial abundance and the prevalence of hypertension, possibly associating periodontal microbiome changes with hypertension [43]. In this study, subgingival plaque sampling revealed increased colonization by periodontitis-causing bacteria, including *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola,* to be associated with elevated BP. Collectively, few human studies have looked into a potential involvement of the microbiome in hypertension and in particular into causative associations and their putative mechanisms. Further studies are merited to evaluate whether such association exists in humans, and its possible contribution to the pathogenesis of essential hypertension.

MECHANISMS OF MICROBIOME–BLOOD PRESSURE INTERACTIONS

The gut microbiome can produce, modify and degrade a large repertoire of small molecules, collectively termed metabolites, which may play important roles in metabolic processes. Among the most studied metabolites are bile acids, vitamins, amino acids and SCFAs, which harbor immune-modulating properties [44]. For example, dietary fiber fermentation by colonic bacteria yields SCFAs; *Bacteroidetes* phylum members produce high levels of the SCFAs acetate and propionate, whereas bacteria of the *Firmicutes* phylum produce high amounts of butyrate [45]. Germ-free mice do not produce SCFAs because of a lack of enteric microbial colonization [46]. SCFAs have an anti-inflammatory impact on both colonic epithelium and immune cells [47–50], and were recently found to bind and activate members of the G protein receptor family to moderate immune signaling [51,52]. Interestingly, SCFAs such as acetate, propionate and butyrate are vasorelaxant *in vitro*. Butyrate and propionate induced dilation of human colonic arteries [26] and featured vasodilatory ability on caudal artery precontracted with KCl, phenylephrine, arginine vasopressin or prostaglandin F2α [27]. Acetate, which has been widely used as the source of buffer in hemodialysis, was linked to the development of symptomatic hypotension, vasodilatation, increased cardiac output and hypoxemia during dialysis [28]. Such events are much less common with the use of bicarbonate-based dialysis buffers [53].

Interestingly, the SCFA olfactory receptor 78 (Olfr78), a G-protein-coupled receptor expressed in olfactory neurons that participates in odorant sensing, is also expressed in the kidneys, where it regulates BP. Olfr78 appeared to be also expressed in smooth muscle cells of the kidney vasculature, including the glomerular afferent arteriole, where it binds acetate and propionate to regulate glomerular filtration rate and renin release [30]. Administration of propionate to normal mice reduced BP by about 20 mmHg, lasting for approximately 2 min and recovering after 5 min. Propionate treatment of Olfr78-deficient mice induced a two-fold higher hypotensive effects compared with wild-type littermates, indicating a role for Olfr78 in BP regulation.

The SCFA receptors Gpr41 and Gpr43 (also called free fatty acid receptor 3 or FFAR3 and FFAR2, respectively) are also expressed in the renal vasculature. Propionate administration to Gpr41-deficient mice induced BP elevation, suggesting that Gpr41 is needed to negate a pressor response to SCFA. Supportive evidence for microbiome-derived SCFA regulation of BP through Olfr78 and Gpr41 came from the finding that oral antibiotic administration was associated with significantly increased SBP, DBP and arterial BP in Olfr78-deficient mice, but not in wild-type mice [54]. More research is needed to find additional metabolites that mediate BP regulation by the microbiome.

MICROBIOME MODULATION FOR THE TREATMENT OF HYPERTENSION

Elevated BP is usually treated with a combination of life style modifications including weight loss, reduced sodium intake, increased physical activity, limited alcohol consumption and nutritional interventions, such as the Dietary Approaches to Stop Hypertension diet [12,13], coupled with a large arsenal of antihypertensive interventions, often given in combinations and collectively utilized in both prevention and treatment of hypertension [55–57]. Targeting the microbiome as a means of hypertension treatment and using microbiome features as a means of personalizing hypertension drug selection are the subject of ongoing research, as described below.

As early as the 1990s, sour milk fermented by *Lactobacillus helveticus* and *Saccharomyces cerevisiae* was suggested to reduce angiotensin I-converting enzyme (ACE) activity in rat aortas, reducing BP by about 20 mmHg, without affecting the rats' weight [58]. ACE converts the hormone angiotensin I to the active vasoconstrictor angiotensin II, which leads to the constriction of blood vessels and to BP elevation. Moreover, ACE inactivates the vasodilator peptide bradykinin. A first-line approach in hypertension treatment includes a family of drugs inhibiting ACE activity or its downstream signaling. Milk fermentates were screened for their ability to inhibit ACE activity *in vitro* [59], with multiple fermentate strains shown to effectively inhibit ACE activity. Two strains of *Lactobacillus helveticus fermentates* were found to be the most potent ACE inhibitors (40% reduction), and when prefed to rats, demonstrated a 30% reduction in BP compared to control rats upon angiotensin injection, constituting the first in-vivo demonstration of fermented milk effect on ACE. Furthermore [60], *Lactobacillus paracasei* and *Lactobacillus plantarum*-fermented milk was shown to inhibit ACE and γ-aminobutyric acid activity, and when administered to hypertensive rats, decreased SBP and DBP. Either a single or chronic administration of the fermented milk reduced BP.

The means by which bacteria-fermented milk inhibits ACE activity were suggested to involve proteolytic activity of endogenous milk enzymes

and enzymes from microbial cultures, which collectively catabolized proteins into hypotensive peptides during fermentation. These bacterial enzymes include cell wall proteinases, digesting proteins into peptides as an energy source (reviewed in [61]). Two of these peptides produced by *Lactobacillus helveticus*-fermented milk were identified, purified and sequenced by Nakamura *et al.* [62]. The peptides that were identified to have the sequences Val-Pro-Pro and Ile-Pro-Pro inhibited 50% of ACE activity at μM concentrations, and were found to be absorbed in rats following fermented milk digestion [63]. A human study examining *Lactobacillus helveticus*-fermented milk effects was conducted in 36 elderly hypertension patients in Japan [64]. The patients received 95 ml of fermented milk or placebo per day for 8 weeks. The fermented milk reduced SBP and DBP in the treated groups as compared to placebo. In the fermented-milk group, SBP and DBP decreased significantly 8 weeks after ingestion by 14.1 +/− 3.1, and 6.9 +/− 2.2 mmHg, respectively. No significant changes in BP were observed in the placebo group. A larger study examined the effect of powdered fermented milk with *L. helveticus* on 40 individuals with high-normal BP and 40 individuals with mild hypertension [65]. In this study, patients were divided into placebo or treated groups receiving tablets containing powdered fermented milk with *L. helveticus* daily for 4 weeks. During the treatment, the decrease in SBP of 11.2 mmHg and DBP of 5.0 mmHg in the fermented milk groups were higher than in the placebo group. At the endpoint of this experiment, the DBP of the treated normotensive group was lower than the placebo group, but there was no significant change in SBP. In the hypertensive group, SBP but not DBP decreased significantly. Following these early results, multiple intervention studies assessing the effects of fermented milk products on hypertension were conducted. However, a 'European food and safety authority' review concluded that sufficient evidence connecting the consumption of antihypertensive peptides and reduced hypertension were not found [61]. Other probiotic supplements, such as yogurt and soymilk, were tested for their effects on hypertension. However, more experimental evidence is needed to establish their efficacy (reviewed in [66]). The regulation of hypertension by probiotics is probably linked to additional mechanisms other than the renin–angiotensin system described above. More research is needed to understand whether probiotics administration affects microbiome-induced beneficial reduction in BP, through mechanisms and modalities described in this review.

Another way in which the microbiome can be manipulated is by prebiotic supplementation. β-Glucan is a major soluble fiber found in oat and barley. Its consumption has been suggested to reduce plasma cholesterol, glycemic responses and weight [67–69]. Wang *et al.* [70] examined whether β-glucans of various molecular weights shift gut microbiota composition and whether the shift correlated with reduced cardiovascular disease (CVD) risk factors, including hypertension. Consumption of high molecular weight (HMW) β-glucan increased *Bacteroidetes* and decreased *Firmicutes* abundance. The increased genus *Bacteroides* and reduced genus *Dorea* were inversely related to BP. Consumption of HMW β-glucan for 35 days was able to alter the gut microbiota, and the altered microbiota were linked with a favorable shift in CVD surrogates. Currently, at least two ongoing clinical trials are assessing the effect of probiotic bacteria or of β-glucans consumption on the intestinal microbiota for the treatment of hypertension, whereas another trial is assessing the role of life style modification of diet, exercise and stress management on microbiome composition (https://clinicaltrials.gov, NCT02041104, NCT02050607 respectively). The quantitative contribution of various microbiome-associated interventions to BP lowering remains to be studied. Likewise, the kinetics of various microbiome-related interventions greatly varies. Although probiotic usage (such as *Lactobacillus*), antibiotics and fecal transfer are associated with a relatively slow BP alteration (weeks–months), the use of bacterial metabolites such as SCFA was suggested to be effective within minutes of administration. More research is needed in understanding the long-term extent, sustainability and kinetics of microbiome-targeting therapeutic strategies in BP treatment.

MICROBIOME CHARACTERIZATION AS MEANS OF PERSONALIZING ANTIHYPERTENSIVE TREATMENT

In recent years, the microbiome was shown to constitute a unique 'fingerprint marking', which may contribute to interindividual phenotypic variation in disease manifestations, prognosis and even response to treatment. For example, the gut microbiome has been recently suggested to affect susceptibility to multiple disorders such as obesity [71,72], type I diabetes mellitus [73▪,74,75], colorectal cancer [76–80] and inflammatory bowel disease [81,82]. These studies indicate that characterization of microbiome patterns can potentially serve as a noninvasive biomarker for disease phenotype in addition to host genetics. A direct prospect of these findings is the potential use of individual microbiome compositional and functional

characteristics as a means of stratifying treatment and predicting treatment responsiveness. This may enable harnessing the microbiome as part of 'personalized medicine' in reducing disease risk, improving diagnosis, enhancing treatment and, whenever possible, preventing or delaying disease onset.

This prospect is of particular interest when assessing individual drug responsiveness, as the gut microbiota is increasingly found to influence the activity of drugs by chemically modifying, metabolizing them or by affecting their bioavailability. The topoisomerase 1 inhibitor chemotherapeutic agent irinotecan, for example, used to treat patients with colon, lung and brain cancers, is known to cause severe diarrhea following gut commensals modification: *in vivo*, the prodrug irinotecan is metabolized into its active compound SN-38G, which is processed in the gut into SN-38 by bacterial β-glucuronidase, the latter responsible for large amount of intestinal side-effects [83]. The glycoside digoxin, which is commonly used to treat heart failure and arrhythmias, has lately shown to be metabolized by gut microbiota to its inactive form dihydrodigoxin. Digoxin acts by targeting Na^+/K^+ ATPases in cardiac myocytes and elevating intracellular Ca^{2+} levels. Actinobacterium *Eggerthella lenta* was found to participate in digoxin reduction to its inactive form by a mechanism involving an operon that is activated by digoxin and inhibited by arginine. Germ-free mice fed a high protein diet (rich in arginine), maintained high levels of digoxin in urine and serum, indicating decreased digoxin metabolism [84]. These results emphasize the necessity to investigate not only the host's, but also the microbiome expression profile in elucidating complex phenomena dictating drug availability, efficacy and side-effects.

Likewise, several medications commonly administered to patients suffering from features of the metabolic syndrome, including the antidiabetic drug metformin [85] and the lipid-lowering drug simvastatin [86], were suggested to be modulated by the gut microbiome. Simvastatin, for example, lowers cholesterol through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity. Its levels are modulated by microbiome-modulated bile acids, such as lithocholic-acids, glycolithocholic-acids and taurolithocholic-acids, which negatively correlated with simvastatin response [86]. Although individual response to antihypertensive intervention is notoriously unpredictable, there are no published studies to date, to the best of our knowledge, assessing or predicting the effects of the microbiome on the availability or activity of antihypertensive drugs.

CONCLUSION

Among the increasing number of diseases found to be associated with microbiome changes, hypertension was directly and indirectly linked with dysbiosis. Future research is needed to validate these associations, elucidate the mechanisms underlying the causes of dysbiosis and whether it indeed plays a causative role in BP regulation, or individualized responsiveness to antihypertensive drugs. If such causal links, and their mechanisms, are documented and deciphered, microbiome characterization may enable future personalized screening of drug efficacy, thereby enabling individualized tailoring of personalized treatment combinations. Furthermore, microbiome composition and function may be manipulated by probiotics, prebiotics and fecal microbiome transplantation, potentially modifying its effects on BP control. With that said, skepticism is warranted until high-quality, mechanistic and casual evidence is introduced that would enable to reproducibly quantify the microbiome effect on BP control and to harness it toward human clinical use.

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Conflicts of interest

There are no conflicts of interest.

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