DOI: 10.1111/jch.13019

COMMENTARY

WILEY

Sodium intake, sodium excretion, and cardiovascular risk: involvement of genetic, hormonal, and epigenetic factors

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1 | INTRODUCTION

Yasutake and colleagues[1] have published an interesting study on the interannual changes in the sodium excretion levels, as estimated from spot urine, of young healthy Japanese women. The authors have reported a significant reduction in urinary sodium excretion during the past 20 years, independent of body weight and consistent with a gradual decline in sodium intake.

The use of salt started about 5000 years ago when the Chinese discovered that it could preserve foods. After the development of refrigeration for food, sodium intake was gradually reduced, but it subsequently increased once salt was introduced for processing foods, particularly in the Western world. Some countries, including Japan, have reduced the sodium content in processed food through official regulations.[2]

2 | SALT INTAKE: JAPANESE STUDIES

Salt intake in Japan was extremely high in the late 1950s and was correlated with an increased rate of stroke and cardiovascular events. In the following decades, salt and sodium intake were reduced and, in parallel, the incidence of hypertension and cardiovascular accidents significantly decreased.[2]

The most important message of the study by Yasutake and colleagues[1] is that Japanese women attending the Department of Nutritional Sciences at Nakamura-Gakuen University have reduced their sodium intake during the past 20 years. It was noted, however, that these women were likely more motivated, as they were a faculty involved in nutrition, and that women in other faculties might be less interested in health and therefore consumed more salt.

3 | US STUDIES

A recent review evaluating mean 24-hour urine sodium excretion from 1957 to 2003 in the United States reported that sodium intake appears to be well above the current guidelines and does not appear to have decreased with time, despite the continued warnings about the risk of hypertension and cardiovascular complications.[3] It is interesting to note that the prevalence of hypertension and heart disease has increased in the US population despite the absence of sodium intake changes, likely due to the increased rate of obesity, regular use of nonnarcotic analgesics, physical inactivity, and nonadherence to a low-sodium diet.[4]

A study by McCarron and colleagues[5] analyzed sodium intake in 19 151 persons in 33 different countries during a 24-year period, confirming higher sodium consumption than that recommended by the experts, with no evidence of change over time.

Interestingly, the intake of salt or sodium has not decreased in the United States, but, rather, has remained unchanged, while the incidence of cardiovascular accidents and hypertension has increased with the time.[3] On the other hand, many studies have demonstrated that restriction of salt intake can decrease the future risk of cardiovascular and metabolic complications in patients with a preliminary risk.[6]

4 | COMPLEXITY OF SODIUM BALANCE AND ROLE OF ALDOSTERONE

The measurement of spot urine sodium is not always an estimated measure of 24-hour sodium excretion, as the values of sodium sometimes vary during the day. Many factors can disturb the interpretation of the sodium value in spot urine, including stress, obesity, individual salt sensitivity, and antihypertensive and diuretic treatments. Aldosterone is the main hormonal factor involved in this misinterpretation. Situations of hyperaldosteronism caused by volume depletion are associated with increased sodium excretion without increased sodium intake. A hyposodic diet or use of diuretics can reduce cardiovascular risk, decreasing blood pressure and volume, but the subsequent increase in aldosterone can have an opposite consequence because of its direct proinflammatory effect at the level of the mineralocorticoid receptor in mononuclear leukocytes and vessels.[7]

In primary aldosteronism or pseudohyperaldosteronism, sodium excretion is high as a result of the escape of kidney to the action of aldosterone, independently from sodium intake. Increased water consumption can also dilute sodium in spot urine and interfere with the correct sodium estimation in urine.[8]

5 | GENETIC AND EPIGENETIC FACTORS INVOLVED IN SODIUM EXCRETION

Sodium metabolism is related to a balance between sodium intake and sodium excretion, but other individual factors can be involved, such as water intake, activity of the renin aldosterone system, antidiuretic hormone, natriuretic hormones, cortisol, body mass index, insulin resistance, and many other factors. The equilibrium of all these elements could be deranged by genetic and/or epigenetic factors, leading to increased cardiovascular risk, hypertension, and diabetes mellitus. In fact, the genetic predisposition to a particular disease derives from genes, but somatic mutations or epigenetic alterations involving gene activity and expression without modifications in the nucleotide sequence can be induced by particular situations related to our altered lifestyle. This can also exacerbate insulin resistance, obesity, physical inactivity, excessive consumption of salt, diabetes mellitus, inflammation, and infections.

Individuals predisposed to diabetes mellitus or hypertension should be instructed to avoid risk factors, following an appropriate diet, lifestyle, water and salt intake, reducing alcohol consumption, and avoiding drugs and cigarettes.

6 | THE MODEL OF POLYCYSTIC OVARY SYNDROME

Guidelines have recommended sodium restriction in people with obesity and hypertension, but perhaps it is also important to recommend lifestyle modification to healthy people predisposed to future diseases, like for example patients affected with polycystic ovary syndrome (PCOS).

PCOS is a classic example of pathological condition characterized by increased metabolic and cardiovascular risk.[9] In the majority of cases, PCOS is a genetic disease related to insulin resistance, which predisposes to obesity, hypertension, preeclampsia, and metabolic syndrome. Insulin resistance is a characteristic of both obese and lean patients with PCOS.[10] Treatment with healthy lifestyle, metformin, or inositol could prevent the progression to diabetes mellitus and metabolic and cardiovascular risk later in life. It is well known that these patients are predisposed to hypertension and preeclampsia, and, therefore, regulated salt intake is also important to reduce the risk associated with genetic predisposition.[11] PCOS is also associated with an increase in aldosterone levels and in the aldosterone to renin ratio, even in the normal range, compared with healthy women of the same age and weight.[9] Aldosterone is one of the main factors involved in sodium balance and is also associated with hypertension, cardiovascular risk, insulin resistance and increased sodium excretion caused by the "escape" phenomenon. Estroprogestinics are a frequent choice of therapy for PCOS patients. However, it is known that they frequently increase renin and aldosterone levels and, therefore, the future risk of cardiovascular and metabolic complications may be enhanced. Recently we proposed, in PCOS treatment,[12] the use of spironolactone, a mineralocorticoid receptor antagonist, which is also a potent blocker of androgen receptors and an inhibitor of androgen synthesis, improving the clinical characteristic picture of hyperandrogenism. Moreover, the block of aldosterone receptors can reduce systemic inflammation, ameliorating insulin resistance and reducing the predisposition to metabolic and cardiovascular risk related to increased aldosterone activity.[13]

7 | CONCLUSIONS

Cardiovascular risk is not only linked to increased sodium intake, but also to many individual factors. Diseases are often preceded by a condition of health and therefore the concept of prevention or delay of future diseases is important. Individuals can be predisposed to the metabolic syndrome, hypertension, cardiovascular diseases, and diabetes, and, therefore, the family history is important, suggesting the need for a healthy lifestyle with limitation of sodium intake when its use is not appropriate. Low-sodium intake should be prescribed with caution to patients with hypertension or cardiovascular diseases. In these cases, we must always consider that low-sodium diet and most of the diuretics can increase aldosterone and its inflammatory effect. We suggest the use of aldosterone receptor antagonists to block mineralocorticoid receptors and reduce cardiovascular risk.

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How to cite this article: Armanini D, Bordin L, Donà G, et al. Sodium intake, sodium excretion, and cardiovascular risk: involvement of genetic, hormonal, and epigenetic factors. *J Clin Hypertens*. 2017;19:650–652. https://doi.org/10.1111/jch.13019