Dietary Salt Can Be Crucial for Food-Induced Vascular Inflammation

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ABSTRACT: Salt enhances the taste as well as the nutritional value of food. Besides, several reports are available on the incidence and epidemiology of various illnesses in relation to salt intake. Excessive salt consumption has been found to be linked with high blood pressure, renal disease, and other cardiovascular disorders due to the result of vascular inflammation. Nevertheless, studies aimed at elucidating the molecular processes that produce vascular inflammation have yet to reach their conclusions. This article emphasizes the significance of investigating the mechanisms underlying both acute and chronic vascular inflammation induced by salt. It also explores the logical inferences behind cellular oxidative stress and the role of endothelial dysfunction as the potential initiator of the inflammatory segments that remain poorly understood. It is therefore hypothesized that salt is one of the causes of chronic vascular inflammation such as atherosclerosis. The hypothesis's secrets, when revealed, can help assure cardiovascular health by proactive efforts and the development of appropriate preventative measures, in combination with medication, dietary and lifestyle adjustments.

KEYWORDS: Atherosclerosis, cardiovascular disease, cellular oxidative stress, dietary salt, endothelial dysfunction, vascular inflammation

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Background

Inflammation serves as a vital component of the body's defense mechanisms, aiding in the removal of harmful stimuli and tissue restoration. Researchers and clinicians have switched their attention to the molecular processes underlying the activation of inflammatory factors and its downstream consequences because of the central role inflammatory mediators play in the pathophysiology of chronic vascular inflammation (VI). In addition, there has been a lot of interest in using this information to create targeted medicines that modify inflammatory activity in the hopes of slowing disease progression and lowering the problems associated with cardiovascular diseases (CVDs). VI holds particular significance, as it perturbs homeostasis by affecting immune cells and nutrient distribution through arteries. Numerous cardiovascular disorders stem from vascular permeability and arterial changes, including atherosclerosis—a chronic VI inducing vessel hardening through plaque buildup. Inflammatory mediators, or occasionally immune-mediated inflammatory disorders, are crucial to the onset and development of acute or chronic VI.[1,2] These molecules are multiprotein complexes that play a significant role in the innate immune response,[3] particularly in pathogen recognition and action. The cells are able to pick up on things like infection and tissue damage. However, in addition to immune cells like leukocytes and dendritic cells, inflammatory proteins are also present in epithelial and endothelial cells.

VI's etiologies include tobacco use, excessive weight, hypertension, diabetes, poor diet, inactivity, and other ailments. It involves immune elements like cytokines, reactive oxygen species (ROS), receptors, and intricate pro-inflammatory signaling pathways (eg, NF-κB, Ras/Raf/MAPK, STAT3, NLRP3 inflammasome, TGF-β, mineralocorticoid receptor activation, canonical wingless-related integration site WNT/β-catenin).[4-6] Despite extensive research into the aforementioned perspectives, the many functions inflammation serves and the identification of new inflammatory mediators remain under investigation.

Dietary salt, sodium chloride (NaCl), is vital for enhancing food flavor, yet excessive consumption associates with hypertension, renal issues, and VI.[7] Regions with high salt intake show elevated CVD rates. Research primarily focuses on high-fat diets, necessitating exploration of the link between high salt intake and VI; therefore, the article aims to bridge scientific facts and epidemiology to address this gap.

Epidemiological Status of Salt-Induced Cardiovascular Abnormalities

It has been estimated through that excessive sodium consumption causes 3 million deaths and 70 million disability-adjusted life years (DALYs) worldwide.[8] CVDs, a group of disorders of the heart and blood vessels, have been found to be the major cause of death, early mortality, and disability in the World Health Organization (WHO) European regions.[7] Notwithstanding the WHO's recommendation that no one, regardless of gender, consume more than 5 g of salt per day, the average dietary consumption of salt across the European regions in 2022 was between 5.39 and 18.51 g for males and 4.27 to 16.14 g for women.[7] According to a recent research, CVD is

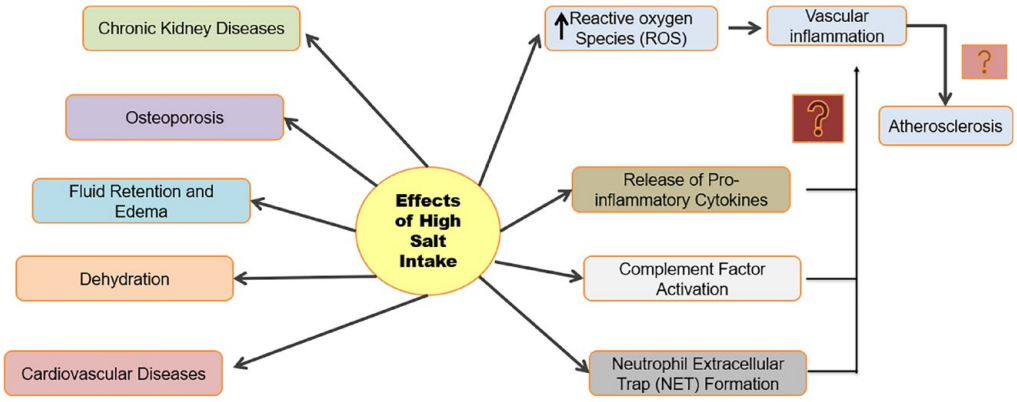

Figure 1. The impact of a heavy salt diet on health. The presence of a question mark indicates inquiry into the potential correlation between elevated salt intake and the occurrence of vascular inflammation.

the leading killer in this area. Premature deaths from CVD in those younger than 70 years old are of special concern, as are the more than 60 million years of life lost to CVD each year in Europe. Moreover, more women than males die from CVD in these regions.[9] In spite of the WHO's salt consumption recommendation, a large percentage of people in sub-Saharan Africa continue to consume excessive amounts of salt in their diets (81% of adults and 33% of children).[10] It is anticipated that 1 million people in those regions lost their lives to CVD in 2013, making up 11.3% of all fatalities in Africa. By 2030, this number is expected to have doubled.[11] Rapid urbanization in emerging and poor nations is a key driver of dietary changes, especially an increase in dietary salt intake due to an increase in the consumption of fast food, and high fat-diets prepared by salty condiments. Furthermore, especially in coastal areas, using raw ground water for drinking purposes can lead to an increase in salt consumption that is above the WHO recommended daily sodium intake. For example, those who live in coastal parts of Bangladesh, a fast growing country, consume an extra 700 mg of sodium per day since the average sodium content in drinking water is over 1.5 g/L.[12] It is therefore possible, in certain countries, to consume more than the WHO's daily guideline simply by drinking 2 to 3 l of water. Almost 80% of CVD fatalities occur in low and middle-income countries, and over 40% of these are designated as premature, indicating that there is still a reputational risk of CVD, which is significantly greater in developing and underdeveloped nations than in high-income developed nations.[13]

Dietary Salt Intake and VI: The Molecular Basis

Because of its role as an electrolyte in human metabolism, salt is a staple ingredient in every culture. Ancestral humans subsisted on less than 1 g of salt per day[14] for millions of years. Most nations throughout the world use between 9 and 12 g of salt per day,[14] and this number is expected to rise in light of the recent surge in the consumption of highly-salted processed food items. Most commercially available NaCl has been adulterated such as iodized. Iodized salt has greatly decreased iodine-deficient illnesses because iodine is a crucial micronutrient for humans. Salt is found in naturally occurring foods such as meats, vegetables, and fruits, but only in trace amounts. There is more salt in animal tissues such as meat, blood, and milk, than there is in plant tissues. Most of the person's daily sodium consumption comes from the salt present in processed foods, and the use of salt in processed foods has increased dramatically in recent years.

Excess sodium consumption with meals is thought to be a crucial element in causing hypertension[15] and increasing cellular oxidative stress.[16] Yet, excessive dietary salt is linked to detrimental effects on human health (Figure 1) especially vascular health irrespective of the context of hypertension. A higher salt consumption is associated with an elevated risk of early vascular events and cardiovascular death, and this association holds true even in the absence of hypertension.[16] Given the significance of NaCl intake in hypertension and the proximity of the gastrointestinal tract to ingested sodium, it would be unwise to ignore the potential interactions between dietary sodium and gut microbiota. Hypertension is recognized as the most frequent risk factor for chronic renal disease and acute or chronic vascular inflammatory disorders. Diet, inactivity, excess weight, tobacco use, obesity, and stress are all environmental variables that raise the likelihood of developing hypertension.[17] There is a growing body of evidence suggesting that the microorganism-rich gastrointestinal tract plays a crucial role in host metabolism. A recent study has shown that changes in gut microbiota can contribute to the onset of hypertension in rats,[18] but similar investigations in humans are in the early stages. Due to its effect on gut microbial setup, abundance, and variety,[18] high dietary salt consumption may lead to gut dysbiosis. In addition to raising blood pressure directly, a high-sodium diet may have a role in the development of VI, a concern that calls for intensive investigation at the molecular level.

At the same time, people in the upper category of dietary sodium intake are more likely to develop congestive heart failure than those in the bottom category, and this association persists even after adjusting for factors like age, gender, race/ethnicity, food habits, lifestyle, and hypertension.[19] Besides, left ventricular hypertrophy may be reversed with salt reduction, and higher sodium consumption is linked to a thicker left ventricle in both normal and hypertensive people.[20] Endothelial dysfunction (ED) is a common precursor to VI[21] and may be an obvious indicator of the harmful consequences of high dietary salt intake. Wenzel et al conducted a review and found that lymphocytes cause an increase in blood pressure by damaging vascular endothelial cells and causing the kidneys to retain salt.[22]

ED is an early correlate for coronary artery disease in humans,[23] and it occurs in some autoimmune diseases such as rheumatoid arthritis, psoriasis, and diabetes. As a result, ED accelerates atherosclerosis and causes cardiovascular mortality.[24] ED and vascular injury are additionally strongly linked to oxidative stress and inflammation in the blood vessels. In addition, the idea that oxidative stress and chronic VI play a role in the pathogenesis of cardiovascular events such as hypertension and atherosclerosis has been articulated.[25] There is an interaction between the oxidative stress and the vascular dysfunction that has been established. An increased level of pro-oxidant may raise the level of ROS in the cell and cause inflammatory cascades (Figure 4).

Oxidative stress plays a significant part in the development of vascular diseases through a number of different mechanisms.[26] In most cases, when ED develops, circulating LDL will transmigrate to subendothelium, where it will be subjected to oxidation and eventually produce oxidized-LDL (ox-LDL).[27] Ox-LDL was found responsible for the expression of chemokines such as CC motif ligand 2 (CCL2) in vascular endothelial cells, chemokine (C-X-C motif) ligands (CXCLs), tumor necrosis factor (TNF), colony stimulating factors, and various adhesion molecules such as integrins and selectins, intracellular adhesion molecule (ICAM)-1 and vascular CAM-1, resulting in leukocyte recruitment and endothelial transmigration.[28,29] Moreover, ox-LDL causes vascular endothelial cells to secrete and produce macrophage colony-stimulating factors (M-CSFs), which in turn promotes the maturation and differentiation of monocytes into macrophages. Foam cells are formed when macrophages amass high levels of ox-LDL. It is assumed that these foam cells emit numerous cytokines, developing inflammation and oxidative stress in the vascular endothelium.[4] When present in atherosclerotic lesions, these systems establish a self-perpetuating cycle that initiates atheroma production and, ultimately, cardiovascular events. It has been suggested that ox-LDL may contribute to atheroma fragility and instability by promoting apoptosis of the luminal side of the atheroma, vascular smooth muscle cell (VSMC) lining.[30] Tissue plasminogen activator (t-PA) synthesis from vascular endothelial cells is inhibited and plasminogen activator inhibitor-1 (PAI-1) production is upped by ox-LDL.[31] Thus, ox-LDL plays a significant role in the onset, development, and progression of atherosclerosis and atherogenesis. Vascular endothelial cells were used to generate a new scavenger receptor for ox-LDL called lectin-like ox-LDL receptor-1 (LOX-1). Interestingly, LOX-1 is substantially expressed in endothelial cells, VSMCs, and macrophages in atherosclerotic lesions,[32,33] but is very weakly expressed in normal arteries. Increased expression of adhesion factors, chemokines, cytokines, and monocyte migration into the vessel wall are all the result of ROS excess, which activates redox transcription factors including nuclear factor-kappa B (NF-κB) and AP-1.[34] Suppressing NF-κB activity reduces interleukin (IL)-6, VCAM-1, and CCL2 expression.[35] Many studies have demonstrated that inflammation may play a role in vascular damage.[4-6,28,36,37] NADPH oxidase is activated in the presence of angiotensin II, ox-LDL, and inflammatory cytokines, leading to oxidative stress and subsequent inflammation. It is therefore believed that oxidative stress, inflammation, and ED are all interconnected and play significant roles in the initiation, advancement, and recurrence of atherosclerosis.[28]

High salt consumption has been linked to ED,[4-6] and studies have shown hypertension-independent and -dependent cellular activation expressing pro-inflammatory cytokines and producing oxidative stress. New evidence suggests that increased sodium levels activate antigen-presenting cells (APCs) (such as dendritic cells (DC), macrophages, and B cells) and T cells via oxidative stress and the NLRP3 inflammasome. The pathophysiology of vascular inflammation and hypertension are both influenced by these mechanisms.[6]

An elevated salt concentration has also been shown to influence neutrophil IL-8 secretion and neutrophil extracellular trap (NET) synthesis.[38] High salt concentrations can activate neutrophils; as a defensive mechanism, activated neutrophils are more likely to release NETs.[39] exposure to high salt for longer periods (6-18 h) resulted in the activation of neutrophils revealed by the production of high levels of IL-8, the activation of the respiratory burst, and a marked synergistic effect on the production of TNF-α induced by lipopolysaccharide (LPS).[40] Consuming a lot of salt has been linked to oxidative stress, which may also cause NET that may ultimately cause VI. By counteracting the effects of TGF-β1 synthesis, nitric oxide (NO) is generated in response to elevated salt ingestion. An increased salt diet, which raises the intravascular synthesis of TGF-β1,[41] may amplify the effect of age-related ED on promoting vascular stiffness through TGF-β1 production. According to Laurent and Boutouyrie, reducing salt intake may reduce arterial stiffness, a risk factor for cardiovascular events.[42]

In animal models used in research, aldosterone's effects on oxidative stress, inflammation, and fibrosis are facilitated by a high sodium intake.[43,44] Oxidative stress may potentially be

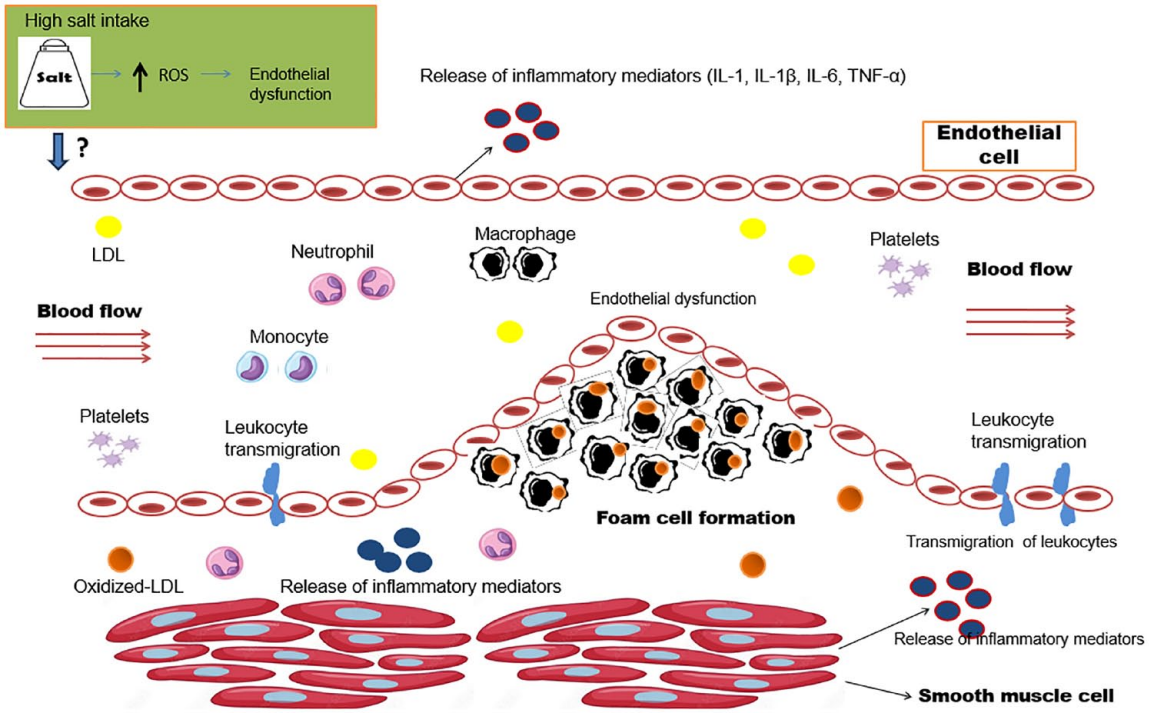

Figure 2. High salt intake and vascular inflammation: Is there any potential connection? It most likely depicts blood arteries with inflammatory cells and indicators. The idea is to illustrate how consuming too much salt can cause blood vessel inflammation. High salt intake produces more reactive oxygen species (ROS) which may cause endothelial dysfunction. In the presence of high amount of ROS, LDL oxidizes and converts into ox-LDL which is considered as harmful components by immune system. Macrophages engulf the oxidized LDL at the site of endothelial dysfunction and development of foam cells occurs. Foam cell formation helps to form atherosclerotic plaques exacerbating inflammation by releasing pro-inflammatory mediators such as .IL-1, IL-1β, IL-6, TNF-α etc.

exacerbated by an increase in the local tissue renin-angiotensin-aldosterone system (RAAS) in response to high sodium ingestion.[44,45] Notably, when aldosterone is present, even minor elevations in plasma sodium result in a reduction in NO release and an increase in the rigidity of endothelial cells in vitro.[46]

High salt intake can potentially lead to VI in several ways (Figure 2). The inner lining of blood arteries, or endothelium, is crucial for controlling blood flow, maintaining vascular tone, and avoiding inflammation. High salt consumption has been associated with ED, which affects the proper operation of endothelial cells.[47] ROS in the body have been found linked to high salt intake through ED, and salt-sensitive hypertension.[48] Consuming an excessive amount of salt can have negative effects on mitochondrial function, including oxidative phosphorylation as well as ATP synthesis, calcium balance, mitochondrial membrane potential, and the activity of the mitochondrial uncoupling protein.[49] The protein expressions involved in the Krebs cycle are altered and oxidative stress in the mitochondria is exacerbated when excessive salt is consumed (Figure 3). Abnormal phenotypic differentiation of VSMCs is a consequence of mitochondrial failure under pathological settings, which leads to mitochondrial ROS production and metabolic abnormalities.[50] Dedifferentiated VSMC are characterized by their ability to migrate, an event regulated

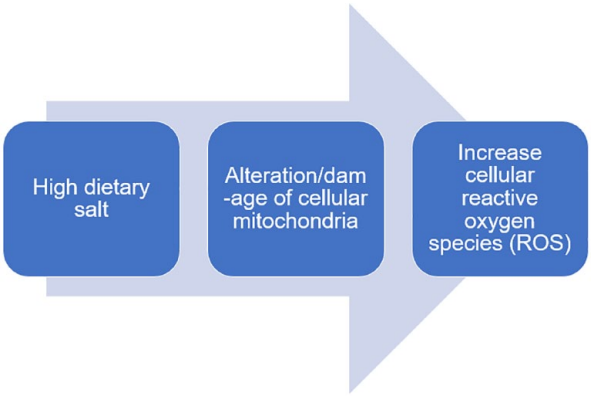

Figure 3. Increased ROS due to dietary salt intake.

by ROS.[51] Lamellipodia development, focal adhesion kinase activation, and actin polymerization are all aspects of these processes in response to specific chemoattractants.[52] Focal adhesion proteins, which serve as sites of cell attachment to the extracellular matrix, are activated or deactivated by ROS.[53] Src tyrosine kinase and actin undergo cytoskeletal rearrangement, but ROS disrupt this process by oxidizing their respective thiols. Notably, the rate and the extent of actin polymerization are enhanced under oxidative circumstances.[54,55] According to a recent study, the pathogenesis of age-related hypertension is

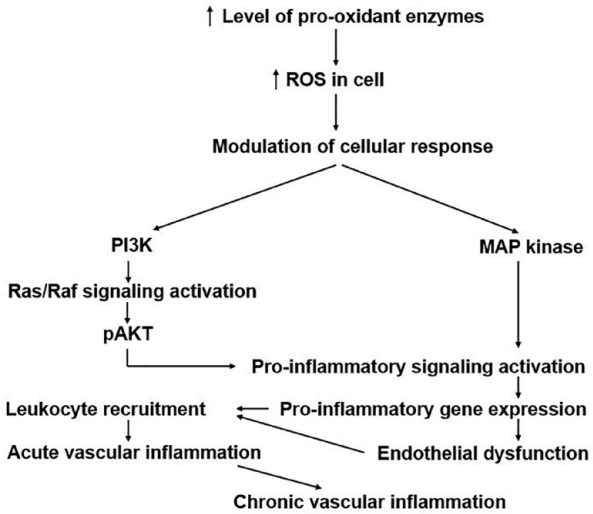

Figure 4. Crosstalk between oxidative stress and vascular inflammation. Increased level of pro-oxidant enzymes and decreased level of antioxidant mediators may raise the ROS level in the cells. Activation and phosphorylation of different pro-inflammatory signaling pathways have been explored in different studies such as PI3K, MAP kinase, NF-κB, ERK-MAP kinases, STAT3 and so forth, that may influence various inflammatory protein expression from leukocytes and vascular endothelial cells such as IL-1, IL-6, IL-18, CCL2, TNF-α, and other pro-inflammatory cytokines. The expressed inflammatory mediators eventually may develop acute VI and chronic VI at a later stage.

associated with the induction of vascular Wnt-RhoA signaling through excessive sodium consumption.[56] Recent work by Kawarazki Sensei and colleagues provides a brief overview of molecular processes controlling Rho and Rac activation in relation to vascular disorders including hypertension.[56,57] The Rho family is part of signaling networks that control the actin-based cytoskeleton.[58] The pathophysiology of hypertension and cardiovascular-renal ailments are influenced by the activation of RhoA/Rho-associated protein kinase (ROCK), which is responsible for increasing Ca^{2+} sensitivity in VSMC and vascular tone.[59] VSMCs are fundamental constituents of vascular structure and function. A phenomenon whereby VSMCs may adopt a dedifferentiated, proliferative synthetic phenotype is referred to as phenotypic transition. Significant alterations occur in VSMC differentiation, proliferation, migration, inflammatory gene expression, extracellular matrix (ECM) deposition, and cellular rigidity during this transition.[57,60]

The induced oxidative stress may induce VI (Figure 4). Consuming excessive amounts of salt can stimulate the immune system, causing a surge in certain immune cells and cytokines that promote inflammation.[48] One significant component is the T-helper 17 (Th17) cell population, which is linked to the production of pro-inflammatory cytokines including IL-17. VI and endothelium dysfunction can be caused by Th17 cells and their cytokines.[61] Furthermore, TNF-α, IL-6, and IL-1b are just a few of the pro-inflammatory cytokines that have been found expressed due to higher salt intake. These cytokines can increase inflammation and help vascular disorders to develop. On the other hand, ox-LDL is pivotal in VI and atherosclerosis, evoking immune responses and foam cell formation. As ox-LDL is perceived as harmful, immune cells, mainly macrophages, work to eliminate it from arterial walls. This prompts foam cell formation, hallmarking early atherosclerotic plaques, exacerbating inflammation, and arterial fatty streak enlargement.[62] The resulting inflammation releases cytokines, chemokines, and signaling molecules, attracting immune cells. Ox-LDL also spurs smooth muscle cell proliferation in arterial walls. These cells migrate to the inflammation site, constructing a fibrous cap atop atherosclerotic plaque. While this cap initially bolsters stability, it can ultimately rupture, precipitating VI.

Present Scenario and Future Directions

Independent of hypertension, VI is one of the leading causes of CVDs. A high salt intake can be a major cause of hypertension, which raises the risk of CVDs such as stroke, myocardial infarction, heart disease, and kidney disease. Although it is common knowledge that salt may raise blood pressure, there has been little impetus for studying sodium's effects on the cardiovascular system beyond the issue of hypertension. Based on the statistics, it can be stated that the prevalence of CVD can be attributed to salt consumption in any way. Even so, less emphasis is placed on salt-induced vascular inflammatory studies. In vitro and in vivo salt-based investigations of inflammatory cytokine production, leukocyte recruitment, and endothelial transmigration data are insufficient to establish a correlation between salt intake and the development of VI. In addition, research on gender variations in the cardiovascular response to dietary salt is overlooked. There is some data suggesting that the vascular response to sodium in food differs between women and men. The NO of the arm's blood flow response to acetylcholine (Ach), a blood vessel dilation factor, was lower in the male population who took the high sodium chloride diet compared to the group who consumed a reduced salty diet, but no significant difference was observed between the 2 distinct groups of women.[63] Besides, recent research has shown that a high-salt diet for a week can diminish flow-mediated dilation in healthy salt-resistant men and women, with the effect being more pronounced in men.[64] These studies raise questions about whether males are uniquely vulnerable to the health risks associated with a high-salt diet. Variations in CVD and hypertension-related genetic polymorphisms in response to daily salt consumption data are also not given emphasis, which is rather novel in the context of eating habit-based CVD burden.

Conclusion

In light of the fact that VI is now widely acknowledged as a major contributor to the global CVD burden, there is an urgent need for researchers to investigate the discrepancies between risk factors and treatment alternatives.[65] The evidences suggest

that genetic, cultural, and environmental differences exist in the etiology of CVD by race and ethnicity. These variances should be taken into account when developing methods for the prevention and treatment of CVD. Clinical trials and observational research developed particularly to investigate disparities among racial/ethnic subgroups are essential for enhancing CVD care worldwide.

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Author's Contributions

SMRD conceptualized, wrote the article, revised, supervised, and submitted the article. SSM and AYP wrote the manuscript draft. MS revised the manuscript.

Ethics Statement

Not applicable.

Consent to Participate

Not applicable.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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