Review Article

Salt reduction and hypertension in China: a concise state-of-the-art review

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Abstract: Hypertension (HTN) and its cardiovascular complications such as stroke and heart failure are a serious public health problem around the world. A growing number of studies confirm that salt plays an important role in the development of HTN. Increasing intake of salt leads to abnormal transport of sodium ions at the cellular level with activation of the sympathetic nervous system and renin-angiotensin-aldosterone system. Studies have shown that salt restriction can reduce blood pressure (BP) in patients with HTN, especially salt-sensitive HTN. Public health interventions to reduce salt intake, with the goal of decreasing adverse outcomes have been launched in numerous countries. In this review we will summarize the epidemiology of cardiovascular diseases and their risk factors, the relationship between salt and HTN, the effect of salt restriction on HTN and the current situation of prevention and treatment of HTN by salt reduction in China.

Keywords: Hypertension (HTN); salt sensitivity; pathogenesis; preventing and treatment

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Introduction

Hypertension (HTN) is a progressive clinical syndrome characterized by increased arterial blood pressure (BP) that can lead to cardiovascular complications such as stroke, heart failure, and aortic dissection. HTN is recognized as one of the major cardiovascular risk factors. Epidemiological investigations demonstrate that the prevalence of HTN has been increasing in China, and it is estimated that about a total of 270 million Chinese patients carried a diagnosis of HTN in 2013 (1). Although modern drug therapy for HTN has improved, morbidity and mortality associated with HTN is still significant. Furthermore, increasing data have demonstrated that HTN has become a significant burden for the Chinese society and a major concern for public health with the changes in socio-economic conditions, changes in lifestyle, and the aging of the Chinese population. Thus, exploring the pathogenesis of HTN is important to improve its prevention and treatment. In the 1970s, Kawasaki introduced the concept of salt sensitivity based on observations in individuals with more pronounced sodium storage and elevated BP following relatively high intake of salt (2). Since then a growing number of studies have confirmed that salt intake plays an important role in the development of HTN and consequently in cardiovascular diseases (3,4). Below we describe this relationship, with emphasis on the Chinese setting and efforts aiming to reduce salt intake in China.

Salt and cardiovascular diseases (CVD)

Epidemiology

CVD are a worldwide major public health problem accounting for e.g., 1.8 million premature (<75 years) death in Europe (5). Likewise in China, CVD was found to be the number one cause of death in 2012, leading to an estimated 3.5 million deaths (41% of the total causes of death) (6). Moreover, the morbidity and mortality of CVD in China remains high. The estimated number of patients with a diagnosis of CVD is about 230 million, including 200 million patients with high BP and more than 7 million

people suffering from stroke. Thus, one of five Chinese adults was suffering from CVD (7). Furthermore, assessing regional differences of morbidity and mortality data shows higher rates in northern regions compared to the south, and higher rates in urban compared to the rural areas. These differences are attributed to changes of lifestyle, socio-economic status, and the acceleration of urbanization (7). It is estimated that by 2030, the number of CVD events will increase by more than 50%, due to overall population growth and the aging population (8). Taking the expected growth in prevalence of HTN, hypercholesterolemia and diabetes into account, an increase of cardiovascular events by 73% is estimated. Without changes in prevention and treatment, the number of Chinese patients with cardiovascular disease will increase by 21.3 million, and deaths of cardiovascular disease will increase by 7.7 million in 2030 (8).

Epidemiology of HTN and salt-sensitive HTN

In China, HTN is one of the main risk factors for CVD, associated with more than 50% of CVD cases. Evidence suggests that HTN develops secondary to interplay of genetic and environmental factors, with salt intake playing an important role. In the 1970s, Kawasaki described the concept of salt-sensitive HTN. Their observations showed increased BP of hypertensive patients after relatively high salt load. Epidemiological studies have demonstrated heterogeneity of salt-sensitive HTN in different countries and ethnic groups (9). Heterogeneity also exists between normal and hypertensive populations with detection rates of 15-46% and 29-60%, respectively (10). In China, the detection rate of salt-sensitive HTN in normal populations is an average of 27.1%, but 58.7% of hypertensive patients (10). However, the awareness rate of salt-sensitive HTN is still low, mainly because of the lack of readily available diagnosis methods. Common detection methods of salt sensitivity include salt-load test and cold-pressor test. The former is complex and difficult to apply in large patient populations, the latter is a new, indirect method of detection designed according to the pathogenesis of salt-sensitive HTN and may become a routine method.

Salt sensitivity and HTN

Salt intake and HTN

Physiologically, salt plays an important role in maintaining the balance of water and fluid, and is also involved in nerve and muscle function. Excess salt intake is associated with many pathophysiological effects such as sodium and water retention, weight gain, and increased BP. In China, the book of *Yellow Emperor's Classic of Internal Medicines* recorded that salt is relevant for the pulse as early as 2,600 years ago, revealing the relationship between salt intake and HTN. With the emerging concept of salt-sensitive HTN, a growing number of animal experiments have confirmed that salt intake is an important factor for HTN. For example: a study of chimpanzees found that high salt intake progressively increased BP; and BP decreased after salt reduction for 20 months (11). At the same time, many clinical studies have confirmed that salt intake is related to the development of human HTN, and BP increases with age. For example, the Intersalt study investigated the relationship between urine sodium and the BP in 10,079 adult subjects enrolled from 52 centers in 32 countries. Standardized BP measurement, urine collection and measurements of sodium concentration were performed. The results showed that in the low-salt group, mean arterial pressure and the extent of BP increase with age was smaller. On the other hand, mean arterial pressure was higher in high salt group, and increased more with the age. The Intersalt study also demonstrated this relationship was maintained after adjusting for potential confounding factors including age, sex, weight and alcohol consumption. Similar data has been described in observational studies of Chinese subjects. For example results from the 2002 *Nutrition and Health Survey of Chinese Residents*, reported by Zhai *et al*. confirmed that dietary salt intake was significantly and positively related to BP level (12). Compared to a daily intake of 6 g/d of salt, 12 g/d of salt intake increased the risk of developing high BP by 14%, and l8 g/d of daily salt intake increased the risk by at least 27% (12). Shi *et al*. (13) investigated a population of 29,914 farmers aged 35 years or older from the rural areas of Fuxin city, Liaoning Province, from 2004 to 2005. Results show that salt intake was significantly higher in the HTN group compared to the non-HTN group, with a prevalence rate of HTN of 36.2% after adjustment, increasing as salt intake increased. However, the level of salt intake was unrelated to the severity of HTN (13). *Taiwan's Hypertension Guidelines* [2015] state that a 1 mg increase in salt intake increases systolic BP by 2.1 mmHg and diastolic BP rise by 0.78 mmHg (14).

While these data demonstrate a direct relationship between salt intake and HTN, clinical outcome data from clinical trials including INVEST [2003], ONTARGET

[2008], TNT [2009], the VALUE [2009], ACCORD [2010] and NAUIGATOR [2010] suggest that the incidence of cardiovascular events increases under a certain value of salt intake despite further decrease in BP levels, consistent with a J-curve relationship of salt intake/HTN and clinical events. However, data is incomplete and future clinical trials are necessary.

Pathogenesis of salt-sensitive HTN

The mechanisms mediating BP increases after salt intake are incompletely understood. Abnormal sodium transportation likely affects renal natriuresis and endothelial function, and activates the sympathetic nervous system (15), the renin-angiotensin-aldosterone system (16), and the endocrine system (including androgens (17) and insulin resistance), eventually resulting in the development of HTN through inflammation and oxidative stress (18). In recent years, the role of gene mutation and polymorphisms in the pathogenesis of salt-sensitive HTN has been investigated (19). Potential targets include guanine nucleotide binding protein (G protein) beta polypeptide 3 (*GNB3*) and α-adducin (*ADD1*) gene, *ACE* gene's polymorphism (such as insertion and deletion) and others. However, due to the differences of studied populations, genetic testing and analysis methods, reliable identification of candidate genes of salt-sensitive HTN is not possible and further studies are necessary. Because China is a multi-ethnic country with large regional imbalances in economic development, it is necessary to carry out research in line with our country's own characteristics for the prevention and treatment of HTN.

Salt reduction and HTN

Status of salt intake in the world

A certain amount of sodium intake is necessary to support cellular function. As described above both lack and excess of salt intake is associated with an increased incidence of cardiovascular events. Research data from NUTRICODE showed that the worldwide sodium intake was about 3.95 g/day for a person in 2010 (20). Similarly, data from the Trials of Hypertension Prevention (TOHP) I and TOHP II indicated that the optimum amount of sodium intake is in the range of 2.0-4.0 g/day. Moreover, this investigation also demonstrated that additional sodium intake of 2 g is associated with 1.65 million cases of cardiac death (21). Therefore, AHA/ACC guidelines state that sodium restriction could reduce the incidence and risk of cardiovascular events (22). In 2012, the World Health Organization (WHO) published a new guideline on sodium intake for adults and children that recommended that adults consume less than 5 g/d. Since salt sensitivity is not widely prevalent in the population, and the presence of J-curve of sodium intake exists, salt restriction to less than 2.0 g per day has been questioned (23). Moreover, some studies have showed that long-term strict salt restriction can lead to contradictory pathophysiological effects of sodium such as the activation of sympathetic and the renin-angiotesin system (RAS), the imbalance of lipid metabolism (24).

Salt intake in China

Surveys about Chinese nutrition and health have been undertaken and have indicated that daily salt intake of Chinese residents is significantly higher than the 5 g/d recommended by WHO. For example the quantity of salt intake is about 8-9 g/day in the south and 12-18 g/day in the North (25). This high-salt diet is related to a combination of cooking methods, dietary habits, folk custom and ethnic diversity. While in Europe and North America 75% of the total salt intake originates from adding salt to food during processing. Chinese residents often apply more salt or condiments containing much salt (soy sauce) to cooking compared with Western countries (26). Moreover, residents like salty food, specifically pickled food. This may be related to food production, transportation, poor storage and poor supply conditions in China.

Advantages and disadvantages of salt reduction

Increasing evidence from clinical and animal studies prove the relationship between increased salt intake and high BP. As early as 1904, Ambard and Beaujard demonstrated that high intake of dietary salt could be harmful for the body and raised BP (27). Many clinical studies have confirmed this observation. For example in the Dietary Approaches to Stop Hypertension (DASH) study, DASH diet significantly reduced systolic BP by 11.2 and 8.0 mmHg, respectively, compared with normal diet and diet rich in fruits and vegetables. In the DASH-sodium trial, researchers showed that salt reduction could lower BP. During DASH diet, systolic BP was reduced in each group and there were obvious differences between the low salt intake group and intermediate to high salt intake group (28). Furthermore, the DASH diet with a low sodium level in patients with

normal BP reduced systolic BP by 7.1 mmHg compared with the control diet with a high sodium level in patients with normal BP. In patients with HTN, the reduction was 11.5 mmHg (29). Similarly, salt reduction was also effective in adults with prehypertension and stage 1 of HTN (30). Compared with that of the control group, BP of the intermediate and lower sodium groups of each diet were significantly lower. The risk of HTN in the intermediate and lower sodium groups of each diet was much lower compared to that of the control group. Other studies have found that natives, who lived on some Pacific islands and rarely ate salt had a very low risk of HTN (31).

On the contrary, there are a few of studies that demonstrated low sodium intake might not reduce the incidence of cardiovascular diseases, but increased the plasma levels of renin and aldosterone and the adverse cardiovascular events. In 2011, Stolarz-Skrzypek and his colleagues recruited 3,681 participants without CVD, including 2,096 normotensives and 1,499 patients with BP, to investigate the relationship between the 24-hour urinary sodium excretion and BP and health outcomes. They found the decrease of systolic BP and urinary sodium excretion by the salt restriction didn't result in a lower risk of CVD complications. Conversely, low urinary sodium excretion (mean 106 mmol/d) was closely related to increasing the risk of CVD complications (32). Similarly, a study reported by Graudal *et al*. indicated that sodium reduction can increase cholesterol by 2.5%, and triglycerides by 7%, in spite of the reduced BP resulting from sodium reduction in both the normotensive and hypertensive participants (24).

Salt reduction in China

Government and health organizations

Dietary salt restriction and a healthy lifestyle has become a worldwide concern. As described in other articles of this Focus Issue, many countries around the world have taken many measures to control salt intake. The Chinese government and health organizations have begun to advocate healthy lifestyles characterized by reduced salt diet, proper nutrition, smoking cessation, limiting alcohol intake, moderate exercise and mental balance. China has also released a number of national standards, such as national standards GB/T 23789-2009 *Foods with Low-sodium Content* [2009], *China's Chronic Disease Prevention and Control Work Plan [2012-2015]* [2012] and national standards GB 28050-2011 *The General Principles of the Prepackaged Food Nutrition Labels* [2013], aiming to regulate salt intake based on scientific data with the goal to improve national health. The Chinese government has established a National Hypertension Day in 1998. In 2009, the theme of National Hypertension Day was "Salt Restriction and Control of Hypertension". In 2013, China formally released the *China Education Guide* for hypertensive patients emphasizing that salt restriction was one way of prevention and treatment of HTN (33). The Cardiovascular Disease Prevention Research Center in the Ministry of Health and the Chinese Hypertension League also published the brochure of salt and HTN in the World Hypertension Day of 2009. This information is communicated with patients by medical professionals, advocacy organizations that offer free health education, health lectures on TV, broadcast and internet. China is also conducting a nationwide survey of HTN, including salt intake level and ways to reduce salt, aiming to guide further the program of salt restriction.

Limit-salt-spoon

The Limit-salt-spoons campaign was designed to help people to reduce salt in their diets. In 2007, the Ministry of Health promoted the use of a small spoon (one spoon equals about 2 g salt) to encourage a "comprehensive healthy lifestyle". As part of the campaign, many provinces and cities, such as Shandong province, Beijing, Shanghai distributed this spoon for free, and carried out activities and projects on salt reduction. The goal was to inform people about healthy diets and reinforce behaviors to prevent and control HTN. The Shanghai 'limit-salt-spoon project' promoted public awareness of salt reduction, and salt intake dropped from 7.13 to 6.38 g/day. Moreover, many regions also conducted consulting and education about salt intake and health education. For example, Lu *et al*. gave the 'limit-salt-spoon' to community residents and taught them how to use the spoon. The authors found that salt intake were reduced after 1 month and 6 months. However, salt intake in China mainly comes from traditional cooking modes that limit the effectiveness of the 'limit-salt-spoon'. Although the limit-salt-spoon is distributed free of charge, its scope is still very small, especially in rural areas. Therefore, it is necessary to take advantages of media to further education.

Low-sodium salt

Low-sodium salt is based on sodium chloride with the addition of a certain amount of magnesium and potassium in order to improve the body's metabolism of sodium, potassium and magnesium. It is also used for prevention and treatment of HTN. Since the first standard of salt

of low sodium was first presented in China in 1994, the standard has been revised for several times. Now, it is divided into three categories: (I) class I: 10 g low-sodium salt contains sodium chloride (7.00±1.00 g), potassium chloride (2.4±1.00 g) and magnesium (0.05±0 015 g); (II) class II: 10 g low-sodium salt contains sodium chloride (7.00±1.00 g), potassium chloride (2.4±1.00 g) and magnesium (0.06±0.02 g); (III) class III: 10 g low-sodium salt contains sodium chloride (7.00±1.00 g), potassium chloride (3.00±1.00 g). Up to now, this new kind of salt has been sold in many cities, including Beijing. From the study of dietary sodium and potassium interventions in rural areas in the North of China, researchers demonstrated that mean systolic and diastolic BP decreased by 8.1/3.5 mmHg with sodium reduction. However, mean systolic and diastolic BP increased by 9.1/4.0 mmHg with high sodium intake. During high sodium intake and potassium supplementation, systolic and diastolic BP was reduced by 4.6/1.9 mmHg, compared to high sodium intake (34). These studies show that salt reduction is an effective way to prevent HTN. Furthermore, the use of low sodium/high potassium salt can lead to salt reduction in the general population (35). However, there are barriers that may limit the feasibility and/or effectiveness of introducing low-sodium salt at a population level: First, the low-sodium salt is more expensive than normal salt. Second, low-sodium salt is currently not well known to the public. Third, a significant percentage of patients with HTN are not salt sensitive, but this is probably not really an issue where we are focusing on population-wide interventions.

Conclusions

There is sufficient evidence that salt reduction can contribute to reducing BP in subjects with or without HTN. Salt reduction can be accomplished through health-education, special programs, and the use of low-sodium salt. However, China is a country with traditionally high salt diet, a large inhomogeneous population, significant imbalances in regional economical development and limited public advocacy for salt reduction. All these conditions lead to a certain gap in the control of salt and HTN in China compared with Europe and the United Stated. There is also a need for systematic data collection about the relation between salt reduction and prevention and treatment of HTN in Chinese residents and a need to further illuminate the pathogenesis of salt-sensitive HTN. Therefore, while learning from the experience of other countries as described in this Focus Issue, we need to pay close attention to our population's own characteristics and develop salt reduction strategies in accordance to our country's traditions. Such strategies will eventually improve control of HTN and the quality of life of Chinese patients.

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