Fibroblast Growth Factor 23: a Bridge Between Bone Minerals and Renal Volume Handling
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 13-12-2019
Chapter 3

Dietary Sodium Restriction: a Neglected Therapeutic Opportunity in Chronic Kidney Disease

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Curr Opin Nephrol Hypertens. 2014 Nov;23(6):533-40
Abstract

Purpose of review
Restriction of dietary sodium is recommended at a population level as well as for groups at high cardiovascular risk, and chronic kidney disease (CKD). This review addresses recent evidence for the protective effect of dietary sodium restriction in CKD patients specifically.

Recent findings
Sodium intake in CKD populations is generally high, and often above population average. Recent data demonstrated that moderately lower sodium intake in CKD patients is associated with substantially better long-term outcome of renin-angiotensin-aldosterone system (RAAS)-blockade, in diabetic and non-diabetic CKD, related to better effects of RAAS blockade on proteinuria, independent of blood pressure. This is in line with better short term efficacy of RAAS blockade during moderate sodium restriction in diabetic and nondiabetic CKD. This effect of sodium restriction is likely mediated by its effects on volume status. Sustainable sodium restriction can be achieved by approaches on the basis of behavioral sciences.

Summary
Moderate restriction of dietary sodium can substantially improve the protective effects of RAAS blockade in CKD, by specific renal effects apparent from proteinuria reduction. The latter precludes straightforward extrapolation of data from non-renal populations to CKD. Concerns regarding the adverse effects of a very low sodium intake should not distract from the protective effects of moderate sodium restriction. Prospective studies should assess the efficacy and sustainability of different strategies to target high sodium intake in CKD, along with measures at population level.

Video abstract: http://links.lww.com/CONH/A14
Review

Introduction
Restriction of dietary sodium to a maximum of 5 grams of salt (sodium chloride) daily for an adult, corresponding to ca. 2000 mg sodium, is among the top-priorities of the WHO for the combat of chronic noncommunicable diseases (1). In line, for chronic kidney disease (CKD) patients, the 2012 Kidney Disease Improving Global Outcomes guideline recommends the reduction of daily sodium intake to less than 2000 mg/90 mmol per day (2). Salt intake varies widely between different countries, but generally exceeds the recommended amount in most communities where data are available. Excess sodium intake is associated with considerable morbidity and mortality, and, hence, substantial costs in terms of health expenditure. It has been estimated that a 3-g reduction of salt intake would reduce healthcare costs by $10–24 billion per year (3). Of note, these estimates were based on cardiovascular disease only: inclusion of the costs related to sodium-related morbidity and mortality in CKD would have increased these figures even further.

Sodium Intake in Chronic Kidney Disease Patients
Among the many studies on CKD patients in the literature, only a minority reports 24-h sodium excretion. In these studies, average 24-h sodium excretion in CKD patients is usually in the range between 160 and 240 mmol (4-7). This is in the same range as in the general population, or even higher. This is remarkable, considering the fact that these patients were under dedicated nephrology care. It could indicate either neglect of sodium status, or failure of current strategies in renal care to achieve sustained reduction of dietary sodium, or reflect the association between risk behavior and risk to develop CKD.

Effect of Dietary Sodium Restriction in CKD Patients
In CKD, blood pressure is usually sodium sensitive. Moreover, renal protein loss is reduced by dietary sodium restriction. This has been shown for sodium restriction as a single measure, as well as for sodium restriction as an add-on to antihypertensive treatment (8, 9). Interestingly, proteinuria reduction by sodium restriction remains significant after adjustment for the fall in blood pressure, suggesting an independent renoprotective effect of sodium restriction, both as a single measure and in combination with blockade of the renin-angiotensin-aldosterone system (RAAS) (8). A blood pressure-independent effect of dietary sodium on the kidney is substantiated by data in healthy volunteers, in which dietary sodium restriction reduces albuminuria within the normal range, without a detectable effect on blood pressure (10).

Interaction between Sodium Intake and Effects of RAAS Blockade
In CKD, RAAS-blockers are first-line therapy for the treatment of hypertension and proteinuria, and accordingly the vast majority of CKD patients are on maintenance treatment with either an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB).
It has been known for over 2 decades that the effects of RAAS-blockers are blunted by high sodium intake (8, 11, 12). Of note, by interfering with the buffering action of the RAAS on the hemodynamic consequences of altered sodium status, RAAS blockade renders blood pressure sodium-sensitive, thus creating better therapeutic opportunities for sodium restriction, even in previously sodium-resistant patients. Sodium restriction increases the top of the dose-response of RAAS blockade for both blood pressure and proteinuria (13). The effect of moderate sodium restriction during RAAS blockade on blood pressure and proteinuria is approximately similar to the effect of adding a diuretic, whereas the maximum effect is achieved by their combination in nondiabetic (8) as well as diabetic CKD (Figure 1) (5). The reduction in blood pressure and proteinuria is accompanied by a slight decrease in renal function.

Of note, in the latter study, habitual sodium intake was very high, that is an average of 224 mmol Na⁺/day. During intervention, sodium intake decreased to 148 mmol/day. Although this was still substantially above the recommended levels, nevertheless, it was associated with a significant reduction in blood pressure and proteinuria.

**Figure 1.** Sodium excretion (upper panel) during four different 6-week treatment periods by a rotation schedule in patients with diabetes and CKD on ACE-inhibitor therapy. NS intake was very high and accordingly also during SR without and with hydrochlorothiazide, sodium intake remained above recommended levels. Nevertheless, proteinuria (lower panel) was reduced significantly, as was blood pressure (data not shown). CKD, chronic kidney disease; HCT, hydrochlorothiazide; NS, normal sodium; SR, sodium restriction. Adapted from (5**).
This study also allows inferences on the clinical relevance of the so-called ‘sodium paradox’ in patients with diabetes and CKD. The ‘sodium paradox’ refers to the rise in glomerular filtration rate and filtration fraction that has been reported during low sodium diet in uncomplicated type I diabetes and experimental diabetes. It is partly attributed to excess intrarenal RAAS activity. Concerns regarding the possible adverse renal effects of hyperfiltration may have contributed to the underrated role of sodium restriction in patients with diabetes and CKD, but the current data do not support the relevance of the sodium paradox for the clinical condition of diabetes with CKD during RAAS blockade.

In a head-to-head comparison, moderate dietary sodium restriction during monotherapy ACE-inhibitor (ACEi) more effectively reduced blood pressure and proteinuria than adding an ARB (11). Dual RAAS blockade has now been deemed obsolete, due to worse renal outcome in long-term studies (14-16) related to increased risk for acute renal function deterioration. The current data show that moderate dietary sodium restriction as add-on to monotherapy RAAS blockade provides a more effective alternative to dual blockade. Of note, this study also contained a dual blockade-sodium restriction arm. This regimen had potent effects on blood pressure and proteinuria, accompanied by a substantial reduction in renal function. The latter was much more pronounced than the mild decrease in renal function during single blockade at similar sodium restriction. The decrease in renal function was fully reversible after changing the regimen, demonstrating its hemodynamic nature, but illustrates that dual RAAS blockade severely compromises the kidneys’ capacity to maintain glomerular filtration during sodium restriction, which may explain the increased risk for acute kidney injury (AKI) associated with dual blockade in long-term studies.

*Interaction between Sodium Intake and Long-Term Outcome of Renin-Angiotensin-Aldosterone System Blockade*

Recently, the effect of sodium intake on long-term outcome of RAAS blockade was analyzed in data sets from the large intervention trials that provided the empirical basis for our current RAAS blockade-based treatment regimens in CKD. Data from the ACE-inhibitor arm from the Ramipril Efficacy In Nephropathy (REIN) trial were analyzed by tertiles of sodium intake, assessed as urinary sodium excretion throughout the study (6). By design, blood pressure was titrated to less than 140/90 mmHg in all patients by adding antihypertensives on top of the ACEi, with a diuretic as the first titration step. Accordingly, blood pressure was not different by sodium intake. However, proteinuria reduction was less effective in the higher tertiles of sodium intake and was associated with a substantially worse long-term renal outcome, with 60% of the patients in the upper tertile reaching the renal end point versus 20% in the lowest tertile (Figure 2).
In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)/Irbesartan Diabetic Nephropathy Trial (IDNT) data set the conventional treatment arm was also analyzed. In these studies, blood pressure was also titrated by design. With conventional treatment, overall outcome was worse, but not different by sodium intake. In the ARB arm, however, the risk to reach a renal or cardiovascular end point in patients in the highest tertile was approximately two-fold higher than in the lowest tertile. Accordingly, the treatment benefit from the ARB over conventional antihypertensives was present in the lower tertile only (Figure 3, [4]). In line with the REIN data, the lack of protective action of RAAS-blockade in those ingesting excessive sodium was associated with lack of antiproteinuric effect, despite similar blood pressure.

Thus, in CKD patients on RAAS blockade, a modestly lower dietary sodium intake, in the range recommended for the general population, is associated with substantial benefits regarding renal and cardiovascular outcome. This difference in outcome occurs despite adequate blood pressure control in those on the highest sodium intake, and is associated with persistence of proteinuria. Of note, in these studies, the titration schedule led to more diuretic use in subjects that ingested excess sodium. Apparently, this did not sufficiently prevent the adverse effect of excessive sodium intake on long-term outcome. This is somewhat disconcerting, considering the similarity of the short-term effects of sodium restriction and diuretics. It could be that control of volume overload was still insufficient, as high sodium intake is associated with diuretic resistance (17) or, the other way round, that diuretic use is associated with side effects that adversely affect long-term outcome, such as for instance potassium depletion, or hyperuricemia (18).
Can We Go Too Low?

Observational data from various studies, showing a J-curve between sodium intake and renal and cardiovascular outcome, have raised concern on the safety of rigorous sodium restriction (19-21). These observational data should be interpreted with caution, as a habitual salt intake below 5 g daily is a rarity in the outpatient population, and may well be an indicator of concomitant conditions compromising nutritional status as well as outcome. Moreover, quantification of sodium intake was questionable in some of the studies, by lack of 24-h urine data on sodium intake. This may have contributed to the substantial differences in the level of the nadir of the J-curve. Obviously, this debate is seriously hampered by lack of prospective long-term sodium intervention data in CKD. Nevertheless, the presence of a J-curve has been reported in several independent studies (albeit not all (22)) and should be given serious consideration.

In experimental renal disease we previously found that a regimen of ACEi and rigorous sodium restriction reduced blood pressure, proteinuria, and glomerular damage, but unexpectedly aggravated tubulo-interstitial damage (23). This was also found in healthy rats, so, it is not a particularity of the model but a generalizable adverse effect of the combination of RAAS blockade and rigorous sodium restriction. This is disconcerting, as, moreover, the interstitial damage was not readily apparent from non-invasive parameters, so if this would occur in patients, it would go unnoticed. This once more underlines the need for better non-invasive markers of

![Figure 3](image-url). Effect of sodium intake by tertile of urinary Na/creatinine (Cr) on the treatment benefit of ARB for renal (upper panels) and cardiovascular (lower panels) outcome in patients with type 2 diabetes and nephropathy. Urinary sodium excretion in the subsequent tertiles corresponded to a dietary salt intake of 8.9, 10.9, and 12.2 g, respectively. ARB, angiotensin-receptor blocker; RAAS, renin-angiotensin-aldosterone system. Adapted from (4).
tubulo-interstitial damage. Considering the consistent association of interstitial damage with long-term renal outcome, this could provide a potential explanation for the association of very low sodium intake with worse renal outcome. Its mechanisms deserve further explanation, but could include intrarenal ischemia, excess reactive renin or aldosterone activation, or other causes.

**Mechanisms Underlying the Interaction of Sodium Intake with Renin-Angiotensin-Aldosterone-Blockade Efficacy**

Several mechanisms could explain the interaction between sodium intake and effects of RAAS blockade. First, high sodium intake suppresses RAAS-activity in the circulation, and blocking a suppressed cascade cannot be expected to have much effect. For tissue RAAS-activity other mechanisms may be relevant as high sodium increases tissue conversion of angiotensin (ang) I (24) and annihilates the effects of ACEi on tissue ang I conversion (25). Moreover, low sodium potentiates the ACEi-induced increase of vasodilator and antifibrotic substances such as ang1-7 (26), and AcSDKP (27). Finally, it is important to realize that high sodium intake is often associated with other nutritional factors that can affect renal function and the response to RAAS blockade by themselves, such as for instance protein intake (10, 11, 28).

**Sodium Intake and Volume Status and Their Effects on Response to Renin-Angiotensin-Aldosterone System Blockade**

Sodium intake is generally recognized as an important determinant of the extracellular volume (ECV), and it is plausible that the effect of high sodium intake on response to RAAS blockade is to an important extent determined by its effect on ECV. This is supported by the similarity of the effects of diuretic and dietary sodium restriction on RAAS blockade efficacy (at least on short term)(5, 8, 29) and by the predictive effect of volume markers on the effect of sodium restriction and/or diuretic on the efficacy of RAAS blockade (30), as outlined in more detail in the next paragraph.

In this respect, it is important to realize for a given sodium intake that volume status can be very different between patients, depending on the avidity of sodium retaining mechanisms. The latter can vary by renal condition, with more avid retention in proteinuric patients (31), in diabetes, and overweight or obesity (32). Accordingly, volume overload can be present even if sodium intake is adequately restricted, as occurs in severely nephrotic patients as an extreme example. Conversely, volume expansion can be absent despite a high sodium intake, due to highly efficient sodium excretion, or highly effective nonosmotic storage mechanism (33). Recent data suggest that fibroblast growth factor 23 (FGF-23) is involved in renal sodium retention (34) and volume status (35), thus providing a mechanistic link between the adverse effects of high sodium intake and high phosphate levels (36) on therapy response to RAAS blockade. In
line with this assumption, high FGF-23 was associated with an impaired response to low sodium diet on top of ACEi (Humalda, *Am J Kidney Dis*, in press).

**Titrating Sodium and Volume Status in Chronic Kidney Disease**

Assessment of volume status may be useful to guide therapy in CKD patients on RAAS blockade. In patients with elevated N-terminal pro-brain natriuretic peptide (NT-proBNP), as a marker for volume expansion, sodium intervention by diet, diuretic, or both, reduces blood pressure and proteinuria, whereas a normal NT-proBNP predicts a minor or non-significant effect (Figure 4) (30). Apparently, in the absence of cardiac disease, mild elevation of NT-proBNP indicates subclinical volume expansion as a suitable target for intervention. Accordingly, the volume intervention reduces NT-proBNP. If it normalizes, further volume targeting does not result in a clinical response; if it still above normal, additional volume targeting (e.g., adding diuretic to the diet) results in a clinical response. These data in proteinuric patients suggest that it could be relevant to not only assess sodium intake, but also corresponding volume status, as this could potentially prevent overzealous sodium restriction or diuretic treatment, and its adverse consequences in CKD patients.

![Figure 4](image)

**Figure 4.** Predictive value of NT-proBNP at baseline (untreated) for the responses of blood pressure (left panel) and proteinuria (right panel) to ARB, add-on sodium restriction, and add-on sodium restriction plus diuretic. NT-proBNP above the upper level of normal (>125pg/ml) was not associated with the response to ARB, but predicted a more pronounced response to volume intervention by sodium restriction and thiazide. A similar predictive value of NT-proBNP for clinical efficacy of volume intervention was found for NT-proBNP during monotherapy ARB (not shown). ARB, angiotensin-receptor blocker; LS, low sodium. Adapted from (32).
Quantification of ECV is not part of the clinical routine in CKD, and validation of the available volume markers such as NT-proBNP will probably be cumbersome, due to interference of cardiac functional status. Yet, it might be worthwhile to put more effort in assessing volume status \textit{per se}, not only for its role in modifying the response to RAAS blockade \textit{per se}, but also as a possible independent cardiovascular risk factor in CKD patients (37).

\textbf{Managing Sodium Intake in Chronic Kidney Disease: Importance of Behavioral Approaches.}

How should sodium status be targeted in the clinic? It is increasingly recognized that current strategies to change dietary habits are ineffective, as illustrated by data from the Masterplan study, in which support by trained nurses was effective in improving compliance with pharmacological guidelines, but not in improving compliance with lifestyle measures (7). There is compelling evidence from behavioral sciences that sustained lifestyle changes require a dedicated, behavioral approach (38-40). Such approaches are not yet part of the clinical routine in renal care, but are being tested currently (SUBLIME, ClinicalTrials.gov identifier NCT02132013).

\textbf{Monitoring Sodium Intake from 24-h Urine}

The gold standard for assessment of sodium intake is from well collected 24-h urine, as dietary recall and food frequency questionnaires are notoriously unreliable for assessment of sodium intake. This relates to the fact that only 15\% of the sodium ingested is added during cooking or during meals, whereas the remainder is present in the food in hidden form, as additives in processed foods (41). As collection of 24-h urine is considered cumbersome by many, and moreover prone to collection errors, these data are not routinely available in many centers. However, assessment of 24-h creatinine excretion allows detection of collection errors by testing observed creatinine excretion versus creatinine excretion expected from anthropometric data (42). Moreover, additional nutritional factors relevant to outcome CKD can also be reliably assessed from 24-h urine, such as phosphate intake, protein intake, potassium (43), magnesium (44), sulphate (45), and finally, the absolute value of 24-h creatinine excretion, by its association with muscle mass, is a robust marker of physical fitness, and predictor of mortality risk (46). Thus, 24-h urine can provide a multidimensional nutrition and fitness profile relevant to CKD patients that renders the investment in terms of patient instruction and urine collection even more worthwhile.

\textbf{Conclusion}

Control of sodium and volume status is crucial in the management of diabetic and nondiabetic CKD patients for control of blood pressure and proteinuria, and eventually prevention of progressive renal function loss and its complications. This is particularly so in patients on RAAS blockade, as sodium overload interferes with its therapeutic efficacy, as apparent from persistence of proteinuria, even when blood pressure is well controlled. In most CKD patients habitual sodium intake is too high, despite medical supervision. In both diabetic and nondiabetic CKD a
moderately lower dietary sodium, even at levels substantially above the recommended amount, is associated with a substantially better response to RAAS blockade in short-term interventions, and a substantially better renal and cardiovascular outcome in post hoc analyses of hard end point studies. Concerns have been raised on the safety of rigorous sodium restriction on the basis of a J-curve for sodium intake and outcome, with higher risk not only at higher sodium intakes, but also the lower end. Safety concerns on rigorous sodium restriction should not distract from the considerable potential benefits of moderate sodium restriction in the vast majority of CKD patients, in whom sodium intake is high or very high. Population measures, including the action of government and industry, are important to facilitate reduction of sodium intake (3). Moreover, it is crucial to develop better strategies for lifestyle management in CKD patients. This should include monitoring of dietary sodium (as well as other relevant dietary factors) from 24-h urine, as well as integration of behavioral approaches into regular care.

**Keypoints**

- High sodium intake blunts the therapeutic benefit of RAAS blockade on short term and long term in CKD patients.
- The blunting of the long-term benefits of RAAS blockade in CKD relates to persistent proteinuria and cannot be overcome by better blood pressure control by adding antihypertensives.
- Moderate sodium restriction substantially improves the responses to RAAS blockade in CKD, even when the remaining sodium intake is still above recommended levels.
- Sodium intake should be assessed from 24-h urine in patients on RAAS blockade, in particular when therapy response is unsatisfactory.
- Concomitant assessment of volume markers may help to preclude overzealous sodium and volume targeting.
- Behavioral approaches are required to achieve long-term changes in dietary habits.

**Acknowledgements**

None.

**Conflicts of interest**

*Disclosure of funding: G.N. is advisor for Astra Zeneca. J.K.H. has nothing to disclose.*
References

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest


**(5) First intervention trial showing the effects of sodium restriction, diuretic, and their combination in patients with diabetes and nephropathy on RAAS-blockade. Moderate dietary sodium restriction considerably increased the efficacy of RAAS-blockade. This article also reports on sodium excretion in the unselected recruitment population, showing that sodium intake in this outpatient population of patients with diabetes and nephropathy was considerably above the population average in The Netherlands.


Elegant study demonstrating salt sensitivity in CKD patients as sodium restriction lowered blood pressure, proteinuria, and ECV.


Dietary Sodium Restriction

(14) Mann JF, Schmieder RE, McQueen M et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 2008;372:547-553.


This study, with 8.5 years of follow-up, unveils that the relation between sodium intake and adverse renal outcome is independent from, and additive to, proteinuria, moreover, they could not discern a J-curve effect.


Excellent review on mechanisms of sodium retention, for example, activation of ENaC by urinary plasmin in nephrotic syndromes.
Chapter 3


First article to demonstrate involvement of bone-mineral disease key-hormone FGF23 to upregulation of NCC and thus fluid retention


In this article, volume overload was assessed by bioimpedance in predialysis CKD patients and found to correlate with proteinuria, blood pressure and higher antihypertensive medication use. This article demonstrates that volume status might be objectified by bedside measurements and may have clinical consequences.


Elegant study quantifying the abundance of sodium in food additives, and thus enforcing the need for structured interventions and aid for CKD patients in order to reduce sodium intake.


