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REVIEW PAPER

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Salt-induced effects on microvascular function: A critical factor in hypertension mediated organ damage

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Abstract

Salt has been linked very closely to the occurrence and complications of arterial hypertension. A large percentage of patients with essential hypertension are salt-sensitive; that is, their blood pressure increases with increased salt intake and decreases with its reduction. For this reason, emphasis is placed on reducing salt intake to better regulate blood pressure. In day-to-day clinical practice this is viewed as mandatory for hypertensive patients who are judged to be salt-sensitive. Previous studies have highlighted the negative effect of high-salt diets on macrovascular function, which also affects blood pressure levels by increasing peripheral resistances. More recent studies provide a better overview of the pathophysiology of microvascular disorders and show that they are largely due to the overconsumption of salt. Microvascular lesions, which have a major impact on the functioning of vital organs, are often not well recognized in clinical practice and are not paid sufficient attention. In general, the damage caused by hypertension to the microvascular network is likely to be overlooked, while reversion of the damage is only rarely considered as a therapeutic target by the treating physician. The purpose of this review is to summarize the impact and the harmful consequences of increased salt consumption in the microvascular network, their significance and pathophysiology, and at the same time to place some emphasis on their treatment and reversion, mainly through diet.

1 | INTRODUCTION

Essential hypertension is a very important modifiable risk factor for the occurrence of severe cardiovascular complications. However, apart from its effects on the large vessels, hypertension may lead, even in its initial stages, to small-vessel disease and dysfunction.[1] This phenomenon occurs in two main ways. First, by increasing the media-to-lumen diameter ratio of the small vessels and second, by causing a decrease in their density (rarefaction).[2] This reduction concerns the arterioles and capillaries and worsens with the stage and severity of the hypertension.[3]

On the other hand, salt has been linked very closely with the occurrence and complications of hypertension.[4,5] It has been estimated that up to 50% of all individuals with essential hypertension are salt-sensitive: that is, their blood pressure (BP) increases with increased salt intake and decreases with its reduction.[4,6] For this reason, emphasis is placed on reducing salt intake to better regulate BP. In everyday clinical practice this is considered mandatory for hypertensive patients who are judged to be salt-sensitive. Previous studies have shown the negative effect of a high-salt diet on macrovascular dysfunction, which also affects BP levels via an increase in peripheral resistances.[7] In previous years this was considered the main mechanism of participation of the peripheral vasculature in essential hypertension, as was illustrated by experimental salt-induced exacerbation of hypertension in animal studies.[8] Several other studies provide a

better picture of the pathophysiology of microvascular disorders due to the overconsumption of salt, which are often not sufficiently recognized in clinical practice.[9-12] In addition, despite the significant role of salt intake in microvascular dysfunction, very little attention has been paid in the literature to how therapeutic interventions may be able to modify these changes. Generally, the damage caused by hypertension to the microvascular network tends to be overlooked, while the possibility of reversion is only rarely considered as a therapeutic target by the treating physician.

The purpose of this review is to summarize the impact and the harmful consequences of increased salt consumption in the microvascular network, their significance and pathophysiology, and at the same time to place some emphasis on their treatment and reversion, mainly through diet.

2 | MICROVASCULAR DYSFUNCTION ASSOCIATED WITH HIGH-SALT INTAKE IN EXPERIMENTAL SETTINGS

Extensive experimental and clinical data have demonstrated the adverse effect of increased salt intake on the microvascular circulation (Table 1).[7-11,13-17] Increased salt consumption may provoke water retention that leads to high renal flow conditions. This high-flow condition—as studies with animal models show—may induce adverse microvascular remodelling through increased mechanical load, such as hear stress and hemodynamic forces.[18] Beyond this, however, there is plentiful experimental evidence showing τηv resulting microvascular dysfunction directly associated with high-salt diet. Microvascular rarefaction, that is, a reduction in the number of arterioles and capillaries, is a frequent complication of organs in hypertension[19] that is rarely examined or considered in clinical practice. Administration of a high-salt diet for four weeks has been shown to induce rarefaction in skeletal muscle, specifically a reduction in capillary density.[9,10] Other experimental animal studies have shown that a high-salt diet, apart from microvascular rarefaction,[9,10] also results in inward remodelling.[9,11] The extracellular matrix is also a significant determinant of various microvascular cellular functions, although these have not been completely defined. In addition, it appears that an increased salt intake can also affect the microvascular network adversely via other mechanisms, such as the potentiation of action of vasoconstrictors[11,20] or disturbances of endothelial Ca^{2+} signalling.[21] Previous experimental studies have shown that hypoxia-induced dilation in the mesenteric resistance arteries of rats fed a high-salt diet is significantly impaired as a result of abnormally high production of 20-hydroxyeicosatetraenoic acid (HETE),[22] a vasoconstrictor metabolite of cytochrome P 450 4A ω-hydroxylase. This may provide a pathogenetic pathway linking increased salt intake to microvascular dysfunction. The CYP4A pathway contributes significantly to the induction of vascular oxidant stress and the concomitant microvascular dysfunction in salt-sensitive rats on a high-salt diet.[23]

3 | MICROVASCULAR DYSFUNCTION ASSOCIATED WITH HIGH-SALT INTAKE IN HUMAN STUDIES

Aside from experimental studies, various human studies have identified mechanisms of microvascular dysfunction in individuals with high-salt intake. (Table 2) The proven harmful effect of increased dietary sodium intake on endothelial function has been demonstrated during the evaluation of cutaneous microvasculature in otherwise healthy adults, independently of changes in BP.[29] Greaney et al has also reported that ingestion of a high Na^+ diet for 7 days had no significant effect on BP, but reduced the dilator response of cutaneous arterioles to localized heating through a selective loss of the NO-dependent component of this dilation.[13] High dietary salt intake in healthy young persons is associated with reduced vascular NO bioactivity.[13,30] Intravenous sodium loading may cause an acute increase in microvascular permeability in healthy male subjects, attributable to adverse effects on the endothelial surface layer.[31] Even short-term salt intake reduces brachial artery endothelial function and switches the mediator of vasodilation in the microcirculation to a non–nitric-oxide dependent mechanism, even in healthy adults.[32]

Also the activity of the renin angiotensin system can be modified, since high-salt intake upregulates prorenin-receptor expression in the nephron, which seems to be involved in the regulation of renal dysfunction and proteinuria.[17] A high-salt intake has a negative influence on the homeostatic regulation of vascular bed in hypertensive patients, to a large degree via mechanisms that activate the local renin–angiotensin–aldosterone system in the vessels,[19] or via pathways that inhibit NO production.[27] Finally, increased generation of cyclo-oxygenase (COX-1 and COX-2)-derived vasoconstrictor factors and endothelial activation may contribute to impaired vascular relaxation during high-salt loading and COX-1 derived vasoconstrictor metabolites play an important role in the regulation of microvascular blood flow during a high-salt diet.[30]

Figure 1 sketches the pathophysiological links between salt in essential hypertension and microvascular dysfunction as described above.

4 | DIETARY SALT INTAKE, MICROVASCULAR DISEASE, AND BLOOD PRESSURE CONTROL

Regardless of whether the patient is salt sensitive or not, the presence of microvascular dysfunction accompanies the pathogenetic processes of essential hypertension. Resistance arteries are key elements in blood pressure control and their remodelling plays a major role in the pathophysiology of hypertension. Microcirculatory dysfunction in patients with hypertension leads to the impairment of organ flow reserve, and thereby forms the basis of hypertension-mediated organ damage. It is also a predictor of future cardiovascular events, and it has been demonstrated that hypertensive patients with an increased media-to-lumen diameter ratio of the small vessels

TABLE 1 Overview of experimental data on the effects of salt on microcirculation

Source	Animal model	Intervention	Summary of main findings
Boegehold et al[7]	Dahl salt-sensitive rats and Dahl salt-resistant rats	High-or normal-salt diet for 4 wk	Increase in total peripheral resistance in the hypertensive Dahl rat, with the renal vasculature undergoing the largest resistance increase
Wu et al[8]	Dahl salt-sensitive rats and Dahl salt-resistant rats	High-salt–low-potassium diet for 8 wk	Increased intra-renal vessel remodeling in Dahl-sensitive rats
Hansen-Smith et al[9]	Dahl salt-sensitive rats and Dahl salt-resistant rats	High-salt–low-potassium diet for 8 wks	Dahl salt rats present a greater degree of intra-renal vessel remodeling
Hernandez et al[10]	Rats	Angiotensin II infusion in rats on high-salt diet	Angiotensin II blocked the rarefaction due to salt
Frisbee et al[11]	Sprague Dawley rats with reduced renal mass hypertension	High-salt or low-salt diet and reduced for over 4 wk	Reduced arteriolar vasodilator reactivity developed with high-salt diet and restored with low-salt diet
Zhao et al[14]	C57BL/6 mice with reduces renal mass	3 mo of normal-or high-salt diet	High-salt diet resulted in a lower arteriolar media/lumen area ratio
Bo et al[15]	Young adults rats	Prenatal high-salt diet	Vessel tension and intracellular Ca(2+) concentrations associated with phenylephrine-induced pressor responses were increased in the mesenteric arteries of the high-salt offspring. PKC α-and δ-isoforms were upregulated in mesenteric arteries of the high-salt offspring
Rong et al[16]	Rats	High-salt vs normal-salt diet for 4 wk	High-salt intake upregulates the pro-renin receptors expression in the glomeruli and proximal tubules and tubules of medullary rays in rat nephron
Weber et al[20]	Sprague-Dawley rats	High-salt (or a low-salt diet for 3 d (short-term) or 4-8 wk (chronic)	Chronic (but not short-term) high-salt diet selectively potentiated angiotensin II-induced constriction of skeletal muscle resistance arteries
Zhu et al[21]	Male Sprague-Dawley rats	Low-salt or high-salt diet for 3 d with or without low-dose angiotensin II infusion	Reduced circulating angiotensin II levels during elevated dietary salt lead to elevated superoxide levels, impaired endothelial Ca^{2+} signaling, and reduced NO production in the endothelium.
Wang et al[22]	Rats	Short-term (3-d) high-or low-salt intake	High-salt HS increased the expression of CYP450-4A enzymes in the rat mesenteric vasculature, 20-hydroxyeicosatetraenoic acid contributed to the vasoconstrictor response to norepinephrine in mesenteric resistance arteries which was greater in rats fed a high-salt diet
Lukaszewicz et al[23]	Dahl salt-sensitive rats and salt sensitive Brown Norway rats	High-salt or normal-salt diet. Middle cerebral arteries were treated with N-methyl-sulfonyl-12,12-dibromododec-11-enamide, 15 (Z)-20-HEDE, N(G)-nitro-L-arginine methyl ester, indomethacin or N-(methylsulfonyl)-2-(2-propynyloxy)-benzenehexanamide	Pharmacological interventions that either inhibit the catalytic function of CYP4A enzymes or antagonize the actions of 20-hydroxyeicosatetraenoic acid both restored vascular relaxation in cerebral resistance arteries of rats
Simon et al[25]	Male Sprague-Dawley rats	Treatment with angiotensin II subcutaneously for 4 or 12 wk on normal-sodium diet or on high-sodium diet	Angiotensin induced structural vascular changes and increased wall-to-lumen ratio that are dose-and time-dependent and synergistically enhanced by dietary sodium supplementation
Simon et al[26]	Rats	12 wk of treatment: angiotensin II; 2% NaCl diet; cold exposure; angiotensin II plus 2% NaCl diet; angiotensin II plus cold exposure; cold exposure plus 2% NaCl diet; angiotensin II plus 2% NaCl diet plus cold exposure; and control	Increase of blood pressure in angiotensin II-treated plus salt-fed rats. The blood pressure rise of the former group was accompanied by an increased wall-to-lumen ratio of cortical resistance arteries and decreased glomerular volume

(Continues)

TABLE 1 (Continued)

Source	Animal model	Intervention	Summary of main findings
Boegehold[28]	Dahl salt-sensitive rats	High-or low-salt diets for 4 wk	High-salt intake reduced the passive diameter of large arterioles by 20% and was associated with increased tone of proximal, but not distal, arterioles

in the subcutaneous tissue show greater mortality and morbidity over a 5-6 year period.[5]

A diet containing large amounts of salt contributes to the increased incidence of the above pathophysiological processes. Our initial approach to regulating BP involves health and dietary interventions that include reducing sodium intake. Diuretics, which make up one of the main categories of antihypertensive drug, are aimed precisely at this mechanism: namely, the elimination of excess salt by the body. This plays an important role in clinical practice, primarily for hypertensive patients who are considered salt-sensitive. However, little attention has been paid to the relationship between salt and microvascular dysfunction, which does not appear to be limited to salt-sensitive hypertensives.

Decreasing salt consumption in hypertensive patients, even if it is not too high, has beneficial effects on the microcirculation by improving both functional and structural capillary rarefactions.[33] In a 12-week randomized controlled trial, skin microcirculation, measured by skin video-capillaroscopy on the dorsum of the finger, and capillary recruitment (percentage difference between structural and functional capillary density) were beneficially affected by a low-sodium diet (<6 g/d).[34] Adherence to a healthy diet, including <5-6 mg/d salt consumption, may help maintain a healthy microcirculation. Dietary sodium restriction confers a high degree of vascular protection, not only through its BP-lowering effects, but also because it largely reverses microvascular endothelial dysfunction by enhancing NO, restoring tetrahydrobiopterin bioavailability and reducing oxidative stress.[35] Other data from large clinical studies indicate that higher dietary salt intake in individuals with type 1 diabetes, as determined by 24-hour urinary sodium excretion, may be positively associated with microalbuminuria, which is an index of microvascular dysfunction in the kidney, particularly in overweight individuals.[36]In contrast, the beneficial effect of angiostatin receptor inhibitors on microalbuminuria by may be blunted by salt supplementation,[37] improving when intake is reduced.[38] Table 1 shows the parameters studied as microvascular dysfunction markers in relation to salt intake. Clinical studies in this field are few and mainly aim at the study of microalbuminuria as a sign of microvascular damage to the kidney.

5 | BP-LOWERING EFFECTS FOLLOWING SALT CONSUMPTION MODIFICATION

Sodium intake is an important component of BP regulation in many hypertensive patients; reduced sodium intake could make a substantial contribution to the management of hypertension. The deleterious effects of a high-salt diet are independent of elevated BP, regardless of salt-sensitivity. They may occur even in normotensive individuals and are associated with impaired endothelial function.[5]

There is abundant evidence that a reduction in dietary sodium not only decreases the BP and the incidence of hypertension but also morbidity and mortality from CVD.[39] However, the existing health policies have not been effective in achieving population goals for dietary sodium.[39]

INTERSALT, an international study of the relations of electrolyte excretion and other factors to blood pressure, involving more than 10,000 persons from 32 countries, has shown that the estimated mean change in systolic blood pressure associated with a 100-mmol decrease in sodium intake was −3.1 mm Hg, with adjustment for age, sex, body mass index, and alcohol intake.[6] The average BP change in a large meta-analysis of 40 sodium trials was −4.1/−2.5 mm Hg for a mean sodium reduction of 91 mmol/24 h, and this seems to be higher in older than in younger individuals.[40] In addition, data from another metaanalysis show that increased potassium intake reduces BP in people with hypertension, in particular, the greatest decrease was seen in the group of studies with the highest sodium consumption (>4 g sodium/d).[41]

6 | EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON MICROVASCULAR DYSFUNCTION

Although pharmaceutical treatment in hypertension aims at improvement of hypertension-mediated organ damage, insufficient attention has been given to its action on the microvascular net. Nonetheless, it appears that certain hypertension medication have a beneficial effect. To begin with, angiotensin converting enzyme inhibitors angiotensin receptor blockers have both proven their beneficial effect on improvement of microvascular dysfunction in essential hypertension.[42] More specifically, medications that modify renin angiotensin aldosterone system activity but also calcium blockers φαίνεται seem to be much more effective in reducing media slash lumen ratio of small vessels compared to diuretics and beta blockers.[42] In particular lercanidipine either as monotherapy for hypertension or in combination with enalapril, led to a significant improvement of retinopathy as well as media slash lumen ratio of microvessels.[2] On the contrary, its beneficial effect disappeared with the co administration of diuretic. Also in combination with enalapril, it caused substantial improvement of the density of the microvascular net.[2] Although not all agree,[33,43,44] it appears that at the clinical level the importance of sodium intake is high, not only for hypertension-mediated organ damage but also for the response to antihypertensive therapy.

TABLE 2 Parameters studied as markers of microvascular dysfunction in relation to salt intake

Authors	Sample	Number of participants	Intervention	Drug treatment	Parameter studied	Findings
Greaney et al[17]	Normotensive adults	12	Randomised to a 7 d low-sodium or a 7 d high-sodium diet	None	Nitric oxide (NO)-dependent vasodilatation, maximal cutaneous vascular conductance	Dietary sodium loading impairs cutaneous microvascular function independently of blood pressure
Rorije et al[31]	Normotensive males	12	A low-sodium diet (less than 50 mmol/d) and a high-sodium diet (more than 200 mmol/d) for 8 d in randomized order	None	Microvascular permeability	Acute intravenous sodium loading resulted in increased transcapillary escape rate of ^{125}I-labeled albumin whereas chronic dietary sodium loading did not affect it
Cavka et al[32]	Young females	54	Randomised to either high-salt diet (~14 g/d NaCl) or low-salt diet (<2.3 g/d) NaCl) for 7 d.	None	Post-occlusive reactive hyperemia in skin microcirculation assessed by laser Doppler flowmetry	High-salt diet significantly impaired post-occlusive reactive hyperemia
Engelen et al[36]	Patients with type 1 diabetes	1,212	Analyses of dietary salt intake	Insulin	Microalbuminuria	Higher dietary salt intake may be positively associated with microalbuminuria
He et al[33]	White, black and asian patients with untreated mildly raised blood pressure	71 whites, 69 blacks, and 29 Asians	12-wk randomised double-blind crossover trial to determine the effect of a modest reduction in salt intake	None	Skin capillary density at the dorsum and the side of the fingers	Improvement in both functional and structural capillary rarefactions
Govoni et al[34]	Healthy participants	137	12-wk randomised controlled trial to compliance or not to UK dietary guidelines	None	Skin microcirculation, measured by skin video-capillaroscopy on the dorsum of the finger, number of capillaries perfused under basal conditions, number of anatomic capillaries perfused during finger cuff inflation	Adherence to dietary guidelines may help maintain a healthy microcirculation
Jablonski et al[35]	Healthy participants	17	Randomised to a 4 wk of both low and normal-sodium intake	None	NO/ tetrahydrobiopterin (BH(4) bioavailability, and oxidative stress	Low salt enhances NO and BH(4) bioavailability and reduces oxidative stress

(Continues)

TABLE 2 (Continued)

Authors	Sample	Number of participants	Intervention	Drug treatment	Parameter studied	Findings
Ekinci et al[37]	Hypertensive patients with type 2 diabetes	32	Randomised to 100 mmol/d NaCl or placebo	Telmisartan	Albuminuria	Albumin excretion rate response to telmisartan under habitual low-salt intake is blunted by NaCl supplementation
Hwang et al[43]	Non-diabetic hypertensive patients	245	Randomised to low-salt diet education or intensive low-salt diet education	Olmesartan	Albuminuria	24-h urinary albumin excretion was decreased more in patients in the intensive low-salt diet education group
Han et al[38]	Participants from the Korea National Health and Nutrition Examination Survey (KNHANES)	5187	No intervention-24-h urinary sodium excretion	Unknown	Albuminuria	Salt intake is associated with the presence of albuminuria
Fox et al[44]	Participants from the Framingham Offspring Study	2700	No intervention-24-h urinary sodium excretion	Unknown	Albuminuria	Urinary albumin excretion was strongly and positively associated with 24-h urinary sodium excretion
Konta et al[45]	Japanese individuals from the general population	2321	No intervention-24-h urinary sodium excretion	Unknown	Albuminuria	Urinary albumin excretion was associated with 24-h urinary sodium excretion
Aaron et al[46]	African-American and white adults	21,636	No intervention-questionnaire for dietary habits	Unknown	Albuminuria	Higher dietary Na/K and sodium intakes were associated with albuminuria
Sakabe et al[47]	Patients with type 2 diabetes	270	No intervention-questionnaire for dietary habits	Unknown	Albuminuria	Low daily salt intake was correlated with albuminuria

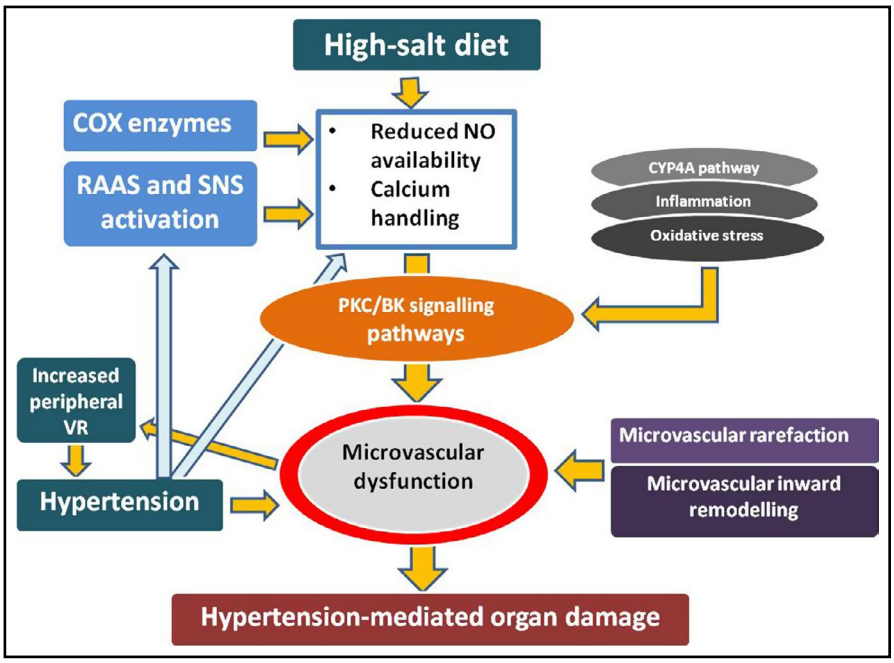

FIGURE 1 Pathophysiological links between salt consumption in essential hypertension and microvascular dysfunction. COX, cyclo-oxygenase; CYP4A, cytochrome P450 4A; NO, nitric oxide; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system; VR, vascular resistance

It should be mentioned that in addition to hypertension treatment, hypolipidemic medications and statins in particular seem to have a beneficial effect on microcirculation even during acute administration[48]; this is recognized as an additional pleiotropic effect of statins.

7 | CONCLUSIONS

The increase in BP with salt consumption shows great heterogeneity among hypertensive individuals. However, as a general rule it has a deleterious effect on the microcirculatory system that both creates future hypertensives, via an increase in peripheral resistances, and exacerbates the manifestations of hypertension. Salt consumption induces a systemic proinflammatory state while causing microvascular endothelial inflammation, anatomic remodelling and functional abnormalities, even in normotensive subjects.

Although some antihypertensive drugs appear to have a beneficial effect on the microvascular network, this is still largely ignored as a primary therapeutic goal and the main focus is on the macrovascular network. However, the microcirculation could be an important target and a possible increase in capillary density could reduce or improve hypertension-mediated organ damage.

In clinical practice, instructions for a salt-free diet are given when it is necessary to better control BP, while the proper importance is not assigned to the adverse effects of salt intake on the microcirculation. For this reason, it should be noted that a reduction in salt consumption is of great importance to everyone, regardless of whether they are salt-sensitive or not.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Maria E. Marketou: conceived of the presented idea, wrote the paper, Spyros Maragkoudakis: Critical revision of the article, Ioannis Anastasiou: Wrote the paper, Helen Nakou: Critical revision of the article, Marina Plataki: Critical revision of the article, Panos E. Vardas: Critical revision of the article, Fragiskos I. Parthenakis: Critical revision of the article, final approval of the version to be published.

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