Review

Salt Restriction in Chronic Kidney Disease: A Simple Need or a Must?

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Key Words

Salt • Chronic kidney disease • Inflammation • Oxidative stress

Abstract

Dietary salt restriction is one of the most important non pharmacological intervention in the management of hypertension and cardiovascular complications. In Chronic Kidney Disease (CKD) patients, observational and recent interventional studies investigating the relationship between sodium intake and renal outcomes suggest that low salt diet is warranted in this high risk category of patients. Moreover reducing and maintaining a low salt intake in these patients plays a fundamental role for maximizing the beneficial effect of ACE inhibitors on CKD progression. On the other hand, in hypertensive patients there is experimental evidence indicating that a very low sodium diet (<50 mEq/day) generates a pro-inflammatory phenotype characterized by an increase in Procalcitonin and TNF-alpha and a reduction in an anti-inflammatory cytokine like Adiponectin. In this brief review the main mechanisms whereby salt intake may determine kidney damage and studies showing that salt restriction may have a beneficial effect in CKD patients will be discussed.

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Introduction

The question whether salt can be eaten or not, has scriptural origins and the notion of a relationship between salt and blood pressure was around as long as 4,000 years ago, when an erudite Chinese emperor Huang Ti described the connection between salt and a "hardened pulse". Nowadays, notwithstanding the fact that for many scientists salt is the most suspected environmental factor which may influence blood pressure and the atherogenesis process, the potential impact of salt on hypertension related morbidity and mortality is still passionately debated. Indeed on one side, i.e. against the recommendation to reduce salt intake, some acquainted scientists argue that results from the dietary sodium intake and mortality of the National Health and Nutrition Examination Survey (NHANES I and III) [1, 2] do not support current recommendations for routinary reduction of sodium consumption. On the opposite side, i.e. in favor of the theory that salt is harmful to human health and therefore reducing salt consumption is an issue of public policy, Mac Gregor published an

editorial where new evidence is supported in favor of reducing salt consumption [3]. The editorial stemmed from a recent meta-analysis by Taylor and coworkers on the effect of salt reduction on Cardio-Vascular (CV) events and mortality [4]. In their meta-analysis, Taylor et al. summarized the results stating that “Cutting down on the amount of salt has no clear benefits in terms of likelihood of dying or experiencing cardiovascular disease”. Mac Gregor et al. statistically revised the data reported in the meta-analysis, reaching a quite strikingly different conclusion that just a modest reduction in dietary salt causes a 20% decrease in CV events. This apparent incongruence was attributed to methodological flaws in Taylor’s manuscript and the “revised” conclusions in the editorial reiterate that “a reduction in population salt intake will have major beneficial effects on health along with major cost savings in all countries around the world” [3]. Moreover, evidence is emerging that reduced salt intake has a beneficial effect on an important clinical outcome such as a stroke. In fact, a meta-analysis of 13 prospective studies including 177,000 participants demonstrated that a high salt intake was associated with a greater risk of stroke [5]. However, in this meta-analysis no association between salt intake and all CV events or total mortality was found. Generally speaking, the relationship of salt intake to blood pressure (BP) documented in many observational studies and clinical trials [6-7] is the basis for the belief that restriction in dietary sodium intake will prevent BP-related CV events and the WHO recommend a reduction to <2 g/day sodium (5 g/day salt) in adults. Current salt intake is high, especially in high-risk groups and the question is whether it is too high in patients with CKD. Therefore the salt controversy is even more challenging in such a high risk population. Apart from the scientific strength of the salt-BP relationship and CV disease the hot topic which deserves thorough discussion is the relationship between salt intake and the kidney. In this manuscript two main areas will be touched upon: 1) The mechanisms whereby salt intake may contribute to kidney damage 2) Evidence that Salt restriction may be directly and indirectly beneficial in CKD patients.

The mechanisms whereby salt intake may contribute to kidney damage

In CKD, attempts to slow down the deterioration of kidney function and its CV complications are the main therapeutic targets. Salt excess may promote renal dysfunction and CKD progression by direct and indirect mechanisms [8], see Figure 1. High sodium intake increases extracellular volume as documented in CKD patients where eGFR and extracellular volume were inversely related, i. e. kidney dysfunction was associated to an increase in extracellular volume. Moreover high salt intake is a potent risk factor for glomerular hyperfiltration [8] and the consequences of these hemodynamic alterations are focal glomerulosclerosis and proteinuria. The interpretative model which is centered on glomerular hemodynamics has been a cornerstone of modern nephrology [8] and it represents a paradigm for the interpretation of renal diseases. On the other hand, high salt intake stimulates the synthesis of pro-inflammatory cytokines such as TGF beta [9] which enhances fibrosis in the kidney and in the heart as well. Moreover an increased oxidative stress due to high salt intake, always accompanied by a suppression of the renin-angiotensin system, was documented in vascular tissues in experimental models of salt-sensitive hypertension in normal rats undergoing a high salt diet and in rats affected by mineralocorticoid hypertension [10]. These experimental findings could be of importance in CKD patients because only a minority of these patients reached the recommended target of salt intake [11] and because salt sensitivity, a well-known phenomenon linking high blood pressure to salt intake, increases as renal function deteriorates [8]. An enhanced production of reactive oxygen species (ROS) was also found in the renal cortex of normal rats and in striated muscle microvessels and cerebral vascular beds of other animal models undergoing a high salt diet [10]. These findings are fully in keeping with other observations in experimental models showing that very strict sodium diet reduces ROS production associated with angiotensin II-mediated hypertension [10]. In the aggregate, these experimental observations are compatible with the hypothesis that an increased oxidative stress may represent a direct mechanism by

Fig. 1.

which high salt intake may trigger renal function loss in CKD patients [10]. High salt intake is also a mechanism of primary importance in CKD patients because it triggers sympathetic activity [12], which in turn contributes to renal function deterioration [13]. Although the World Health Organization recommends a target salt intake of 100 mEq/day, large scale studies show that as much as 80-90% of CKD patients are out of the recommended target [10]. This may partially explain why hypertension is so prevalent in CKD patients, with data indicating that up to 70% of them are hypertensive. Therefore, high sodium intake affects BP, proteinuria and glomerular filtration and considered that salt intake is a modifiable risk factor, it is of paramount importance to consider the role of dietary sodium restriction on the response of anti-hypertensive therapy in CKD patients.

Salt restriction may be directly and indirectly beneficial in CKD patients

There is recent evidence that salt excess may attenuate the antihypertensive and anti-proteinuric effects of renin-angiotensin system blockers in CKD patients. Slagman MCJ and co-workers performed a randomized controlled trial [14] to assess the efficacy on proteinuria and BP of non-pharmacological (dietary restriction) or pharmacological [angiotensin receptors blockers (ARB) at maximal dose] interventions, or the combination of these two treatments, in 52 patients with non-diabetic nephropathy who were already treated with ACE inhibitors at maximal dose. Patients were treated, in random order, by angiotensin receptor blockers (ARB) or placebo, each combined with a low (50 mEq/L) and a high (200 mEq/L) sodium diet. It was found that the reduction of proteinuria by the addition of a low sodium diet to the ACE inhibitor was higher than that achieved by the addition of ARB to the same drug and was comparable to that provided by the simultaneous use of ARB and low sodium diet, suggesting a fundamental role of salt intake in the anti-proteinuric response to pharmacological treatments in CKD patients. Low salt intake as a modifier of the anti-proteinuric effect of ACE inhibitors in CKD patients was also investigated in a recent post-hoc analysis of the REIN 1 and 2 trial [15]. Vegter S et al. studied the association between salt intake, proteinuria and progression to End Stage Kidney Disease (ESKD) in 500 non-diabetic CKD patients who were treated with Ramipril and who underwent a serial 24h urinary collection for measuring sodium and creatinine over a 24-month follow-up period [15]. The study hypothesis was that the reduced anti-proteinuric effect of Ramipril in CKD patients with high salt intake might translate into less effective protection by ACE

inhibition against ESKD progression [15]. During a 4-year follow-up period, Vegter S et al. showed that the incidence of ESKD increased in close parallel with salt intake, the incidence of ESKD being 6x 100 patient-years in patients on a low sodium diet (< 100 mEq/g), 8x100 patient-years in those on a medium sodium diet (100-200 mEq/g) and 18x100 patient-years in those with a high sodium diet (> 200 mEq/g). To put this in perspective, a 100 mEq/g increase in urinary sodium/creatinine excretion ratio was associated with a 40% increase in the risk of ESKD regardless of baseline proteinuria and other risk factors. Interestingly, in these patients the link between salt intake and the risk of ESKD disappeared after data adjustment for changes in proteinuria over time suggesting that in CKD patients treated by ACE inhibitors, the increase in proteinuria is a primary mechanism by which high sodium intake accelerates the progression of CKD toward ESKD. On the other hand, the most intriguing finding in this study is that sodium intake seems to be an effect modifier of the protective role of RAS inhibition on proteinuria because the efficacy of Ramipril on this important outcome was highest in patients with a low sodium intake, intermediate in those with a medium sodium intake and virtually abrogated in patients with a high sodium intake. However, because these results originate from a secondary analysis of a RCT, the hypothesis that sodium intake could modify the anti-proteinuric effect of Ramipril deserves to be further confirmed in other specifically designed randomized clinical trials. The findings which emerged in Vegter's study are consistent with other studies in the same field which coherently show that the reduction in salt intake is associated with a marked reduction in proteinuria [8]. However, recommending a very low salt intake in humans should be carefully considered because at least in hypertensive patients, a recent randomized clinical trial documented that an extremely low sodium diet (< 50 mEq/day in urinary sodium) generates a pro-inflammatory phenotype characterized by an increase in procalcitonin and TNF- α and an opposite effect on an anti-inflammatory cytokine like Adiponectin [16]. More recently in CKD patients, McMahon EJ et al. performed a double-blind placebo controlled randomized cross-over trial [17] aimed at evaluating the effects of dietary sodium intake on blood pressure, proteinuria, arterial rigidity and extracellular volume in stages 3-4 CKD patients. In this study, salt restriction was linked to a significant reduction in 24h ambulatory BP, extracellular volume, albuminuria and proteinuria and the magnitudes of these effects were higher than that reported in patients without CKD. These results emphasize the effect of a non-pharmacological intervention, namely sodium restriction, on a reliable marker of kidney disease such as proteinuria and they are closely related to the observations reported by Vogt et al. [18] in proteinuric patients without diabetes in whom the effect of sodium restriction (≤ 90 mMol/day) on proteinuria was similar to the effect of Losartan 100 mg in the same patients [18]. An interesting observation emerging in McMahon's study is that the reductions in proteinuria and albuminuria were fully independent of BP changes over time. Taken together, these observations are in keeping with the hypothesis that CKD patients may benefit from salt restriction and evidence is provided to support the recommendations of salt restriction in CKD patients.

Conclusions

Salt intake is a strong and independent predictor of cardiovascular and renal events in CKD patients. Reducing and maintaining a low salt intake is a pre-requisite for maximizing the beneficial effect of ACE inhibition on CKD progression. Although studies with longer intervention times and larger sample sizes are needed to confirm these benefits, sodium restriction should be emphasized in the management of patients with CKD as a means to reduce CV risk and risk for CDK progression.

Due to the fact that the issue of high salt intake in CKD patients is of similar magnitude to that of blood glucose control in diabetics, a randomized clinical trial testing the effectiveness of a self-management approach based on urine sodium monitoring at home to improve hypertension control and clinical outcomes and autonomy in CKD patients represents an absolute public health priority.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

References

- 1 Alderman MH, Cohen H, Madhavan S: Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). *Lancet* 1998;351:781-785.
- 2 Cohen HW, Hailpern SM, Alderman MH: Sodium intake and mortality follow-up in the Third National Health and Nutrition Examination Survey (NHANES III). *J Gen Intern Med* 2008;23:1297-1302.
- 3 He FJ, MacGregor GA: Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet* 2011;378:380-382.
- 4 Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S: Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). *Am J Hypertens* 2011;24:843-853.
- 5 Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP: Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009;339:b4567.
- 6 Titze J, Ritz E: Salt and its effect on blood pressure and target organ damage: new pieces in an old puzzle. *J Nephrol* 2009;22:177-189.
- 7 Aburto NJ, Ziolkowska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ: Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013;346:f1326.
- 8 Krikken JA, Laverman GD, Navis G: Benefits of dietary sodium restriction in the management of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2009;18:531-538.
- 9 Hovater MB, Sanders PW: Effect of dietary salt on regulation of TGF- β in the kidney. *Semin Nephrol* 2012;32:269-276.
- 10 Weir MR, Fink JC: Salt intake and progression of chronic kidney disease: an overlooked modifiable exposure? A commentary. *Am J Kidney Dis* 2005;45:176-188.
- 11 De Nicola L, Minutolo R, Chiodini P, Zoccali C, Castellino P, Donadio C, Strippoli M, Casino F, Giannattasio M, Petrarulo F, Virgilio M, Laraia E, Di Iorio BR, Savica V, Conte G; TArget Blood Pressure LEvels in Chronic Kidney Disease (TABLE in CKD) Study Group: Global approach to cardiovascular risk in chronic kidney disease: reality and opportunities for intervention. *Kidney Int* 2006;69:538-545.
- 12 Guild SJ, McBryde FD, Malpas SC, Barrett CJ: High dietary salt and angiotensin II chronically increase renal sympathetic nerve activity: a direct telemetric study. *Hypertension* 2012;59:614-620.
- 13 Petras D, Koutrotsos K, Kordalis A, Tsioufis C, Stefanadis C: The role of sympathetic nervous system in the progression of chronic kidney disease in the era of catheter based sympathetic renal denervation. *Curr Clin Pharmacol* 2013;8:197-205.
- 14 Slagman MC, Waanders F, Hemmelder MH, Woittiez AJ, Janssen WM, Lambers Heerspink HJ, Navis G, Laverman GD; HOLLAND NEphrology STudy Group: Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011;343:d4366.
- 15 Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P: Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol* 2012;23:165-173.
- 16 Mallamaci F, Leonardi D, Pizzini P, Cutrupi S, Tripepi G, Zoccali C: Procalcitonin and the inflammatory response to salt in essential hypertension: a randomized cross-over clinical trial. *J Hypertens* 2013;31:1424-1430.
- 17 McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, Campbell KL: A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 2013;24:2096-2103.
- 18 Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G: Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;19:999-1007.