Review

The Gastrointestinal Tract: an Initial Organ of Metabolic Hypertension?

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Abstract
Hypertension is an important global public-health challenge because of its high prevalence and concomitant risks for cardiovascular and kidney diseases. More than 60% of the risk factors for hypertension are associated with metabolic disorders. Furthermore, many metabolic risk factors can directly cause the vascular dysfunction and the elevated blood pressure. Metabolic disorders not only increase the risk for hypertension but also participate in the development of hypertension. Thus, some types of hypertension induced by metabolic disturbances can be defined as metabolic hypertension. However, the pathogenesis of metabolic hypertension remains largely unknown. The gastrointestinal tract is a unique gate through which external food, metabolites, and microbes enter the human body. Thus, metabolism-related risk factors may affect blood pressure through the gastrointestinal tract and alter processes such as taste perception, mucosal absorption, gut hormone homeostasis, GI nerve activity, and gut microbiota. Meanwhile, gastrointestinal intervention through dietary approaches, gut microbiota modification, and metabolic surgery could profoundly improve or remit the vascular dysfunction and metabolic hypertension. It suggests that the GI tract could be an initial organ of metabolic hypertension. However, more clinical and basic studies are necessary to further validate this novel concept.

Introduction
Hypertension, defined as a condition associated with ≥140 mm Hg systolic blood pressure (BP) or ≥90 mm Hg diastolic BP, is an important global public-health challenge because of its high prevalence and concomitant risks for cardiovascular and kidney diseases.
Hypertension is identified as the leading risk factor for mortality and is ranked as the third most frequent cause of disability-adjusted life-years [2]. Hypertension affects more than 1 billion adults worldwide, and this number is predicted to increase by approximately 60% to a total of 1.56 billion in 2025 [1]. The prevalence of hypertension in developed countries is 37.3%, and the prevalence is 22.9% in developing countries [2]. 28% of American adults and a similar proportion of the adult Western European and Canadian populations have essential hypertension [3]. The absolute number of hypertension patients is considerably higher in developing countries because of the larger population, as in China where 26.6% of adults suffer from hypertension [4, 5]. More than 60% of the risk factors for hypertension are associated with metabolic disorders [6]. Metabolic abnormalities not only increase the risk for hypertension but also directly cause high blood pressure. Therefore, hypertension due to metabolic disturbances can be defined as metabolic hypertension [7]. According to the types of metabolic abnormalities, metabolic hypertension mainly includes obesity-related hypertension, diabetic hypertension, familial dyslipidaemia-associated hypertension, metabolic syndrome, hypertension with hyperhomocysteinaemia, hypertension with hyperuricaemia, salt-sensitive hypertension and so on [7].

**Metabolic risk factors play a crucial role in the pathogenesis of metabolic hypertension**

The initiating etiology and pathogenesis of essential hypertension remain largely unknown [8]. Currently, the pathogenesis of hypertension is thought to be associated with genetic and environmental factors as well as the interactions among the two. Major risk factors for hypertension include stress, lack of physical exercise, obesity, excessive consumption of carbohydrates and alcohol, and diets high in fat and salt [9]. Among these risk factors, most are linked with metabolic disturbance. These metabolism-related risk factors could play a predominant role in the development of hypertension [10]. Epidemiological studies have shown that obesity is associated with an increasing prevalence of hypertension and the relationship between body mass index (BMI) and BP appears to be almost linear in different populations [11]. Weight loss prevents the development of hypertension [11]. A substantial number of studies have found that diabetes mellitus is commonly concomitant with hypertension, independent of age and obesity [12]. The prevalence of hypertension is higher among diabetics than the general population [13]. Approximately three out of four patients with type 2 diabetes have hypertension [14]. Treated or untreated hypertension patients are usually insulin-resistant, hyperglycemic, and hyperinsulinemic [15]. Hypertension complicated by insulin resistance and hyperinsulinemia can also be observed in normal rats fed a fructose-enriched diet [15]. Clinical studies have demonstrated that high-fat meals impair endothelial function in humans [16]. Some evidence suggests an association between hypertension and lipid abnormalities [17]. Hypertension is more frequently observed in hypercholesterolemic subjects compared with normal controls [18]. High-sodium or low-potassium diets are well-known environmental factors for hypertension, especially in some hypertensive patients who are salt sensitive [19]. Furthermore, hypertension often occurs with dyslipidemia, insulin resistance, glucose intolerance, and obesity, which are a manifestation of metabolic syndrome. Currently, the incidence of hypertension without any metabolic risk factors is less than 20% [9]. Thus, we introduce the concept of metabolic hypertension. These findings indicate that metabolic disturbances play a critical role in the pathogenesis of metabolic hypertension.

**The gastrointestinal tract is an important organ involved in metabolic hypertension**

The gastrointestinal (GI) tract is a unique gate through which external food and microbes enter the human body [20]. Enterogenous factors such as gut hormones, GI nerve
innervations, and gut microbiota have potential effects on BP regulation [21-26]. Daily food and medicine intake may influence these factors and contribute to the pathogenesis of metabolic cardiovascular diseases, including metabolic hypertension.

**GI hormones in BP regulation**

The gut hormones play a critical role in the regulation of metabolic homeostasis. GLP-1, a gastrointestinal hormone, is released in response to the presence of food in the distal small intestine. It has a glucose-dependent insulinotropic action on pancreatic β-cells and inhibits gastric emptying. Both animal and human studies have suggested a role for GLP-1 in water and salt homeostasis [27]. GLP-1 might protect type 2 diabetes patients against the development of hypertension and its related cardiovascular diseases [27-29]. Ghrelin and leptin have opposite effects on energy balance and also participate in cardiovascular homeostasis [30]. Ghrelin acts as a cardioprotective factor through central and peripheral mechanisms, including negative inotropism, vasodilation, and inhibition of apoptosis and inflammation in cardiomyocytes and endothelial cells [31-35]. Increased circulating leptin levels were found in both hypertensive animal models and patients, suggesting a possible correlation between hyperleptinemia and hypertension [36-39]. Hyperleptinemia might be linked to elevated sympathoexcitatory mechanisms in obesity-related hypertension [40]. Leptin has two opposite roles during BP regulation. Leptin exerts a hypertensive effect due to sympathetic activation [41]; meanwhile, it also mediates vasodilatation via the release of NO and endothelial-derived hyperpolarizing factor in vascular walls [42]. Recently, a novel role for leptin in mediating the increased blood pressure in obese individuals was found [43]. This effect of leptin on BP was mediated by neuronal circuits in the dorsomedial hypothalamus [43]. Furthermore, plasma leptin level was associated with cardiac autonomic dysfunction in patients with type 2 diabetes [44]. Cholecystokinin (CCK) was shown to induce a centrally mediated bimodal sympathetic reflex in response to activation of CCK1 receptors located in the subdiaphragmatic vagal afferents, resulting in a modest hypotensive response accompanied by splanchnic and renal sympathoinhibition and simultaneous lumbar sympathoexcitation [45]. Gastrin, an effector of the gastro-renal axis, can stimulate the gastric receptor in the renal proximal tubule cells and promote natriuresis. The aberrant interaction between the renal gastric receptor and D1 dopamine receptor may contribute to the pathogenesis of hypertension [46]. These studies suggest that gut hormones also participate in BP regulation.

**Gut sympathetic nerve activity in hypertension**

Increased sympathetic activity and impaired sympathoinhibition are tightly linked to the development of hypertension and cardiometabolic diseases [40, 47]. Many factors, including baroreflex dysfunction, hyperinsulinaemia and insulin resistance, and dysfunction in both the hypothalamic-pituitary-axis and the renin-angiotensin-aldosterone system, contribute to elevated sympathetic nerve activity in obesity-related hypertension [48]. The renal and splanchnic vascular beds, which are controlled by abdominal sympathetic nerve, play important roles in cardiovascular homeostasis. Blood flow to these vascular beds is significantly lower in hypertensive patients [40]. Selective renal or splanchnic denervation in hypertensive patients could achieve sustained reduction in BP [49, 50]. Some GI hormones exert important functions in cardiovascular regulation through sympathetic control of renal and gastrointestinal blood flow. Gastric leptin elicited renal sympathoinhibitory responses and vasodilator responses in the renal vascular bed, which were attenuated in obesity-prone rats [51]. The splanchnic sympathoinhibitory effects of leptin and CCK were also blunted in rats fed on high-fat diets [52]. These blunted sympathoinhibitory responses were associated with blunted responses in the rostroventrolateral medulla (RVLM), which are thought to govern sympathetic vasomotor outflow to the GI and renal vascular beds, resulting in withdrawal of sympathetic vasomotor tone to these areas and promotion of vasodilatation [40]. The effect of GI autonomic nerves on BP regulation is also well documented that an appropriate amount of electrical stimulation to the central cut end of the abdominal vagus
raised BP by 30 mmHg [53]. Vagal modulations including baroreflex activation therapy, renal sympathetic denervation, and direct vagal nerve stimulation efficiently lowered BP, especially in patients with resistant hypertension [54]. Vagal remodeling and denervation have been observed following metabolic surgery; thus, it was proposed that metabolic surgery might alter the existing gut-brain communication and result in cardiometabolic benefits [55]. These results suggest that GI sympathetic activity plays an important role in the development of hypertension.

Unhealthy dietary factors contribute to metabolic hypertension

Many epidemiological studies have shown that the consumption of a Western diet, such as a diet high in meat and fried foods, contributes to the higher incidence of metabolic syndrome [56]. One study also suggested that participants in the highest quartile of Western dietary pattern scores had significantly higher BP, serum total cholesterol, and triglyceride levels than did those in the lowest quartile [57]. Several population studies found that consumption of carbohydrates or beverages containing high sugar are associated with increased weight gain, serum uric acid levels, systolic BP, and risk of type 2 diabetes [57-61]. In children, increased consumption of added sugars may be associated with adverse cardiovascular health factors, specifically elevated diastolic BP and triglyceride levels [62]. Saturated fat consumption raises plasma LDL in humans and causes vascular injuries [63]. However, long-term calorie restriction is highly effective in lowering serum total cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin, and both systolic and diastolic BP [64]. Even the circadian rhythm of energy and macronutrient intake affects cardiometabolic risk factors. Higher energy intake at breakfast is related to lower hypertension prevalence [65]. Greater energy intake in the evening is related to higher hypertension prevalence and incidence and greater increases in BP [65]. Mounting evidence suggests an interaction between salt intake and hypertension [66]. High salt intake is an important risk factor for hypertension. The amount of salt in the diet may play a critical role in determining blood pressure levels within a particular community. Some individuals are sensitive to salt intake and develop salt-sensitive hypertension. A family-based association study found that genetic variants in the RNLS gene were associated with BP responses to dietary salt intake [67]. High-salt intake increased vasoconstrictor 20-hydroxyeicosatetraenoic acid excretion, which potentially mediated the early-phase high-salt diet-induced BP elevation [68]. Up-regulated intrarenal rennin-angiotensin system might contribute to high-salt induced hypertension and renal damage [69]. These studies indicate that unhealthy dietary factors result in metabolic hypertension via the GI tract.

Taste perception and hypertension

Taste perception is an important sensory function of the GI tract. The taste buds on the anterior two-thirds of the tongue are innervated by the chorda tympani nerve, and those on the posterior one-third of the tongue are innervated by glossopharyngeal nerves (GPNs). Sensory neurons of the GPNs are localized to the petrous ganglion. An inverse relationship was observed between the neuron number of the petrosal ganglion and blood pressure values, with potential implications for the study of hypertension etiology [70]. Nifedipine, a calcium channel antagonist, exerts its antihypertension role partly through stimulating the GPNs [71]. This antihypertensive effect decreased after GPN denervation in accordance with the increased degeneration of neurons in the petrous ganglion [71]. Salt taste sensitivity is the capacity to identify the flavor of salt. It is possible that salt taste sensitivity can influence salt consumption, which is associated with hypertension [72]. An epidemiological study found salt taste impairment was associated with increased prevalence of hypertension in Japanese women [73]. 24-hour urinary sodium and urinary potassium excretion levels were higher in hypertensive subjects than in non-hypertensive subjects [74]. The high salt threshold group also had significantly higher 24-hour urinary sodium [74]. Several studies have shown
elevated thresholds for salt perception in hypertensive patients [72, 75, 76]. After adjusting for gender, age, sedentary lifestyle and BMI, adolescents with high salt taste thresholds have higher diastolic blood pressure [77]. Another study showed a negative correlation between blood pressure and salty taste sensitivity in adolescents [78]. Angiotensin II (AngII), a major mediator of body fluid and sodium homeostasis, was found to modulate salty and sweet taste sensitivities. This AngII modulation critically influenced GI ingestion behaviors in mice [79]. The specific inhibition of amiloride-sensitive salt taste sensitivity by AngII may contribute to increased sodium intake [79]. AngII may also contribute to increased energy intake by enhancing sweet responses [79]. Increased levels of aldosterone and AngII were associated with inhibition of salty taste sensitivity [80]. In addition, some hypotensive drugs can decrease taste sensitivity or result in total loss of taste perception [81]. Taste perception is also modulated by gastric hormones, such as ghrelin [82]. Salty and lipid taste sensitivity was attenuated in ghrelin knockout (ghrelin−/−) mice [82]. These results suggested that abnormal taste perception might be involved in hypertension by increasing salt intake.

Gut microbes in cardiometabolic diseases

The human gut is densely populated by trillions of symbiotic microbes. Symbiotic microbes provide protection from invading pathogens and aid in nutrient absorption [83]. Diet is regarded as the main factor contributing to the make-up of the gut microbiota, and the gut microbes influence eating activity [84]. The link between the gut microbes and the development of cardiometabolic disease is a popular topic [85]. Studies in both humans and mice show that gut microbes influence metabolic processes, such as energy extraction from food, and should be regarded as an environmental factor that contributes to obesity and its comorbidities, such as diabetes and cardiovascular disease [85]. Alterations in gut microbiota can occur as a result of changes in the composition or function of the gut microbiota as well as microbiota-host interactions [86]. It is well known that changes in food production and preparation profoundly impact gut microbes [84]. Indeed, long-term dietary habits show a considerable effect on human gut microbiota. One study showed that children in a rural African village who consumed a high-fiber diet had low levels of Firmicutes and increased levels of Bacteroidetes in their fecal microbiota compared with Italian children, who consumed a modern Western diet and had high levels of Enterobacteriaceae [84]. The level of short-chain fatty acids was higher in the children from the rural African village, and short-chain fatty acids have profound effects on gut health, as energy sources, inflammation modulators, vasodilators and regulators of gut motility and wound healing [84]. These alterations in gut microbiota composition may contribute to the host's metabolic phenotype [85]. Furthermore, obese humans and obese mice had different gut microbe populations when compared with those of lean individuals [87, 88]. The caecal microbiota of genetically obese ob/ob mice contains more Firmicutes and fewer Bacteroidetes than do their lean WT littermates [89], and the same trend is observed in the fecal microbiota of obese humans [90]. The mix of gut microbes from obese individuals could extract a small amount of calories from what would normally be undigested food, and these calories may contribute to weight gain [87, 88]. Mice lacking Toll-like receptor 5 (TLR5), which is a component of the innate immune system expressed in the gut mucosa, exhibited hyperphagia and had many characteristics of metabolic syndrome, including hyperlipidemia, hypertension, insulin resistance, and obesity [91]. These metabolic abnormalities correlated with changes in the gut microbiota [91]. By transferring the gut microbiota from TLR5-deficient mice to WT germ-free mice, many features of metabolic syndrome were recapitulated [91]. These results support the view that the gut microbiota contribute to metabolic disturbances. Currently, how gut microbiota contribute to the development of hypertension remains unknown.
Gastrointestinal intervention ameliorates hypertension

Currently, therapeutic lifestyle changes, medication and interventional treatment are the three major management strategies for hypertension. However, these treatments are closely associated with gastrointestinal intervention.

Dietary approaches to stop hypertension

A wealth of evidence strongly supports the fact that multiple dietary factors affect BP [10]. It is noteworthy that these dietary factors mediate their effect through gastrointestinal absorption. Nutritional compounds might modulate the development of metabolic diseases [92]. Nutritional approaches, such as increased vegetable, fruit and potassium consumptions as well as reduced sodium chloride and alcohol intake, have been recommend to prevent and treat hypertension. The well-known trial Dietary Approaches to Stop Hypertension (DASH) has shown that healthy dietary factors such as a diet low in fats and rich in fiber and high in low-fat dairy products, fruits, and vegetables play an important role in hypertension control. Thus, lifestyle modifications should be the initial treatment strategy for lowering BP [93]. In addition, some specific nutrients were found to benefit BP control. Loss of zinc homeostasis may participate in BP regulation and hypertension pathogenesis [94]. Dietary zinc intake was inversely associated with SBP in obese Korean women after adjusting for body weight, energy intake and sodium consumption [95]. Oral administration of zinc also improved type 2 diabetes and metabolic syndrome in mice [96]. In observational studies, significant inverse associations between BP and magnesium, potassium, and calcium consumption have also been reported [97]. Capsaicin, a major pungent ingredient in hot peppers, which is consumed worldwide, exerts beneficial effects on cardiometabolic diseases. The transient receptor potential vanilloid 1 (TRPV1) cation channel activated by capsaicin exerts antihypertension effects in both genetically hypertensive rats and high-salt-intake induced hypertensive mice [98-100]. Importantly, dietary capsaicin was shown to further reduce hypertension-related cardio cerebrovascular risks [101], delay the onset of stroke in stroke-prone spontaneously hypertensive rats, and attenuate cardiac hypertrophy in high-salt fed...
mice [102, 103]. Furthermore, TRPV1 activation by capsaicin can also improve glucose and lipid metabolic profiles and attenuate hyperglycemia- and hyperlipemia-induced vascular damages in rodents [104-108]. Activation of TRPV1 by dietary capsaicin contributes to vascular and metabolic benefits and may represent a promising target for therapeutic intervention of cardiometabolic diseases. Menthol, a compound in mint with a naturally cold sensation, was shown to improve flow-mediated dilatation and moderately lower BP levels in prehypertensive individuals after an 8-week consumption period [109]. Dietary curcumin, which has an antioxidant effect, can improve aging-related cerebrovascular dysfunction in rodents [110]. Resveratrol, a natural polyphenol in grapes and red wine, has been shown to have beneficial effects on glucose and lipid metabolism, vascular function, and antioxidative properties [111, 112]. A Mediterranean diet rich in resveratrol is associated with a significantly reduced risk of cardiovascular diseases [113]. Therefore, increasing healthy dietary factors and preventing harmful dietary intake through the gastrointestinal tract are key steps for the prevention of metabolic hypertension.

**Modification of gut microbiota to improve hypertension**

Interactions between gut microbiota and cardiometabolic diseases have received increased attention in recent years. The host’s metabolic abnormalities are correlated with changes in the gut microbiota. Probiotic consumption is commonly used to rebalance disturbed intestinal microbiota and to treat gastrointestinal disorders. Recent studies have shown that probiotics may improve obesity, diabetes, hypercholesterolemia, and arterial hypertension through modifications of gut microbiota [114]. A meta-analysis of randomized, controlled trials demonstrated that probiotic administration may improve BP control in humans, reducing SBP by 3.56 mmHg and DBP by 2.38 mmHg compared with control groups [115]. Subgroup analysis suggested that probiotic consumption may regulate BP by a modest degree [115]. Probiotic fermented milk, a product obtained from the fermentation of milk by the action of suitable microorganisms, may exert protective effects against type 2 diabetes, cardiovascular diseases and stroke [116]. Probiotic yogurt consumption also has an effect on lipid metabolism, significantly reducing total cholesterol and LDL-cholesterol levels [117]. Another meta-analysis of randomized placebo-controlled trials involving 702 participants suggested that probiotic fermented milk could lower BP in prehypertension and...
hypertension individuals [116]. Soy milk fermented with specific probiotics could enhance NO production and the coupled state of eNOS, which leads to vasodilation [118]. However, beneficial effects of gut microbiota modification on hypertension need to be further validated through more clinical trials and experimental studies.

**Gastric bypass surgery treats hypertension**

Gastrointestinal bypass surgery, also called metabolic surgery, is currently an effective treatment for morbid obesity and its related comorbidities [119]. Metabolic surgery includes gastric banding, gastric bypass, gastroplasty, biliopancreatic diversion and duodenal switch. Effective weight loss can be achieved in morbidly obese patients after metabolic surgery [119-121]. Mounting reports have also shown that a substantial majority of patients with diabetes, hyperlipidemia, obstructive sleep apnea, and hypertension are resolved or remitted after they underwent metabolic surgery [119-122]. A meta-analysis reported that hypertension was resolved in 61.7% of patients and improved in 78.5% of patients after metabolic surgery [119]. After metabolic surgery, antihypertensive treatment was reduced or discontinued in 70% of patients [123]. Furthermore, short- and long-term control rates of hypertension were higher in the surgery group compared with the non-surgical group [120]. The mechanisms by which metabolic surgery ameliorates hypertension are not fully understood. Several studies have suggested that BP reduction might be related to metabolic surgery-induced weight loss [122, 124]. However, clinical observations found that a quick reduction in BP could be achieved before a remarkable reduction in weight loss [125]. Thus, the beneficial effect of metabolic surgery on BP is independent of weight loss and is also independent of surgery-related trauma and energy intake [126]. Although some studies showed that changes in gut hormones, insulin sensitivity, reduction in salt intake, increased urinary sodium excretion, and changes in gut microbiota might contribute to reduced high blood pressure following metabolic surgery, the underlying mechanisms remain poorly understood [21-26, 127]. Recently, we showed that metabolic surgery efficiently lowered blood pressure and improved cardiovascular dysfunction and remodeling through inhibition of both peripheral and central sympathetic nerve activity in diabetic hypertensive patients and genetic hypertensive rats [126]. Thus, metabolic surgery might be a novel treatment strategy for the management of hypertension, especially for hypertensive patients with metabolic disorders [128].

**Summary**

The gastrointestinal tract is not only an organ involved in nutrient digestion and absorption but also has a critical role in the pathogenesis of cardiometabolic diseases, such as metabolic hypertension. Daily dietary factors and enterogenous factors such as GI hormones, liver insulin sensitivity, GI nerve innervations, and gut microbiota participate in the regulation of BP through different pathways and mechanisms. However, GI intervention through healthy dietary approaches, gut microbiota modification, and metabolic surgery profoundly improve or remit cardiometabolic disease, including hypertension. Thus, numerous clinical and basic studies indicate that GI tract could be one of organs that initiate the development of metabolic hypertension. Meanwhile, more future investigations are necessary to validate this novel concept.
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