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EDITORIAL

Salt Controversy Stirred by "PURE" but Settled by "NUTRICODE"

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ABSTRACT

Hypertension is a modifiable risk factor for cardiovascular disease and death. On a worldwide scale, it is estimated that over 1 billion adult individuals are afflicted by hypertension, and hypertension is responsible for over 9 million deaths annually. Among dietary strategies to counter this epidemic, principal role has been assigned to reducing dietary sodium which has been included in many guidelines for the treatment of hypertension and prevention of cardiovascular disease. However, recent studies have raised questions about potential harmful effects associated with low sodium intake. Ensuing the tumult stirred by these studies reporting on the role of salt intake restriction on blood pressure and cardiovascular mortality, we are herein providing a brief overview of the topic. Despite the "controversy', the data appear compelling toward the need for reducing salt intake as one of the most cost-effective measures to control blood pressure and reduce cardiovascular disease worldwide at the population level.

KEY WORDS: *hypertension; sodium; salt; cardiovascular disease; low-salt diet*

INTRODUCTION

Hypertension is a modifiable risk factor for cardiovascular disease and death. On a worldwide scale, it is estimated that over 1 billion adult individuals are afflicted by hypertension, and hypertension is responsible for over 9 million deaths annually.[1,2] Hypertension affects 1 in 4 adults worldwide.

Apropos with the most recent studies examining the role of sodium in blood pressure control and the association of salt intake with hypertension and cardiovascular mortality,[3-6] we attempt to provide an overview of this important topic.

Abbreviations
EU = European Union
WHO = World Health organization

ROLE OF SODIUM

Sodium appears to play a key role in blood pressure control. Salt intake influences cardiovascular morbidity and mortality mainly because of its positive association with blood pressure. In the 1980s, the INTERSALT study indicated that populations with low dietary salt intake (i.e., <3 g/24h or 1.1 g of sodium/24h) presented a lower blood pressure increase with age and that the increase in systolic blood pressure with age was linked to dietary salt intake.[7] In the 1990s, an overview of data collected for 47,000 non-African individuals from 24 communities showed a positive and age-dependent

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association between blood pressure and urinary sodium excretion across and within populations.[8,9] In the 2000s, in the INTERMAP study, the difference in the blood pressure between the populations in Northern and Southern China, was found to be partly due to dietary salt intake.[10] In the past 30 years, a large number of randomized controlled trials have analyzed the effect of reducing salt intake on blood pressure.[11] Most trials examined the effect of short-term salt reduction. Salt reductions of 4-6 g per day significantly reduce systolic/diastolic blood pressure both in hypertensive (~3-5/1-2 mm Hg) and in normotensive individuals (~1-2/0-1 mm Hg). Such small reductions are expected, if sustained and applied to the general population, to lead to a substantial reduction in cardiovascular events.[11]

Thus, among dietary strategies to counter this hypertension epidemic, principal role has been assigned to reducing dietary sodium at the population level as one of the most cost-effective public health strategies worldwide. Dietary salt reduction has been included in many guidelines for the treatment of hypertension and prevention of cardiovascular disease. The World Health Organization (WHO) recommends "salt reduction through mass-media campaigns and reduced salt content in processed foods"; "adults should consume <2 grams of sodium, or <5 g of salt per day"[1] [most sodium is consumed in the form of sodium chloride (salt); amount of sodium multiplied by the factor 2.5 gives the equivalent amount of salt]. However, recent studies have raised questions about potential harmful effects associated with low sodium intake.[3-5,12]

PURE AND NUTRICODE STUDIES

The Prospective Urban Rural Epidemiology (PURE) study was a large epidemiological study which followed 156,424 persons, aged 35-70 years, from 628 urban and rural communities in 17 low-, middle-, and high-income countries.[3,4] The investigators used as a surrogate for salt intake an estimated 24-hour sodium excretion by obtaining morning fasting urine samples; in the same samples they also estimated 24-hour potassium excretion.

In one report, they examined the relationship between sodium and potassium excretion and *blood pressure* measured with an automated device in 102,216 adults from 18 countries.[3] Regression analyses showed increments of 2.11 mm Hg in systolic blood pressure and 0.78 mm Hg in diastolic blood pressure for each 1-g increment in estimated sodium excretion. This association was proportional to sodium excretion with a steeper slope with higher sodium intake (an increment of 2.58 mm Hg in systolic blood pressure per gram for sodium excretion >5 g per day, 1.74 mm Hg per gram for 3 to 5 g per day, and 0.74 mm Hg per gram for <3 g per day; P<0.001 for interaction). The slope of association was also steeper for hypertensive individuals (2.49 mm Hg per gram) compared with non-hypertensives (1.30 mm Hg per gram, P<0.001 for interaction) and for older persons (2.97 mm Hg per gram at >55 years of age, 2.43 mm Hg per gram at 45 to 55 years of age, and 1.96 mm Hg per gram at <45 years of age; P<0.001 for interaction). Potassium excretion was inversely associated with systolic blood pressure, with a steeper slope of association for hypertensive vs non-hypertensive persons (P<0.001) and older ages (P<0.001). The authors concluded that the association of estimated intake of sodium with blood pressure was nonlinear and was most pronounced in persons consuming high-sodium diets, hypertensive individuals, and older persons; a significant inverse association with systolic blood pressure was found for estimated potassium excretion, with steep slopes of association among persons with hypertension, older, and obese persons.

In a second report the PURE study investigators examined the association between estimated urinary sodium and potassium excretion and outcome of *death and major cardiovascular events*.[4] The mean estimated sodium excretion was 4.93 g per day and potassium excretion was 2.12 g per day. With a mean follow-up of 3.7 years, death or cardiovascular events occurred in 3317 participants (3.3%). A higher estimated sodium excretion (≥7.00 g per day) was associated with an increased risk (odds ratio, 1.15), compared with an estimated sodium excretion of 4-6 g per day (reference range). The association was strongest among participants with hypertension (P = 0.02 for interaction), having an increased risk at an estimated sodium excretion of >6 g per day. Interestingly, a low estimated sodium excretion <3 g per day was also associated with an increased risk of the composite outcome (odds ratio, 1.27). On the other hand, higher potassium excretion was associated with a reduced risk of the composite outcome. The authors concluded that an estimated sodium intake between 3 g per day and 6 g per day was associated with a lower risk of death and cardiovascular events than was either a higher or lower estimated level of intake; higher potassium excretion was associated with a lower risk of death and cardiovascular events.

A major limitation of the PURE study, by the authors' own admission, is that their validated method of estimating sodium and potassium intake used a formula-derived estimate of 24-hour urinary excretion which is less reliable compared to actual 24-hour urinary collection.[3,4,6,13] The major criticism is directed against the provocative finding that low (in addition to high) levels of sodium excretion may be also associated with an increased risk of death and cardiovascular-disease outcomes. All agree that the associated risk is high with high sodium intake, but most disagree with the notion that this may also hold true with low sodium levels. The latter finding was further refuted by the second study reported in the same issue of the New England Journal of Medicine, the NUTRICODE study.[5]

The NUTRICODE study, part of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group, collected data from surveys on sodium intake determined by urinary excretion and diet in persons from 66 countries and

used these data to quantify the global consumption of sodium according to age, gender, and country.[5] The effects of sodium on blood pressure, according to age, race, and the presence or absence of hypertension, were calculated from data in a new meta-analysis of 107 randomized interventions, and the effects of blood pressure on cardiovascular mortality, according to age, were calculated from a meta-analysis of cohorts. Using comparative risk assessment, the investigators estimated the cardiovascular effects of current sodium intake, as compared with a reference intake of 2.0 g of sodium per day, according to age, sex, and country. In 2010, the estimated mean level of global sodium consumption was 3.95 g per day, and regional mean levels ranged from 2.18 to 5.51 g per day. Globally, 1.65 million annual deaths from cardiovascular causes were attributed to sodium intake above the reference level; 62% of these deaths occurred in men and 38% occurred in women. These deaths accounted for nearly 1 of every 10 deaths from cardiovascular causes (9.5%). Four of every 5 deaths (84.3%) occurred in low- and middle-income countries, and 2 of every 5 deaths (40.4%) occurred prematurely (before 70 years of age). Although the rate of death from cardiovascular causes associated with sodium intake above the reference level was highest in Central Asia and lowest in Kenya, it remained high (>750 deaths per 1 million adults aged ≥70 years) in all regions. The meta-analysis showed a linear dose–response relationship between reduced sodium intake and blood pressure, jointly modified according to age, race, and the presence or absence of hypertension. The authors concluded that in this modeling study, 1.65 million deaths from cardiovascular causes that occurred in 2010 were attributed to sodium consumption greater than 2 g per day.

GLOBAL APPROACH

The WHO recommends sodium reduction <2 g/day or salt reduction to ≤5 g/day.[1] These new data from PURE provide no reasons to change this recommendation.[3,4] NUTRICODE provided data on the effects of sodium consumption on blood pressure and cardiovascular risk.[5] The Global Burden of Disease data highlight the need for governments and the food industry to intensify their efforts to reduce salt in our diets. Although precise targets for sodium reduction remain controversial, various organizations having reviewed the existing evidence have proposed target levels from 1.2 to 2.4 g per day. Any suggestion that national or international guidelines should be changed on the basis of the PURE data is contrary to global best practice. Randomized trials of salt reduction show clear benefits on blood pressure, the leading cause of premature death in the world. This is the best evidence we have to date and it's the evidence that should guide health policy.

During the joint conference (Hypertension 2014) of the European and International Societies of Hypertension in Athens in June 2014, it was pointed out that any "controversy" over whether dietary salt is a cause of heart disease and stroke is the result of weak research methodology or industry interference (www.medscape.com).[13] Most researchers dismissed the use of spot urine analyses as a means of estimating sodium consumption, which was the method employed in the PURE study.[1,2] The researchers emphasized the striking statistic that a 2-g drop in the amount of salt consumed per day would translate into a 20% reduction in cardiovascular events. Citing a 2010 Institute of Medicine (IOM) report (http://www.iom.edu), Dr Campbell stated that approximately 32% of hypertension cases are caused by high dietary salt – a number that translates into about 300 million people. The same researcher indicated that the "Global Burden of Disease study estimates over 3 million deaths, 61 million years of disability, and 57 million years of life lost, all related to high dietary salt in 2010, which is really a massive and catastrophic public-health problem".

Reducing population salt intake requires measures from all parties involved, including the government, the food industry, non-governmental organizations, health professionals and the public.[1,14,15] According to WHO and European Union (EU), several countries have successfully carried out salt reduction programs as a result of which salt intake has fallen.[1,15] A reduction in salt intake contributed to the reduction of mortality from heart disease and stroke in Finland. The United Kingdom, the United States and several other high-income countries have also successfully developed programs of voluntary salt reduction in collaboration with the food industry.

A new study, published in BMJ Open,[14] determined the relationship between the reduction in salt intake that occurred in England, and blood pressure and cardiovascular mortality, by analyzing the data from the Health Survey for England between 2003 and 2011. According with these findings, there was a decrease in mortality from stroke by 42% ($p<0.001$) and ischemic heart disease by 40% ($p<0.001$). At the same time, there was a reduction in blood pressure of 3.0±0.33/1.4±0.20 mmHg ($p<0.001/p<0.001$), a decrease of 0.4 ±0.02 mmol/L ($p<0.001$) in cholesterol, a reduction in smoking prevalence from 19% to 14% ($p<0.001$), an increase in fruit and vegetable consumption (0.2±0.05 portion/day, $p<0.001$) and an increase in body mass index (BMI; 0.5±0.09 kg/m2, $p<0.001$). Salt intake, as measured by 24 h urinary sodium, decreased by 1.4g/day ($p<0.01$) (15% drop). The authors concluded that a 15% reduction in daily salt intake was likely an important contributor to the reductions in blood pressure from 2003 to 2011 in England, which further conferred a reduction in stroke and ischemic heart disease mortality during this period. Despite considerable progress being made on salt reduction, the mean salt intake in England (8.1 g/day in 2011) was still 35% higher than the recommended level of 6 g/day, and 70% of the adult population had a daily salt intake above the recommended level.

The WHO report indicates that sodium content is high in processed foods, such as bread (~250 mg/100 g), processed

meats like bacon (~1500 mg/100 g), snack foods such as pretzels, cheese puffs and popcorn (~1500 mg/100 g), as well as in condiments (seasoning/flavoring) such as soy sauce (~7000 mg/100 g), and bouillon or stock cubes (~20 000 mg/100 g).[1] The EU report blames bread, meat and meat products and dairy products (including cheese), ready meals and soups as the most important sources of salt in the national diet of most EU countries.[15] On the other hand, potassium-rich food helps to reduce blood pressure. WHO recommends that adults should consume ≥3,510 mg of potassium/day. Potassium-rich foods include beans and peas (~1,300 mg of potassium per 100 g), nuts (~600 mg/100 g), vegetables such as spinach, cabbage and parsley (~550 mg/100 g) and fruit such as bananas, papayas and dates (~300 mg/100 g).[1] Processing reduces the amount of potassium in many food products.

CONCLUSION

Although the new studies (PURE and NUTRICODE)[3-5] stirred some controversy about the importance of salt intake in controlling blood pressure and affecting cardiovascular mortality, the evidence for the significant role of salt intake in this epidemic remains strong and should not lead us to deviate from the primary goal of reducing dietary salt intake, while at the same time increasing dietary potassium, as a means to counter the adverse effects of hypertension on cardiovascular disease and population health, in general.[1,15,16]

On the average, salt intake remains excessive in most populations (with the majority ranging between 8 and 12 grams of salt per day) and several countries have started to implement population-based strategies to reduce it.[15] There is dire need to observe and comply with the WHO recommended values (<2 grams of sodium or <5 grams of salt per day). Despite the "controversy", there is considerable benefit of salt reduction effected via reduced blood pressure and cardiovascular events, and it appears that the worry of doing harm is negligible or absent.[11,16] Furthermore, there appears to be evidence that high salt intake is also likely associated with diseases other than cardiovascular disease (such as gastric cancer, obesity and osteoporosis).[17-20] Thus, the strategy of limiting dietary salt intake is considered as one of the most cost-effective public health strategies worldwide and should be applied through legislation at both the industry and the consumer levels.[1,11,15,16]

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