Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 689–696

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Concordance of dietary sodium intake and concomitant phosphate load: Implications for sodium interventions

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Received 13 January 2016; received in revised form 29 March 2016; accepted 18 April 2016
Available online 27 April 2016

KEYWORDS
Sodium;
Phosphate;
Excretion;
Dietary counseling

Abstract *Background and aims:* Both a high dietary sodium and high phosphate load are associated with an increased cardiovascular risk in patients with chronic kidney disease (CKD), and possibly also in non-CKD populations. Sodium and phosphate are abundantly present in processed food. We hypothesized that (modulation of) dietary sodium is accompanied by changes in phosphate load across populations with normal and impaired renal function.
Methods and Results: We first investigated the association between sodium and phosphate load in 24-h urine samples from healthy controls (n = 252), patients with type 2 diabetes mellitus (DM, n = 255) and renal transplant recipients (RTR, n = 705). Secondly, we assessed the effect of sodium restriction on phosphate excretion in a nondiabetic CKD cohort (ND-CKD: n = 43) and a diabetic CKD cohort (D-CKD: n = 39). Sodium excretion correlated with phosphate excretion in healthy controls (R = 0.386, $P < 0.001$), DM (R = 0.490, $P < 0.001$), and RTR (R = 0.519, $P < 0.001$). This correlation was also present during regular sodium intake in the intervention studies (ND-CKD: R = 0.491, $P < 0.001$; D-CKD: R = 0.729, $P < 0.001$). In multivariable regression analysis, sodium excretion remained significantly correlated with phosphate excretion after adjustment for age, gender, BMI, and eGFR in all observational cohorts. In ND-CKD and D-CKD moderate sodium restriction reduced phosphate excretion (31 ± 10 to 28 ± 10 mmol/d; $P = 0.04$ and 26 ± 11 to 23 ± 9 mmol/d; $P = 0.02$ respectively).
Conclusions: Dietary exposure to sodium and phosphate are correlated across the spectrum of renal function impairment. The concomitant reduction in phosphate intake accompanying sodium restriction underlines the off-target effects on other nutritional components, which may contribute to the beneficial cardiovascular effects of sodium restriction.
(f) **Registration numbers**: Dutch Trial Register NTR675, NTR2366.

Introduction

Dietary interventions form an essential component of the treatment of chronic kidney disease (CKD). Sodium restriction is beneficial for patients in all stages of CKD, reviewed in Ref. [1], and a restriction to <5 g of salt [<2000 mg of sodium] daily is advised in CKD guidelines [2]. Notwithstanding these recommendations, most CKD

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http://dx.doi.org/10.1016/j.numecd.2016.04.012
0939-4753/

patients consume almost twice as much salt: about 9 g a day, which reflects the high sodium intake in the Western general population [3,4]. This directly hampers the efficacy of renin-angiotensin-aldosterone system (RAAS) blockade, the standard therapy for patients with chronic kidney disease [5].

Phosphate restriction is nowadays only advised in the setting of end stage renal disease (ESRD), but has been proposed as treatment target earlier in predialysis CKD [6,7]. This recommendation is based on evidence that higher serum phosphate concentrations are associated with increased mortality in patients with moderately impaired renal function [8] and even in the healthy population [9]. High-normal serum phosphate concentrations also correlate with an impaired response to RAAS blockade in CKD patients [10,11].

Dietary interventions typically address one single nutrient, i.e. 'avoid phosphate-rich products'. This reductionist nutrient approach is one of the reasons why preventive nutrition did not succeed in the prevention of diet-related chronic diseases over the last decades [12]. Assessing food as whole products or dietary patterns may be a more fruitful strategy.

Reducing dietary phosphate intake is a challenge, as phosphate is present ubiquitously in food products [13]. Additive-rich, processed products can easily contain 66% more phosphate than its non-phosphate based preservative equivalent [14]. Moreover, the bioavailability of additive-derived inorganic phosphate is almost 100%, whereas phosphate from animal or vegetable sources is far less avidly absorbed (60% and 40%, respectively [15]). As many additives contain both sodium and phosphate (e.g. disodiumdiphosphate), it is not surprising that a recent RCT found that an additive-enriched diet increases sodium and phosphate intake concomitantly by 60% [16]. These data suggest that intake of sodium and phosphate are concordant in subjects on a western diet. If so, dietary sodium restriction can also be anticipated to modulate phosphate intake, as an off-target effect.

To test these assumptions we first analyzed the association between sodium and phosphate excretion in 24-hourly urinary collections obtained from prospective cohort studies in CKD and non-CKD populations. Secondly, we studied the effect of a dietary sodium intervention on both sodium and phosphate excretion, in a post-hoc analysis of two clinical trials in CKD patients.

Methods

Study population

Observational cohorts

We studied three independent observational cohorts recruited in two different centers in the Netherlands.

First, we recruited a cohort of healthy controls (HC), consisting of participants in a kidney donor screening program at the University Medical Center Groningen, The Netherlands. Participants had no history of CKD, cardiovascular disease or diabetes, nor did they receive dietary counseling on sodium restriction. Mild hypertension (below 140/90 mmHg with 1–2 antihypertensive drugs) was allowed. More details regarding the healthy controls have been published previously [17].

Second, a cohort of diabetics (DM) without overt renal dysfunction was recruited in the ZGT Hospital in Almelo, The Netherlands (METc2008/240), and served as reference diabetes patients as reported earlier [18].

Third, a cohort was recruited consisting of renal transplant recipients (RTR) who visited our outpatient clinic between 2008 and 2010 with a functioning graft $>$ 1 year (METc2008/186). Detailed information about this cohort has been published previously [18].

For all cohorts, patients with missing 24-hourly urinary values on sodium or phosphate were excluded for this analysis.

Intervention studies

The intervention study in nondiabetic CKD patients (ND-CKD) was performed in patients with CKD with blood pressure $>$125/75 mmHg, creatinine clearance $\geq$ 30 mL/min with no upper limit, and $>$1.0 g per day proteinuric kidney disease (Dutch Trial Register NTR675), in four Dutch centers (Medical Center Leeuwarden, University Medical Center Groningen, ZGT Hospital Almelo, Martini Hospital Groningen). Main exclusion criteria were diabetes mellitus, blood pressure $>$180/110 or renal function loss $>$6 mL/min/year. The original study investigated the antiproteinuric efficacy of combination of angiotensin receptor blockade (ARB) with angiotensin-converting enzyme inhibitors (ACEi) –also known as dual blockade– and compared this to the effect of a low sodium diet. All patients underwent 4 six-week treatment periods in a randomized, cross-over design: use of ACEi monotherapy with placebo versus ACEi combined ARB, in the setting of a low sodium diet or regular sodium diet. For the current study we focus on the six week sodium restriction period targeting a 50 mmol/d Na intake compared to a six week regular sodium intake period, both during background ACEi (lisinopril 40 mg daily) therapy. Patients received 2–4 counseling sessions with a dietitian, a list with the sodium content of common food products in the Netherlands, were asked to refrain from adding salt to food and to replace sodium-rich with sodium-poor products. The dietitian did not receive a script or training other than the instruction to target 50 mmol/d and 200 mmol/d sodium per day for the low and regular sodium intake treatment arms, while keeping other dietary factors, including protein intake, as stable as possible. Dietary compliance was assessed halfway during treatment period by 24-hourly urinary collection. During regular sodium diet patients were asked to maintain nutritional habits. Data collection was performed at the end of each treatment period. For extensive details we refer to the protocol documented elsewhere [5].

In another study with a similar design, 45 diabetic CKD patients (D-CKD) underwent a six week treatment period with regular sodium intake (maintaining dietary habits) and sodium restriction targeting 50 mmol/day (NTR2366)