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EDITORIAL

Kidney and cardiovascular risk in primary hypertension

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Abstract

In patients with primary hypertension, therapeutic strategies should be based on global cardiovascular risk profile rather than on the severity of blood pressure alone. Accurate assessment of concomitant risk factors and especially of the presence and extent of subclinical organ damage is of paramount importance in defining individual risk. Given the high prevalence of hypertension in the population at large, however, extensive diagnostic evaluation is often impractical or unfeasible in clinical practice. Low cost, easy to use markers of risk are needed to improve the clinical management of patients with hypertension. Early renal abnormalities such as a slight reduction in glomerular filtration rate and/or the presence of microalbuminuria are well known and powerful predictors of cardio-renal morbidity and mortality and provide a useful, low cost tools to optimize cardiovascular risk assessment. A greater use of these tests should therefore be implemented in clinical practice in order to optimize the management of hypertensive patients.

Key words: Hypertension; Albuminuria; Cardiovascular risk; Glomerular filtration rate; Risk assessment; Kidney

Core tip: Accurate assessment of global cardiovascular risk, including the search for subclinical organ damage is key for devising effective therapeutic strategies in patients with primary hypertension but is often unfeasible for economic and logistic reasons given the very high prevalence of this condition. Early renal abnormalities such as slight reduction in glomerular filtration rate and/or the presence of microalbuminuria are well known and powerful predictors of cardio-renal morbidity and mortality and provide the useful, low cost tools to optimize cardiovascular risk assessment. A greater use of these tests should therefore be implemented in clinical practice in order to optimize the management of hypertensive patients.

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INTRODUCTION

The worldwide prevalence of arterial hypertension, currently the most important modifiable risk factor for cardiac and cerebrovascular diseases, is going to increase dramatically over the next decades[1]. Recent surveys indicate that 30%-45% of adult population has high blood pressure (BP) in Western countries, with greater figures in at risk subgroups such as the elderlies, diabetics and patients with chronic kidney disease (CKD)[2]. Prevention and treatment of high BP therefore represent a big public health issue worldwide and a priority for many National Health Systems in developed countries.

Most International Guidelines recommend that therapeutic targets and strategies should be based not only on the severity of BP increase but rather on global cardiovascular (CV) risk profile in any given patient[2]. Accurate assessment of concomitant risk factors and especially of the presence and extent of subclinical target organ damage (OD) is of paramount importance in defining individual risk profile and therefore often becomes a key factor to improve cost effectiveness in the therapeutic algorithm[3].

Given the high prevalence of hypertension in the population however, extensive evaluation of risk factors including in-depth search for asymptomatic OD is often impractical or unfeasible both from a logistic and an economic point of view[4]. Low cost, easy to use, integrated markers of risk are therefore needed to improve the clinical management of patients with hypertension[5].

MILD RENAL ABNORMALITIES: USEFUL CLINICAL TOOLS FOR CARDIOVASCULAR RISK STRATIFICATION

Even modest abnormalities of renal function, such as the presence of microalbuminuria or a slight reduction in glomerular filtration rate (GFR), have been shown to predict future cardiovascular events and death[6]. While these two features of CKD do not always coexist in the same patient, they are thought to reflect, at least in part, different pathogenic mechanisms and to carry independent predictive power in patients with high BP[7].

Microalbuminuria is currently regarded as an early sign of widespread vascular damage[8]. It has been shown to cluster with a variety of unfavourable risk factors such as metabolic syndrome, lipid abnormalities, hyperuricemia as well as with a greater haemodynamic load and blood pressure profile[9]. Furthermore, it has been shown to be an integrated marker of OD, as its presence often entails the concomitant occurrence of left ventricular hypertrophy (LVH) and systemic atherosclerosis (Figure 1)[10,11]. Increased urine albumin excretion (UAE) is a strong independent predictor of CV events, renal complications and death[12]. The relationship between UAE and risk is linear and holds also for albuminuria values well within the normal range[6]. These data, together with the relatively low cost and wide availability of this test, make searching for albuminuria an ideal screening and diagnostic tool to be used in clinical practice[5].

Even a mild reduction in GFR entails a cluster of unfavourable haemodynamic and metabolic modifications that negatively impact global and cardiovascular prognosis in hypertensive patients[13]. In fact, CKD, albeit often asymptomatic and therefore largely undetected in clinical practice, is known to bring about a number of atherogenic mechanisms such as insulin resistance, secondary hyperparathyroidism, vitamin D deficit, anaemia, subclinical inflammation, increased oxidative stress, lipids abnormalities, mild hyperuricemia and endothelial dysfunction[14].

Needless to say that the coexistence of GFR reduction and increase in UAE, a condition thought to occur in 20%-30% of CKD patients, entails an even higher risk as the two components of CKD retain independent prognostic power. Hence, GFR and UAE should be measured together to improve the assessment of risk[13].

SHOULD WE LOOK AT CHANGES IN ALBUMINURIA TO DETECT CHANGES IN CARDIOVASCULAR RISK?

The presence of subclinical OD at the cardiac, vascular and renal level has traditionally been regarded as an intermediate step between long-term exposure to risk factors and the incidence of major events[15]. As the development of OD signals a condition of greater risk, so prevention or regression of OD as a result of an effective treatment has been demonstrated to entail a parallel reduction of risk. Thus, regression of LVH has been shown to be associated with a better prognosis and has been proposed as an independent therapeutic target[16].

More recently, it has been suggested that albuminuria changes under treatment may provide additional information on the effectiveness of treatment[2,17]. Several clinical trials however, have yielded contrasting data on this issue. Thus, results of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study indicated that on-treatment modifications of UAE go in parallel to the incidence of fatal events[17,18]. On the contrary, in the ACCOMPLISH trial, antihypertensive treatment with angiotensin converting enzyme-inhibitors (ACE-I)/Calcium Channel Blockers combination was associated with better CV outcome as compared to ACE-I/diuretic combination, although the latter entailed a significantly greater reduction in urine albumin excretion[19]. In this context, results of the ONTARGET trial may give rise to conflicting interpretations. In fact, while a larger reduction in UAE was recorded in the arm treated with ACE-I/angiotensin Ⅱ receptors blockers (ARB) combination, this treatment provided no clear benefit in

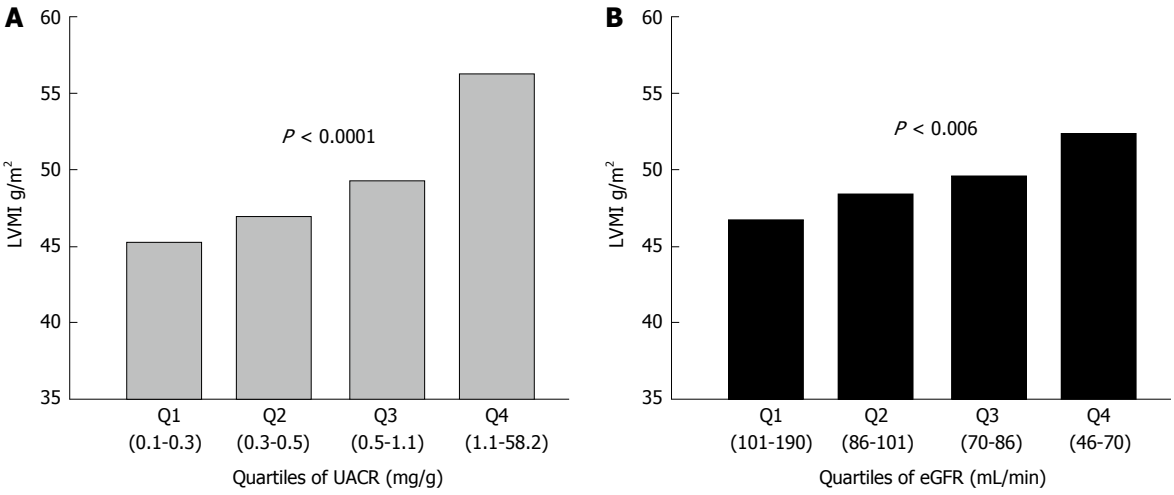

Figure 1 Cardiac organ damage is associated with subclinical renal abnormalities. Left ventricular mass increases along with changes in albuminuria (A) and reduction of eGFR (B) in patients with primary hypertension (n = 400). Modified from Leoncini *et al*[11]. LVMI: Left ventricular mass index; eGFR: Estimated glomerular filtration rate; UACR: Urine albumin to creatinine ratio.

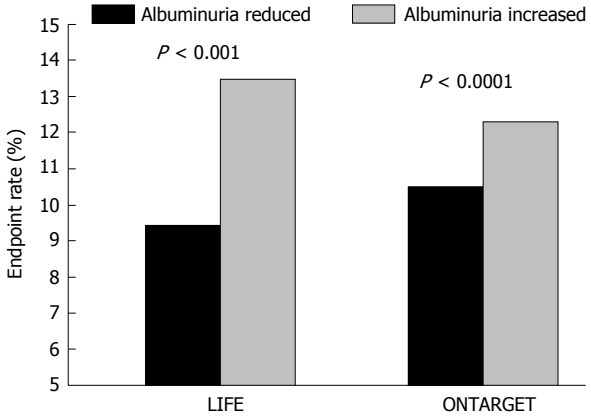

Figure 2 Changes in albuminuria translate into parallel changes in cardiovascular risk. In the LIFE study (left) and in the ONTARGET study the incidence of cardiovascular events was significantly greater in patients showing increases in urine albumin excretion over time as compared to those who showed reduction or no change. Modified from Ibsen *et al*[17] and Schmieder *et al*[21]. LIFE: The Losartan Intervention For Endpoint reduction in hypertensionstudy.

the incidence of major endpoints as compared to ACE-I or ARB monotherapy[20]. However, when changes in UAE were analysed independently of randomization to specific treatment, those patients experiencing a greater reduction of albuminuria under treatment also showed better CV outcome as compared to patients with an increase or no change in albuminuria[21] (Figure 2). This issue has recently been the object of a large meta-regression analysis, involving thirty-two randomized studies and a total of 80812 hypertensive and/or diabetic patients[22]. In fact, Savarese *et al*[22] reported that reduction in UAE was associated with reduced risk of myocardial infarction and stroke, suggesting that UAE changes may represent a valuable intermediate end-point for CV risk evaluation in clinical practice. However, the conclusions of the above mentioned study were weakened by a number of biases, such as the heterogeneity of therapeutic interventions and length of follow-up that may limit the value of reported findings.

CONCLUSION

Accurate risk stratification is of paramount importance to devise cost-effective diagnostic and therapeutic strategies in patients with primary hypertension. An extensive search for subclinical OD is essential to assess global risk profile in most patients, but is often unfeasible for economic and logistic reasons due to the very high prevalence of hypertension. Early renal abnormalities such as slight reduction in GFR and/or the presence of microalbuminuria are well known and powerful predictors of cardio-renal morbidity and mortality and provide useful, low cost tools to optimize CV risk assessment. Furthermore, monitoring treatment-induced changes of UAE may be helpful in the management of high-risk patients.

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REVIEW

Dashing away hypertension: Evaluating the efficacy of the dietary approaches to stop hypertension diet in controlling high blood pressure

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Abstract

The dietary approaches to stop hypertension (DASH) diet has been developed and popularized as a non-pharmaceutical intervention for high blood pressure reduction since 1995. However, to date, a comprehensive description of the biochemical rationale behind the diet's principal guidelines has yet to be compiled. With rising interest for healthy and reliable life-style modifications to combat cardiovascular disease, this review aims to compile the most recent and relevant studies on this topic and make an informed assessment as to the efficacy of and underlying mechanisms operant in the DASH diet. Specifically, the merits of lowering dietary intake of sodium and saturated fat, as well as increasing the intake of fruits, vegetables, fiber, and dairy, have been shown to attenuate hypertension individually. Upon review of this evidence, we conclude that the combination of dietary patterns proposed in the DASH diet is effective in attenuating high blood pressure. We also suggest that efforts to more widely implement adoption of the DASH diet would be beneficial to public health.

Key words: Dietary approaches to stop hypertension diet; Hypertension; Salt restriction; Oxidative stress; Biochemistry

Core tip: As a non-pharmaceutical intervention for hypertension, the dietary approaches to stop hypertension (DASH) diet have emerged as the most prevalent choice. Based on the principles of salt restrictions, lowering fat and sugar intake, increasing fruit, vegetable, and fiber intake, this program serves great promise for patients diagnosed with high blood pressure. This

review aimed to assess the biochemical rational behind the diet's principle guidelines to evaluate the efficacy of the DASH diet in the treatment of hypertension. We conclude that the combined tenets of the DASH diet are effective in lowering blood pressure.

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INTRODUCTION

Currently suspected as an underlying cause of approximately 7.1 million (13% of) deaths worldwide, hypertension remains a prevalent affliction[1]. To complicate the matter, the etiology of primary (essential) hypertension which accounts for 90%-95% of adult cases is still unclear[2]. Uncontrolled hypertension serves to be a major risk factor for the development of a multitude of neural[3], cardiac[4], and renal[5] disorders. Similar to the "All roads lead to Rome" adage, several factors have been implicated in the pathogenesis of hypertension including, but not limited to: Oxidative stress, genetic factors, renal injury, inadequate nutrient intake, overproduction of sodium retaining hormones, disruption of the renin-angiotensin or kallikrein-kinin systems, deficiencies in vasodilators[6]. This review utilized studies dating back to the early 1900's in order to establish a background for the research being conducted today, however, the majority of data compiled for review in this paper was conducted from the INTERSALT study[7] in 1988 through present day.

Until recently, hypertension has been classified into three stages that increase in severity: Pre-hypertension, [systolic blood pressure (BP) of 120-139 mmHg and diastolic BP of 80-89 mmHg], stage 1 (systolic BP of 140-159 mmHg and diastolic BP of 90-99 mmHg), and stage 2 (systolic BP of 160-179 mmHg and diastolic BP of 90-99 mmHg). These classifications arose in 2003 with the 7th JNC report on hypertension[8]. More recently in 2014, the 8th JNC report was released to the public. The 8th edition of the report modified the above specifications, and took an alternate approach regarding the BP threshold of intervention, which treatment should be administered, and also the target BP to be achieved. JNC 8 proposes to begin treatment for those over the age of 60 at an increased BP threshold of > 150/90 mmHg, while the goal BP for those below the age of 60 is still < 140/90[9]. The change originated from multidisciplinary analysis of many randomly controlled trial studies. The idea behind this decision was based on the reevaluation of the risks of side effects *vs* the benefits of treatment of hypertension[9]. A great deal of controversy has arisen surrounding the 8th JNC report, some dissent arising from the JNC panel itself. In a paper published shortly after the JNC 8, Wright *et al*[10] cited insufficient evidence for increasing the benchmark of treatment in patients over 60, proposing that the goal BP eligible for treatment should be lowered. Wright *et al*[10] argued that increasing the benchmark BP of this age group would also increase the group's risk of cardiovascular disease (CVD), especially in high risk populations, and would undo the progress of steadily decreasing levels of cardiovascular mortality. The team proposed that it would be more appropriate to raise the BP threshold for treatment in individuals aged 80 and above, as the benefits of therapy would be far more likely to exceed the risks[10]. For the purpose of this review, we refer to JNC 7 stages of hypertension, due to the vast majority of research published before the presentation of the new guidelines.

To help manage and attenuate disease pathogenesis, intervention by way of lifestyle modification and/or pharmaceutical therapies are strongly recommended. However, due to the economic burden and potential adverse side effects associated with pharmaceutical therapies, a growing demand for alternate means of treatment quickly arose. Consequently, before the turn of the century, a dietary plan known as dietary approaches to stop hypertension (DASH) was publicized after successful results following two multicenter, randomized outpatient feeding studies[11-13]. The principal guidelines of the DASH diet[14] (depicted in Table 1) focus on increased consumption of fruits, vegetables, whole grains, fish, poultry, beans, and seeds; in addition to consuming low- and non-fat dairy products, the diet calls for limited intake of: Sodium, saturated and trans fats, sugar, and red meat. This diet further encourages consumption of mineral-rich foods containing potassium, calcium, and magnesium, and foods rich in fiber.

This review aims to breakdown and examine the biochemical rationales behind specific tenets of the DASH diet in an effort to evaluate its efficacy.

DIETARY SODIUM RESTRICTION

Sodium plays an integral role in the biomechanical function of muscle and nerve fibers, and is largely responsible for the auto regulation of fluid balance at the cellular level. Yet, similar to other essential nutrients, excessive sodium levels can yield damaging effects physiologically. Research has delved into the relationship between sodium intake and hypertension for the past 50 years, and it is widely regarded as a major component to the development of high BP[15]. Investigators Ambard *et al*[16] first evidenced this relationship in 1904, in which six hypertensive patients were placed on three separate diets with modified salt and protein content. Outcomes of the study revealed that sodium content, irrespective of protein content, was inversely related to BP within and across each diet. Specifically, when sodium intake was reduced, corresponding decreases in BP were observed.

Similar beneficial effects of dietary sodium restriction were reported in 1948, when Walter Kempner's Rice

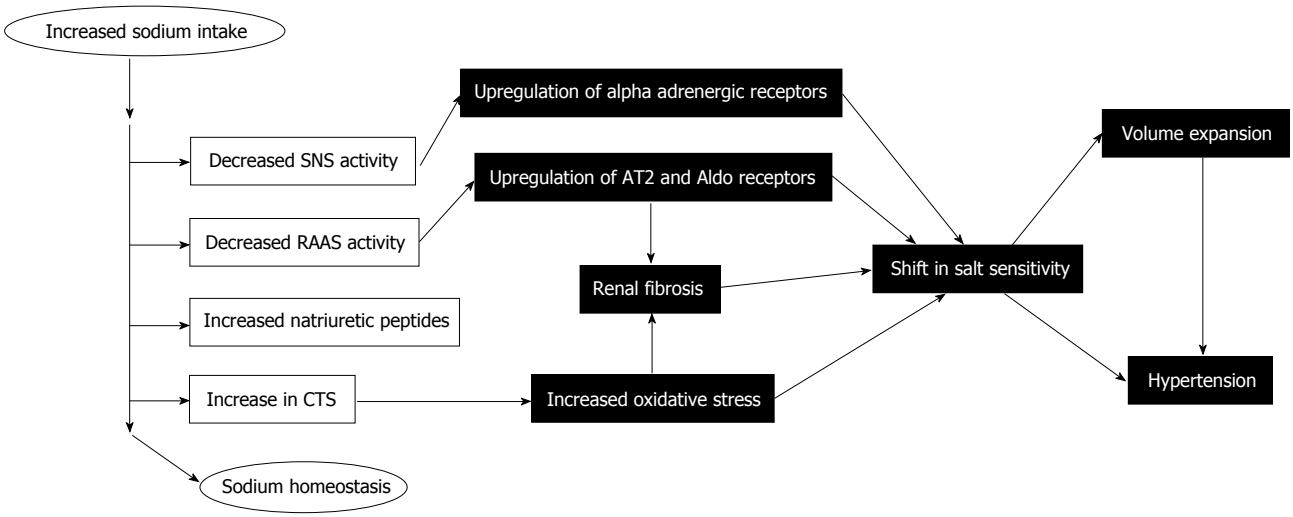

Figure 1 Schematic summarizes tradeoff by which physiological mechanisms that lead to sodium homeostasis in face of increased sodium intake might, over time, lead to a shift in salt sensitivity and sustained hypertension. SNS: Sympathetic nervous system; RAAS: Renin, angiotensin, aldosterone, system; CTS: Cardiotonic steroids; AT2: Angiotensin Ⅱ; Aldo: Aldosterone.

Table 1 Breaking down the dietary approaches to stop hypertension diet

Food group	Daily servings	Nutritional value
Grains/dietary fiber	7-8	Rich in dietary fiber
Vegetables	4-5	Rich in nitrate, fiber, potassium, and magnesium
Fruits	4-5	Rich in nitrate, fiber, potassium, and magnesium
Protein (poultry, fish, *etc.*)	2-5	High in bioactive proteins and magnesium
Low and non-fat dairy	2-3	High in calcium, vitamin D, and bioactive proteins
Nuts, seeds, and dry beans	4-5	High in potassium, magnesium, proteins, and fiber
Fats and oil	2-3	Accounts for 27% of caloric intake and essential fats and oils
Sugar	5 per week	Sweets should be low in fat

A breakdown of the dietary approaches to stop hypertension (DASH) diet by food group, serving size per diem, and the nutritional goal of each of the DASH guidelines. These specific guidelines have been endorsed and published by the National Institutes of Health[14].

Diet became publicized. The initial study involved 500 hypertensive patients placed on a diet predominantly consisting of rice, supplemented with fruits. Dietary salt content was maintained below 500 mg, and the subsequent effects of the diet were tremendous; along with attenuation of high BP, the patients' demonstrated reduced cardiac hypertrophy and amelioration of hypertensive retinopathy[17]. Although the practicality of maintaining this fairly tasteless diet proved bleak, the implications of the study were inescapable.

More recently, in 1980 Srinivasan *et al*[18] tested the effects of a high salt *vs* high salt/sucrose diets on spider monkeys. Findings from the study indicated that both high salt and high salt/sucrose diets resulted in elevated BP, and most importantly, in a dose-dependent manner[18]. In 1988, the monumental Intersalt study was compiled. Examining approximately 10000 patients from 52 examination centers worldwide, Intersalt remains the largest study of its kind to date. The major findings extended over international population and individual levels, and supported the direct correlation between sodium intake and hypertension. Regional differences in salt intake were also found to correlate with regional levels of hypertension. Perhaps of even greater relevance, the increases in systolic BP noted with age appeared to correlate on a population level even better with sodium intake than absolute levels of BP[7].

Although the relationship between salt and BP is readily accepted, the exact biochemical mechanism behind salt's role in the development of hypertension remains unclear. The renal renin-angiotensin-aldosterone system (RAAS) appears to be largely implicated in the development of salt driven hypertension and is the site of many pharmacological treatments for stage 2 hypertension, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin Ⅱ (Ang Ⅱ) receptor blockers[19].

Under physiological conditions, high salt diets typically suppress Ang Ⅱ levels through BP control mechanisms[20]. Despite this, 40%-50% of patients with essential hypertension do not engage this expected renal response to Ang Ⅱ and thus, do not react appropriately to changes in dietary sodium intake (depicted in Figure 1)[20,21]. This is one avenue of salt sensitivity, and while it has been documented clinically, its mechanisms have yet to be resolved[22,23]. Salt sensitivity has also been attributed to genetic mutations of the renin and *ACE* genes[24]. These individuals appear to exhibit high BP and low plasma renin levels in response to salt intake[25].

Additionally, RAAS, nitric oxide (NO), and superoxide anion (O_2^-) in the kidney, work together in a regulatory fashion. Activation of RAAS leads to the production of

O_2^-, a vasoconstrictor, and NO, a vasodilator, and both molecules readily react with one another. Dysfunction within the RAAS can lead to an imbalance of NO and O_2^-, which has been linked to salt sensitivity and hypertension[26,27]. In short, high levels of dietary sodium appear to induce inappropriate RAAS activity, leading to vascular maladaptation[28]. While certainly not the only avenue of hypertension, these studies highlight the importance of the RAAS in management of hypertension.

Sustained levels of high dietary sodium intake have been implicated not only in the pathogenesis of hypertension, but also albuminuria, altered gene expression, and even renal structural damage[29]. Further experiments have been crafted to test the efficacy of lowering sodium intake on hypertensive patients. He *et al*[30] demonstrated that a diet modified to lower only sodium content, with no other dietary restrictions, caused a significant reduction in BP in both normotensive and hypertensive patients. Moreover, as recently as 2015, a study conducted by Barros *et al*[31] highlighted the use of "light salt", a salt developed with lower sodium content and higher potassium levels as a significantly effective agent in reducing BP.

The first major tenet of the DASH diet is a substantial reduction in sodium intake[11]. It is estimated that the average adult American consumes roughly 3700 mg of sodium per day; by contrast, the DASH diet recommends that dietary sodium should be limited to < 2300 mg/d (< 1500 mg/d for high-risk individuals)[32]. In a comprehensive analysis of the effect of sodium consumption on BP, Bray *et al*[33] evaluated variations of sodium intake within the context of the standard American diet *vs* the DASH diet. In total, the study consisted of six groups: A control diet similar to the standard American diet and a DASH diet group were each divided into low, moderate, and average (high) sodium groups[33]. The researchers demonstrated a dose-dependent relationship between sodium consumption and BP; the findings corresponded with the results of previous experiments (discussed above): The lower the sodium intake, the greater the drop in BP. Furthermore, while both control and DASH groups experienced a drop in BP, limiting dietary sodium had an additive relationship when coupled with the DASH diet; these results demonstrate that patients consuming lower dietary sodium, in accompaniment with the rest of the DASH dietary patterns, experience an even greater drop in BP[30,33]. Biochemical analysis of the DASH diet yield similar optimistic results. Using the same six-group approach as Bray *et al*[33], analysis was performed by examining their corresponding pressure-natriuresis curves. The DASH diet appeared to decrease tubular sodium reabsorption without increasing glomerular filtration rate[34]; thus, the DASH diet is natriuretic in a sustainable way. Compiling the evidence-based research together, as a whole, we find overwhelming support of sodium restriction aiding the efficacy of the DASH diet in controlling hypertension.

EFFECTS OF INCREASING FRUIT AND VEGETABLE INTAKE

As discussed above, the origin and development of hypertension is complex, yet substantial literature also suggests that a sustained increase in peripheral vascular resistance due to arterial structural remodeling plays a prominent role in the pathogenesis of this disease[6,35,36]. Research suggests that the high inorganic nitrate (NO_3^-) content present in many vegetables may play vasoprotective[37-39] and cardioprotective[40] roles, *via* endogenous conversion to NO - a potent vasodilator. Consequently, endothelial dysfunction often characterized by a reduction in NO bioavailability has been largely implicated in patients with essential hypertension[41-43]. Discussion considering the physiological biosynthesis and function of NO can be found in several references[40,44-48].

It is estimated that the largest source of dietary nitrates (roughly 80%) comes directly from vegetable consumption; alternate dietary sources of nitrate and nitrite (a reduced form of nitrate) can also be found in fruits, vegetables, and processed meats[38]. In 2008, Webb *et al*[37] provided the first clinical evidence supporting the vasoprotective role of dietary nitrate harbored by a vegetable-rich diet in normotensive volunteers. The team of researchers utilized beetroot juice to display that consumption of an acute nitrate load corresponds with a significant reduction of both systolic and diastolic BP, as well as a reduction of platelet activation; these effects appear to be associated with the simultaneous rise in circulating nitrite levels[37] *via* entero-salivary conversion of the original dietary nitrate load, and further reduction of nitrite to NO[37,49,50].

The DASH diet calls for 4-5 servings of fruits and 4-5 servings of vegetables per day (based on a 2000 calorie diet); the range of daily servings per food group may fluctuate depending on an individual's daily caloric needs, which take one's age and activity level into account[14]. In response to the substantial literature present supporting the physiological benefits of dietary nitrate and nitrite, Hord *et al*[38] extended these findings to assess the high fruit and vegetable recommendations emphasized by the DASH diet. The researchers utilized High-performance liquid chromatography (HPLC) on a convenience sample of foods in order to quantify and compare various nitrate and nitrite concentrations. Results from HPLC indicated a wide range of nitrate and nitrite content amongst various fruits and vegetables. From this data, the researchers generated two hypothetical high- and low-nitrate vegetable and fruit DASH diet patterns (*i.e.*, 1222 mg nitrate *vs* 174 mg); the analysis revealed that the general dietary pattern of fruits and vegetables outlined in the DASH guidelines have the potential to vary drastically in terms of nitrate intake, based on specific vegetable and fruit selection[38]. The results further suggest that simply increasing fruit and vegetable intake does not directly translate to

higher dietary nitrate and nitrite consumption, this may alter the extent of vasoprotective and cardioprotective implications mediated by these molecules (as discussed above).

In the pathologic state, increasing evidence implicates oxidative stress to largely influence the induction and progression of hypertension[51]. The unregulated production of reactive oxygen species (ROS) can largely disrupt function of essential cellular lipids and proteins[52,53]. Accordingly, several natural antioxidant components of fruits and vegetables (*i.e.,* vitamins, minerals, polyphenols) are shown to assist the bodies' ROS scavenging system *via* multiple mechanisms, and are greatly implicated in controlling high BP and endothelial dysfunction[54-56]. The rich vitamin and mineral content found within fruits and vegetables contribute to both the enzymatic and non-enzymatic (direct ROS scavengers) antioxidant defense systems[57]. In regards to enzymatic ROS quenching, many of these enzymes exist as metalloenzymes. Three isoforms of superoxide dismutase help confer vascular protection as potent defenders of superoxide *via* dismutation[58], and utilize metals such as zinc, copper, and manganese. Additionally, glutathione peroxidases readily quench reactive hydrogen peroxide (by product of previous reaction), and are selenium-dependent enzymes[57]. Fruits and vegetables are often great sources of these essential minerals, and thus can contribute to enzymatic ROS defense.

In a similar vein, other micronutrients abundant in fruits and vegetables further bolster antioxidant defense by non-enzymatic means *via* direct scavenging of ROS. Lipid-soluble vitamin E and water-soluble vitamin C are both capable of reacting with peroxyl radicals[59]. It was later reported that vitamin E might synergistically interact with vitamin C in order to enhance its role as a peroxyl radical scavenger[60]. Additionally, Pierdomenico *et al*[61] observed drastically reduced plasma levels of vitamin C in hypertensive patients compared to their normotensive counterparts. Subsequently, Block *et al*[62] supported this observation by demonstrating that vitamin C depletion in normotensive subjects resulted in increased diastolic and systolic BP[62]. However, it should be noted that the relative antioxidant capacity[63] and content[64] of various constituents in fruits and vegetables is variable. This disparity is seen with plant-derived polyphenolic flavonoids, which are found to possess nearly four times the antioxidant activity than vitamin E analogue[63].

As of recent, fructose and its relation to BP has been a popular topic of contention. In the United States, this monosaccharide - naturally available in fruits - is most abundantly obtained from added fructose-glucose sweeteners such as, table sugar (sucrose) and high-fructose corn syrup[65]. Although, high fructose consumption is evidenced to be associated with insulin resistance[66], obesity[67,68], and renal[69] complications, epidemiological studies are controversial[70-72]; moreover, the source of dietary fructose may be of importance. The rich antioxidant properties associated with fruits (discussed above) may counter the potential harmful effects suggested by fructose. While this relationship or mechanism has yet to be established, Forman *et al*[70] found no association with fructose consumption and hypertension, in which individuals consumed a high intake of fruits. Excluding fructose content from natural fruit, a 2010 cross sectional analysis of United States adults with no prior history of hypertension reported an independent association between high fructose intake (from added sugar) and elevated BP[71]. Cumulatively, the multitude of micronutrients found in fruits and vegetables (as evidenced above) make them a beneficial and necessary inclusion in the major tenets of the DASH diet program.

BENEFITS OF FAT-FREE AND LOW-FAT DAIRY PRODUCTS

Dairy products and fatty acids are closely intertwined biochemically, and comprise one of the major tenets of the DASH diet program. The effect of saturated fats on BP has been a popular research topic during the last twenty years. It has been observed that populations consuming diets low in both total and saturated fats, are often the ones exhibiting low to moderate BPs[73]. Analysis of three vegetarian diets: the first consisting of high carbohydrates and low fat, the second high in polyunsaturated fat, and the third low in saturated fat content, revealed that all conditions were shown to reduce BP in their respective populations[73-75]. Further support for the relationship between dietary saturated fat content and BP was demonstrated by a study compiled in Finland; the experimental group that consumed high levels of saturated fats subsequently had higher BP than their control counterparts[76,77].

Unlike saturated fatty acids, diets high in polyunsaturated fats[78] and monounsaturated fats[79] have been shown to have an inverse relationship with BP. Fish oil, high in polyunsaturated fat, has been shown to have protective effects against the risk factors for CVD, including hypertension[80]. The fatty acids found in fish oil are precursors for 3-series prostaglandins, known for their antiaggregatory and vasodilator properties[81]; furthermore, polyunsaturated fats (such as linoleic acid and those found in fish oil) have been shown to lower low-density lipoprotein (LDL) cholesterol levels. This is vitally important in protection against CVD because the oxidized form of LDLs are absorbed by macrophages, creating foam cells that latch onto the walls of arteries, leading to atherosclerosis[82]. Frenoux *et al*[81] study went on to show that polyunsaturated fatty acids had antihypertensive effects, and also boosted resistance to free radical aggregation and lipid peroxidation.

Dairy, in contrast, consists of a more complex makeup of constituents: 89% water, 3.5% protein, 4.6% carbohydrates, and 3.3% lipid[83]. The protein constituents in dairy products are made up of bioactive peptides, known as lactotripeptides[84], and are similar to those found in lean red meat; both varieties of bioactive peptides have

been shown to block ACE[85]. The lipid components of dairy products generally consist of about 60% saturated fatty acids (FA) and about 30% unsaturated FA[86]. The other about 10% consist of short to medium length FA chains that are readily absorbed into the bloodstream, where they preferentially become oxidized rather than stored as triglycerides; and, in short, is associated with weight loss[86,87]. An inverse relationship was found to exist between dairy intake and BP; and, this relationship was strengthened if saturated fat intake was below about 11%[88].

Additionally, dairy intake, while not associated with overall mortality, appears to be inversely related to the multitude of risk factors for CVD including hypertension[89]. More recently, Drouin-Chartier *et al*[84] reported dairy intake to improve endothelial function and attenuate mild to moderate hypertension. Subsequent studies have shown that vitamin D alone also displays a curative effect on hypertension and other CVD risk factors[90]. The body of evidence here supports the DASH diet's recommendations in emphasizing the consumption of fat-free and low-fat dairy products, as well as reducing the intake of saturated and trans fats.

RICH ENERGY SOURCES: WHOLE GRAINS AND DIETARY FIBER

Dietary fiber is the indigestible cell wall component found in plants[91]. It is divided into two categories, soluble fiber and insoluble fiber. Soluble fibers include pectins, gums, mucilages, and some hemicelluloses; alternatively, insoluble fibers include lignins, cellulose, and the remainder of the hemicelluloses[92]. Early studies, conducted by Burkitt[93] in 1975, demonstrated that low dietary fiber intake is linked to many diseases, such as cardiovascular disease. This lent credence to the idea that dietary fiber may also be related to hypertension, a major risk factor in CVD. The recommended daily intake value of dietary fiber is between 20-35 g/d[94]. This is twice the amount of fiber that the average American typically consumes[95]. Initially, studies sought to analyze high-fiber vegetarian diets, which were previously shown to attenuate hypertension[91]. Subsequently, there was a rise in controversy; critics suggested that the decrease in BP seen in these studies could have easily arisen from other factors present in a vegetarian diet. Another setback arose with the discovery that increases in dietary fiber alone had little to no effect on normotensive patients[96].

Despite these setbacks, new research emerged showing the benefits of dietary fiber in regards to cardiac distress. In 1997, Stamler *et al*[97] demonstrated an inverse relationship between increased dietary fiber intake and BP. Additionally, whole grains were shown to be associated with lowering BP[98]. Whole grains themselves offer much nutritional value, providing complex carbohydrates, resistant starch, dietary fiber, minerals, vitamins, phytochemicals (which serve as antioxidants) and other nutrients[99,100]. A 4-fold decrease was seen in the cardiovascular death rate between men who ingested a high fiber diet (> 37 g/d) *vs* those who ingested a low fiber diet (< 20 g/d)[101]. Similar results were demonstrated, during a 6-year prospective study, in which an inverse relationship was found between dietary fiber intake and CVD rates[102]. Additionally, cereal fiber was revealed to be strongly associated with a reduction in CVD death rates; this result was further supported by the documented protective nature of whole grains[103,104].

Adding support to the inverse relationship between dietary fiber and cardiovascular risk factors, Lairon *et al*[105] further demonstrated that this correlation existed for all forms of fiber (Soluble, insoluble, fruits, grains, vegetables, cereal, *etc*.), specifically in regards to the prevalence of hypertension. While mechanistic data is yet to be confirmed, it is thought to be associated with a reduction of abdominal obesity and increased vascular reactivity[105]. Fiber has also been shown to attenuate endothelial dysfunction associated with hypercholesterolemia[106]; this finding suggests that fiber may indirectly play a protective role against hypertension, as the endothelium serves as an important regulator of vascular tone in response to altering needs for blood amongst different organs and tissues[107,108]. Taken together, a substantial body of evidence suggests that increasing dietary fiber plays a beneficial role in the battle against hypertension.

CONCLUSION

The DASH diet has provided the general public with a non-pharmaceutical option to combat hypertension. The last twenty years have been filled with studies breaking down each aspect of the DASH program. Many of these studies showed great success in highlighting the benefits of lowering sodium and saturated fat intake, while increasing intake of fruits, vegetables, dairy, and dietary fiber. However, the biochemical mechanisms behind these dietary guidelines have only been vaguely illuminated. Dietary biochemistry itself is a very complex story to tell, consisting of a diverse array of mechanistic pathways and byproducts. Although a complete understanding of each of these mechanisms and their implications has not yet been established, substantial effort has been made to fill in the gaps. This review attempted to compile the most recent available research in order to paint as vivid a picture as possible of how individual aspects of the DASH diet effect BP, and ultimately draw a conclusion as to the efficacy of such a diet for the treatment of hypertension. Despite the limitations of the total scope of our analysis, the abundant evidence in support of these dietary modifications is compelling, and we recommend the DASH diet to be an effective non-pharmaceutical treatment of hypertension. Further publicity and implementation could dramatically reduce the number of hypertensives both nationally and internationally. In American culture, focus should be placed on the maintainability of the diet. Stigmata has been placed

on healthy diets for being overly expensive, and out of reach for the average family. According to Sacks *et al*[109], the DASH program should cost approximately $130.00 per week for a family of 4. Adjusting for inflation, this translates to less than $200.00 per week today, still a very low total for a family of 4. Internationally, focus should be shifted to modification of diets depending on the cultural tendencies of the various groups of people who are regionally predisposed to high salt diets. These actions taken together could have a great impact on the health of individuals worldwide. Future research will need to elucidate the biochemical mechanisms inherent in the DASH diet. This could lead to further, more tailored and effective, dietary modifications for the masses; we predict that as further comprehensive understanding of this anti-hypertensive diet grows, we will see an overall attenuation of this disease.

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ORIGINAL ARTICLE

Prospective Study

Estimated net endogenous acid production and risk of prevalent and incident hypertension in community-dwelling older people

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Abstract

AIM: To investigate the associations of dietary acid-base load with prevalent and incident hypertension in community-living Chinese older adults in Hong Kong.

METHODS: Participants aged ⩾ 65 years participating in a cohort study examining the risk factors for osteoporosis completed a validated food frequency questionnaire (FFQ) at baseline between 2001 and 2003. Estimated net endogenous acid production (NEAP) was calculated using Frassetto's method based on the diet's protein to potassium ratio derived from the FFQ. Prevalent and 4-year incident hypertension was defined as systolic blood pressure ⩾ 140 mmHg and/or diastolic blood pressure ⩾ 90 mmHg and/or self-reported use of anti-hypertensive medications. Multivariable logistic regression was used for cross-sectional analysis (*n* =

3956) to assess the association between estimated NEAP and prevalent hypertension, and for longitudinal analysis (n = 795) on its association with 4-year incident hypertension, with adjustment for various potential socio-demographic and lifestyle factors.

RESULTS: Median estimated NEAP of the participants was 47.7 (interquartile range: 36.2, 60.9) g/mEq. Participants in the highest quartile of energy-adjusted estimated NEAP was associated with increased likelihood of prevalent hypertension than those in the lowest quartile of energy-adjusted estimated NEAP [multivariable OR = 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002)]. No significant association was observed between energy-adjusted estimated NEAP and risk of incident hypertension.

CONCLUSION: A high dietary acid load was independently associated with an increased likelihood of prevalent hypertension in ambulant older Chinese people in Hong Kong. The longitudinal analyses failed to show any causal relationship between dietary acid load and hypertension in this population.

Key words: Acid-base balance; Cohort; Hypertension; Nutrition; Chinese

Core tip: This prospective study investigated the associations between baseline dietary acid-base load and prevalent and 4-year incident hypertension in community-dwelling Chinese older adults in Hong Kong. Baseline dietary data were collected using a validated food frequency questionnaire (FFQ). Estimated dietary net endogenous acid production (NEAP) was calculated based on the diet's protein to potassium ratio from the FFQ. Higher quartile of energy-adjusted estimated NEAP was associated with increased likelihood of prevalent hypertension [multivariable OR = 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002)]. No significant association was observed between energy-adjusted estimated NEAP and risk of incident hypertension.

Chan R, Leung J, Woo J. Estimated net endogenous acid production and risk of prevalent and incident hypertension in community-dwelling older people. *World J Hypertens* 2015; 5(4): 129-136 Available from: URL: http://www.wjgnet.com/2220-3168/full/v5/i4/129.htm DOI: http://dx.doi.org/10.5494/wjh.v5.i4.129

INTRODUCTION

Hypertension is a global health challenge in view of its prevalence and burden on morbidity and mortality. Diet is one of the modifiable factors affecting blood pressure and hypertension[1]. A diet high in sodium content and low in potassium, calcium and magnesium intake is associated with an elevated blood pressure[1,2]. Other dietary approaches, like The Dietary Approaches to Stop Hypertension diet also play a prominent role in the etiology of hypertension[3].

A possible link between acid-base balance and cardiometabolic risk has been recently proposed[4]. Long-term excessive intake of acid-generating foods, like meat together with an inadequate consumption of the alkaline-producing foods, like fruits and vegetables may cause acidosis and have negative effects on blood pressure and hypertension[4]. However, there have been few studies investigating how dietary acidity was related to hypertension. Dietary acidity was positively linked with blood pressure in healthy young women[5], middle-aged women[6] as well as healthy children and adolescents[7,8]. In contrast, no association of baseline dietary acidity with incident hypertension was observed among Western older adults[9,10].

With ageing, the body's ability to excrete acid drops to a great extent because of a decline in kidney function[11]. Therefore, consuming diets that induce minimal or no net acid load may be particularly vital when people are getting old. More importantly, the prevalence of hypertension rises with age, and recent data from China show a high prevalence of hypertension (58.2%) for the older adults as compared to the younger adults (17.5%)[12]. Therefore, identifying modifiable lifestyle factors that are associated with hypertension is important to determine the effective way for hypertension prevention and control. Considering the scanty evidences on this area and the differences in the dietary habits between Chinese and Caucasians, we explored how dietary acid-base load was linked with prevalent and incident hypertension in Chinese ambulatory older people. We expected that higher dietary acidity was linked with an elevated risk of hypertension.

MATERIALS AND METHODS

Study population

The sample population was subjects from a longitudinal study investigating the risk factors for osteoporosis in Hong Kong and the study details have been reported elsewhere[13]. Briefly, 4000 Chinese (50% men) aged ⩾ 65 years were recruited in a community health survey between 2001 and 2003. They attended the 4-year follow-up between 2005 and 2007. The 4-year follow-up was carried out through a mailed reminder and phone reminders for a follow-up health check appointment. The average follow-up year was 4 years. This study was carried out according to the Declaration of Helsinki. This study was granted an approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All subjects provided written informed consent.

Forty-four participants were excluded because of baseline missing/invalid data on diet or demographics. A final sample of 3956 participants was included for the cross-sectional analysis. The 4-year longitudinal analysis further excluded participants with hypertension

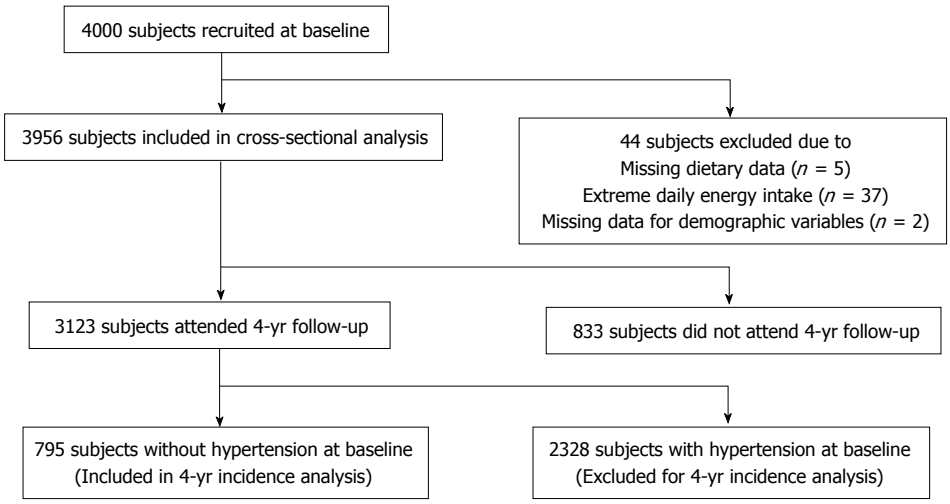

Figure 1 Number of subjects included and excluded for baseline and 4-year follow-up analyses.

at baseline, thus 795 participants were finally included (Figure 1).

Demographic and general lifestyle data

A structured interview was done to capture data on age, gender, education achievement, smoking habit, alcohol use and self-reported health conditions. Smoking status was categorized into three categories, namely former (100 or over cigarettes smoked in a lifetime), current or never. Alcohol use was categorized as never, past or current. Subjects self-reported their health conditions and the research staff validated the data by checking the relevant physician's reports and the medications used.

Physical activity assessment

The Physical Activity Scale of the Elderly (PASE) was used to assess the physical activity level[14]. The scale consists of twelve items and measures the average time (in hours) each day on leisure, household and occupational physical activities by participants in the past week. Higher summary scores indicates higher daily level of physical activity.

Dietary assessment

Baseline dietary intake was evaluated with a validated semi-quantitative food frequency questionnaire (FFQ)[15]. The FFQ consisted of 280 food items. Participants reported the frequency and the amount of consumption of each food over the previous year. Nine frequency categories were presented and ranged from never or seldom to more than once a day. A food photo album with pictures of standardized food portion size was presented to assist quantifying the amount of food consumption. Daily intake of various food groups covering cereals, egg and egg products, marine foods, fresh or dried fruits, legumes/nuts/seeds, meat and poultry, dairy and dairy products, and vegetables was derived. Average daily nutrient intake was generated with food composition tables of various sources[16,17]. Residual method was applied to generate energy-adjusted intakes[18].

Estimation of net endogenous acid production

Estimated net endogenous acid production (NEAP) of diet can be derived using different algorithms[19]. While Frassetto *et al*[20] derived the dietary estimated NEAP with reference to the dietary protein to potassium ratio, Remer *et al*[21] calculated the estimated NEAP based on the average intestinal absorption rates of the dietary intake of protein and other minerals and the anthropometry-based estimate for organic acid excretion. Each algorithm has its rationale and pitfalls[22]. Frassetto's method was applied in the present study to make it consistent with our previous study[23]. The estimated NEAP by this method was expressed using g/mEq and could explain approximate 70% variation in renal net acid excretion[20]. Residual method was also applied to generate the energy-adjusted estimated NEAP[18].

Anthropometry

Body weight and height were measured with the Physician Balance Beam Scale (Healthometer, Illinois, United States) and the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, United Kingdom) respectively. Body mass index (BMI) was calculated.

Assessment of hypertension

Trained staff measured participant's blood pressure using a standard mercury sphygmomanometer (WA Baum Co. Inc., Copiague, NY, United States). The first and fifth Korotkoff phases were measured twice after 5 min rest in the sitting position and the average of the two readings was taken as systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively. Hypertension was defined as SBP $\geqslant$ 140 mmHg and/or DBP $\geqslant$ 90 mmHg and/or use of anti-hypertensive medication[24]. Participants were asked to bring and show all the drugs he/she was currently using and the interviewer recorded the names, types and doses

accordingly.

Statistical analysis

SPSS version 21.0 (SPSS Inc., Illinois, United States) was used for the statistical analyses. Normality was checked using histograms and logarithmic transformation was performed where necessary. Independent *t* test and χ^2 test were applied to check for differences in baseline characteristics between participants included and participants excluded for data analysis.

Since the distribution of the energy-adjusted estimated NEAP (continuous) was skewed, it was categorized using quartile values according to the distribution of the final sample. Differences across energy-adjusted estimated NEAP quartiles were checked using χ^2 test for categorical variables and analysis of variance for continuous variables unless otherwise specified. Spearman's correlation was applied for assessing the correlation of energy-adjusted nutrient intakes or food group intakes with the estimated NEAP.

Multivariable logistic regression was performed to calculate the odds ratio (OR) and 95%CIs for prevalent hypertension as well as 4-year incident hypertension according to the energy-adjusted estimated NEAP quartiles. The first model was controlled for age (years) and sex at baseline. The second model was further controlled for baseline BMI, PASE, education attainment, tobacco use, alcohol use, and baseline energy-adjusted intakes of fiber, sodium, magnesium, calcium and potassium. P_{trend} was assessed by inputting quartiles of energy-adjusted estimated NEAP into all models. Since participants might have made dietary changes due to chronic diseases, several sensitivity analyses were further done by ruling out participants with a history of stroke, diabetes mellitus, or heart diseases, such as myocardial infarction. We also examined if the association between estimated NEAP and hypertension varied according to sex, age ($\leqslant$ 69 years *vs* > 69 years), and BMI (underweight < 18.5 kg/m^2 *vs* normal 18.5 kg/m^2 to < 23 kg/m^2 *vs* overweight/obese $\geqslant$ 23 kg/m^2). Stratified multivariable analyses were also done and appropriate interaction terms were generated to test for the presence of signification interactions. An α level of 5%, 2-sided was considered as statistically significant.

RESULTS

There were no significant differences in the baseline characteristics between participants who were included and those who were excluded for baseline analysis. Those who did not attend 4-year follow-up were older, physically less active, had lower education level and lower BMI, and suffered from more chronic diseases (P < 0.05) than those who attended the follow-up (details not listed).

Mean (SD) baseline age of the studied sample (1979 men, 1977 women) was 72.5 (5.2) years. Mean (SD) baseline BMI was 23.7 (3.3) kg/m^2. Mean (SD) baseline SBP and DBP was 142.6 (19.4) mmHg and 77.8 (9.2) mmHg respectively. Majority (75.2%) of the participants had hypertension at baseline. Among 795 participants included in the incidence analysis, 310 incident cases were identified and the cumulative incidence was 0.39. Median baseline estimated NEAP was 47.7 (interquartile range: 36.2, 60.9) g/mEq. Participants' baseline characteristics according to the quartiles of energy-adjusted estimated NEAP are listed in Table 1. Those with higher energy-adjusted estimated NEAP were of lower BMI, physically more sedentary, higher education attainment, and were prone to be non-smokers, and had lower dietary intakes of fiber, magnesium, potassium and sodium.

Estimated NEAP was positively correlated with total protein, calcium and phosphorus intake, and inversely linked with vitamin C, fiber, magnesium, vitamin K and potassium intake (P < 0.05, Table 2). Increasing estimated NEAP was linked with greater intake of protein rich animal foods, and lower fruits and vegetables consumption (P < 0.05, Table 2).

Participants in the highest quartile of energy-adjusted estimated NEAP had significantly increased likelihood of having prevalent hypertension than those in the lowest quartile in unadjusted and adjusted models (Table 3). The multivariable OR comparing those in the highest quartile with those in the lowest quartile was 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002). Although increasing trend was detected between energy-adjusted estimated NEAP and risk of incident hypertension, the trend did not reach statistical significance (Table 4).

Sensitivity analyses ruling out participants with some major chronic diseases showed similar results (details not listed). Risk estimates for the relationship of estimated NEAP with prevalent hypertension tended to be higher in male, in those aged $\geqslant$ 69 years, and in those with BMI below 18.5 kg/m^2, but the differences did not reach statistical significance (all with P-interaction > 0.05) (details not listed).

DISCUSSION

Our study indicated that higher estimated NEAP was associated with greater likelihood of prevalent hypertension but was not with the risk of incident hypertension in older Chinese adults. To our knowledge, such association in Chinese population has not been previously reported.

Few studies examined the link between dietary acid-base load and hypertension risk in older adults. Our cross-sectional findings were consistent with those reported in healthy children and adolescents[7] and young women[5], but different from those reported among community-based older Swedish men[10]. A cross-sectional analysis in 267 healthy children and adolescents showed that various markers of a higher dietary acidity were associated with higher blood pressure independent of BMI and other potential factors[7]. Similar findings were reported from a cross-sectional study investigating the relationship of dietary acid-base load with cardiometabolic risk factors in apparently healthy

Table 1 Baseline characteristics and prevalent hypertension by quartiles of energy adjusted estimated net endogenous acid production (*n* = 3956)

Variable	Quartile of energy adjusted estimated NEAP (g/mEq)								P_{trend}[1]
	Q1 (*n* = 987)		Q2 (*n* = 991)		Q3 (*n* = 989)		Q4 (*n* = 989)		
	Mean	SD, %	Mean	SD, %	Mean	SD, %	Mean	SD, %	
[2]Estimated NEAP (g/mEq)									
Original	26.9	21.3, 32.7	41.2	37.0, 45.7	53.4	48.7, 58.2	71.2	64.5, 79.7	< 0.001
Energy adjusted	28.7	23.8, 32.7	41.8	39.0, 44.7	54.0	50.7, 57.3	71.2	65.7, 79.8	< 0.001
Age (yr)	72.3	4.9	72.4	5.3	72.5	5.2	72.7	5.4	0.055
BMI (kg/m^2)	23.8	3.3	23.7	3.3	23.6	3.3	23.5	3.3	0.027
Male (%)		50.1		49.9		50.1		50.1	0.989
Education level (%)									
Primary or below		77.7		72.4		67.2		68.8	< 0.001
Secondary/matriculation		16.8		19.0		19.8		19.4	
University or above		5.5		8.7		12.9		11.8	
Smoking habit (%)									
Never smoke		58.5		62.6		65.4		66.5	< 0.001
Former smoker		33.0		31.1		29.3		26.1	
Current smoker		8.5		6.4		5.3		7.4	
Alcohol use (%)									
Never		84.1		84.8		84.6		86.6	0.155
Former drinker		2.4		1.4		1.6		2.1	
Current drinker		13.5		13.8		13.8		11.3	
[3]Prevalent hypertension (%)		72.8		74.9		75.2		77.8	0.014
Energy intake (kcal/d)	1832.5	587.3	1847.5	555.1	1848.6	568.7	1821.6	561.2	0.696
[2]Energy adjusted fiber (g/d)	9.1	7.0, 11.7	8.9	6.8, 11.2	8.5	6.6, 10.5	7.5	5.7, 8.9	< 0.001
[2]Energy adjusted calcium (mg/d)	535.6	418.9, 692.4	573.6	452.3, 725.8	590.7	460.1, 763.1	547.5	418.8, 726.2	0.098
[2]Energy adjusted magnesium (mg/d)	358.5	297.9, 487.8	356.6	292.7, 471.5	344.4	291.2, 434.8	312.0	262.1, 373.2	< 0.001
[2]Energy adjusted potassium (mg/d)	3782.3	3180.4, 4507.6	2977.9	2536.0, 3437.3	2462.8	2092.3, 2935.4	2021.0	1677.8, 2440.5	< 0.001
[2]Energy adjusted sodium (mg/d)	1453.4	1036.9, 1963.4	1379.7	1040.7, 1886.0	1345.6	1030.3, 1793.3	1254.3	930.1, 1651.4	< 0.001
PASE score	93.2	43.6	92.5	42.4	91.2	43.0	88.4	42.9	0.011

[1]P_{trend} was assessed by linear-by-linear association χ^2 test linear and ANOVA test for trend, or non-parametric Jonckheere-Terpstra test; [2]Data are presented as median (interquartile range); [3]Defined as average systolic or diastolic blood pressure ⩾ 140 or 90 mmHg respectively, or use of anti-hypertensive medications. NEAP: Net endogenous acid production; PASE: The Physical Activity Scale of the Elderly; BMI: Body mass index; ANOVA: Analysis of variance.

Table 2 Spearman's correlation between estimated net endogenous acid production and selected nutrients and main food groups (*n* = 3956)

Energy adjusted nutrients/ main food groups	Energy adjusted estimated NEAP (g/mEq)	
	r_s	*P*
Total protein (g)	0.27	< 0.001
Vitamin C (mg)	-0.27	< 0.001
Calcium (mg)	0.04	0.015
Phosphorus (mg)	0.16	< 0.001
Fiber (g)	-0.23	< 0.001
Magnesium (mg)	-0.20	< 0.001
Vitamin K (mcg)	-0.17	< 0.001
Potassium (mg)	-0.68	< 0.001
Sodium (mg)	-0.10	< 0.001
Cereals (g)	-0.03	0.063
Egg and egg products (g)	0.03	0.034
Fish and shellfish (g)	0.07	< 0.001
Fruits and dried fruits (g)	-0.31	< 0.001
Legumes, seeds and nuts (g)	0.01	0.678
Meat and poultry (g)	0.13	< 0.001
Milk and milk products (g)	0.03	0.041
Vegetables (g)	-0.18	< 0.001

NEAP: Net endogenous acid production.

young female adults[5]. Several possible mechanisms by which acid-base balance affects blood pressure have been suggested. Diet-induced mild metabolic acidosis may influence blood pressure possibly through increased cortisol production[25], increased calcium excretion[26,27] or reduced citrate excretion[28,29].

The absence of association in our prospective analysis was in line with the results by Engberink *et al*[9] and Luis *et al*[10] but was different from the findings by Zhang *et al*[6]. Several reasons may explain these inconclusive findings. Different study design and participants' characteristics may lead to these mixed findings. First, both Engberink's and Luis as well as our studies included older men and women whereas Zhang *et al*[6] recruited middle-aged women in their study. However, this age difference seems to be unlikely to explain the null findings as older people are expected to be more vulnerable to dietary acid base load in view of their declining renal function. In contrast, we are uncertain whether there is age-dependent difference regarding the influence of dietary acidity on hypertension through other mechanisms. Second, multiple measures of dietary intakes were available in Zhang's study whereas dietary data were only collected at a single time at baseline in Engberink's study, Luis's study and our study. Although sensitivity analyses not including participants with chronic diseases that might lead to dietary alterations did not change the null findings between estimated NEAP and incident hypertension in Engberink's and our studies, we cannot

Table 3 Logistic regression linking to quartiles of energy adjusted estimated net endogenous acid production to prevalent hypertension (*n* = 3956)

	Quartiles of energy adjusted estimated NEAP (g/mEq)				P_{trend}[1]
	Q1 (*n* = 987)	Q2 (*n* = 991)	Q3 (*n* = 989)	Q4 (*n* = 989)	
No. of case and control	719/268	742/249	744/245	769/220	
Unadjusted OR (95%CI)	1 (reference)	1.11 (0.91-1.36)	1.13 (0.93-1.38)	1.30 (1.06-1.60)	0.014
Age and sex adjusted OR (95%CI)	1 (reference)	1.11 (0.91-1.36)	1.13 (0.92-1.38)	1.29 (1.05-1.58)	0.020
[2]Multivariable adjusted OR (95%CI)	1 (reference)	1.22 (0.97-1.52)	1.35 (1.03-1.76)	1.66 (1.22-2.26)	0.002

[1]P_{trend} by entering quartiles of energy adjusted NEAP as a fixed factor and testing the contrast by using the polynomial option in all models; [2]Model adjusted for age, sex, BMI, PASE, education level, smoking status, alcohol use, and quartiles of energy adjusted intakes of fiber, calcium, magnesium, potassium and sodium. NEAP: Net endogenous acid production; BMI: Body mass index; PASE: The Physical Activity Scale of the Elderly.

Table 4 Logistic regression linking to quartiles of energy adjusted estimated net endogenous acid production to incident hypertension (*n* = 795)

	Quartiles of energy adjusted estimated NEAP (g/mEq)				P_{trend}[1]
	Q1 (*n* = 198)	Q2 (*n* = 201)	Q3 (*n* = 198)	Q4 (*n* = 198)	
No. of case and control	78/120	80/121	75/123	77/121	
Unadjusted OR (95%CI)	1 (reference)	1.02 (0.68-1.52)	0.94 (0.63-1.41)	0.98 (0.65-1.47)	0.842
Age and sex adjusted OR (95%CI)	1 (reference)	1.03 (0.69-1.54)	0.95 (0.63-1.43)	0.99 (0.66-1.49)	0.873
[2]Multivariable adjusted OR (95%CI)	1 (reference)	1.15 (0.74-1.80)	1.11 (0.66-1.86)	1.32 (0.72-2.43)	0.436

[1]P_{trend} by entering quartiles of energy adjusted NEAP as a fixed factor and testing the contrast by using the polynomial option in all models; [2]Model adjusted for age, sex, BMI, PASE, education level, smoking status, alcohol use, and quartiles of energy adjusted intakes of fiber, calcium, magnesium, potassium and sodium. NEAP: Net endogenous acid production; BMI: Body mass index; PASE: The Physical Activity Scale of the Elderly.

rule out the possibility that some participants might have changed their diets for other reasons during the follow-up. Third, different dietary habits of the study participants of various studies might explain these different findings. The median estimated NEAP in our study (approximately 47 mEq/d), Engberink's study (39 mEq/d) and Luis's study (40.7 mEq/d) might be too low to have an effect on blood pressure. Zhang *et al*[6] showed an elevated risk of incident hypertension starting at an estimated NEAP of 44 mEq/d or above.

Several methods have been derived to estimate dietary NEAP, thus we compared the Frassetto's model with the Remer's model. Estimated NEAP derived from both methods were strongly correlated (r_s = 0.95, P < 0.001). By including both protein and potassium as independent variables in a multivariate regression model, estimated NEAP derived using the latter varied proportionally with the protein intake (P < 0.001) and inversely with the potassium intake (P < 0.001). The multiple correlation coefficient was 0.95. Therefore, the Remer's model's ability in predicting estimated NEAP was mainly from the dietary protein and potassium contents. Furthermore, the results were consistent when all analyses were repeated using estimated NEAP by the Remer's model.

Our study had some limitations. Unlike previous similar studies among older adults, our study did not have data on kidney function but kidney function was unlikely to modify the associations between dietary acid load and blood pressure[10]. Moreover, recall bias may arise from dietary data captured using FFQ. The assessment of salt intake using FFQ but not using 24-h urine method was a limitation. Dietary assessment of the salt intake, in particular the discretionary salt intake often results in an underestimation and this may partially account for the unexpected inverse association between estimated NEAP and sodium intake in our study. Another possibility may be due to the differences in the way of serving vegetables in Chinese diets as compared to Western diets. While vegetables are commonly served raw or boiled in Western diets, stir fried vegetables with salt added during cooking is a common way of serving vegetables in Chinese diets[30]. Furthermore, we did not have dietary data at 4 years whereas participants might have altered their diet over the 4 years period. We performed sensitivity analyses ruling out participants with major chronic diseases and the results were similar. Moreover, we did not include markers, like serum anion gap or bicarbonate in the study, which are more reflective of acid base load. Although we controlled for different factors in the analysis, residual potential confounding from other factors related to hypertension, like family history and sleep patterns might still be present. The differences in demographic and lifestyle characteristics between those included and those excluded for the analysis, and between those who attended and those who did not attend the follow-up may also limit the study generalizability. Finally, our study may be underpowered in view of the small sample size for the prospective analysis.

In summary, our results suggest an increased likelihood of prevalent hypertension in older adults with

an elevated dietary acid load. However, as limited by the small number of the participants and the study methodology, our prospective analyses were unable to demonstrate a causal relationship between dietary acid load and hypertension in this population. Further longitudinal studies in populations of different dietary habits are required to confirm the influence of dietary acid load on hypertension. Moreover, the underlying mechanisms linking dietary acid-base load and blood pressure require further investigations.

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COMMENTS

Background

Long-term excessive intake of acid-generating foods in combination with a low intake of the alkalizing fruits and vegetables may lead to acidosis and have negative effects on blood pressure and hypertension. The authors studied the association of dietary acid-base load with risk of prevalent and incident hypertension in Chinese community-dwelling older adults in Hong Kong. The authors speculated that higher dietary acid-base load was associated with an elevated risk of hypertension.

Research frontiers

Diet is one of the modifiable factors for blood pressure and hypertension. The ability to excrete acid drops significantly with age because of a decline in kidney function. Therefore, consuming diets that induce minimal or no net acid load may be vital at the older age, and identifying modifiable lifestyle factors that are associated with hypertension is important to determine the effective way for hypertension prevention and control.

Innovations and breakthroughs

There have been few studies investigating the association between dietary acid-base load and hypertension. Positive associations have been reported in healthy young women, middle-aged women as well as healthy children and adolescents. Negative findings were observed among Western older adults. However, no such study has been conducted in Chinese population. In this study, data from participants aged 65 years or above participating in a cohort study examining the risk factors for osteoporosis at baseline and 4-year follow-up were examined. Baseline estimated net endogenous acid production (NEAP) was calculated based on the diet's protein to potassium ratio derived from the Food Frequency Questionnaire and was related to the hypertension status at baseline (n = 3956) and 4-year follow-up (n = 795). The authors' findings show that participants in the highest quartile of energy-adjusted estimated NEAP was associated with increased likelihood of prevalent hypertension than those in the lowest quartile of energy-adjusted estimated NEAP [multivariable OR = 1.66 (95%CI: 1.22 to 2.26, P_{trend} = 0.002)]. No significant association was observed between energy-adjusted estimated NEAP and risk of incident hypertension.

Applications

This study serves as an additional evidence supporting the potential link between dietary acid-base load and hypertension. The authors' findings show that a diet lower in dietary acid-base load might be beneficial for lowering risk of hypertension. However, further prospective studies in populations with different dietary habits are warranted to confirm the role of dietary acid-base balance in hypertension as well as the underlying mechanisms linking dietary acid-base load to blood pressure.

Terminology

Estimated NEAP: A diet's net acid load that is estimated from the composition of the diet based on collected dietary data; Hypertension: Abnormally high blood pressure.

Peer-review

The authors had declared some of the limitation in which may affects the generalizability of this study, such as the differences in demographic and lifestyle characteristics between those included and those exclude for the analysis; and vegetables intake of those participants in their study groups. It is also an interesting prospective cohort study which may accept for publication.

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