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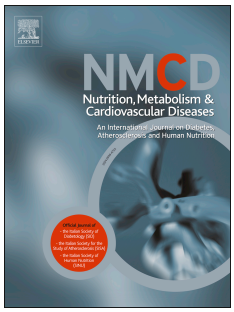

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PII: S0939-4753(16)30044-8

DOI: 10.1016/j.numecd.2016.04.012

Reference: NUMECD 1593

To appear in: *Nutrition, Metabolism and Cardiovascular Diseases*

Received Date: 13 January 2016

Revised Date: 29 March 2016

Accepted Date: 18 April 2016

Please cite this article as: Humalda JK, Keyzer CA, Binnenmars SH, Kwakernaak AJ, Slagman MCJ, Laverman GD, Bakker SJL, de Borst MH, Navis GJ, Concordance of Dietary Sodium Intake and Concomitant Phosphate Load: Implications for Sodium Interventions, *Nutrition, Metabolism and Cardiovascular Diseases* (2016), doi: 10.1016/j.numecd.2016.04.012.

Concordance of Dietary Sodium Intake and Concomitant Phosphate Load: Implications for Sodium Interventions

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Word count: abstract 245/250 Manuscript 3000/3000

28/30 references, 3 tables, 2 figures.

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-hour 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 (1), and a restriction to <5 grams of salt [<2000 mg of sodium] daily is advised in CKD guidelines (2). Notwithstanding these recommendations, most CKD patients consume almost twice as much salt: about 9 grams 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 ≥30 mL/min with no upper limit, and >1.0 gram 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) (18), in three medical centers (ZGT Hospital Almelo, Medical Center Leeuwarden, University Medical Center Groningen). Data collection was performed at the end of each treatment period. Here, patients received 1-2 counseling sessions with a dietitian and further similar advises as mentioned above. Patients without 24-hourly urinary values on sodium or phosphate were excluded for this analysis.

Measurements

Creatinine and elektrolytes were measured with routine laboratory methods. Sodium intake and phosphate intake were estimated from 24-hourly urinary excretion in all cohorts. In the observational cohorts, 24-hour urine was collected in containers with 5 mL oil and 50 mL chlorhexidine. The intervention trials did not use preservatives for 24-hour urine collections. As there are concerns that phosphate may precipitate when urine pH > 7.0, we performed a sensitivity analysis excluding individuals with urine pH > 7.0. Estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI equation (19). Clinical measurements were performed at the time of the outpatient clinic visit in all patients.

Statistics

We report mean and standard deviations or median (1^{st}-3^{rd} quartile) as appropriate. Differences in means for continuous variables were assessed by ANOVA, Kruskal-Wallis or χ^2 for as appropriate. As urea excretion was not available in the DM cohort, means between healthy controls and RTR were compared by t-test. The correlation between phosphate and sodium excretion was assessed by Pearson's correlation test. We used linear multivariable regression analysis with sodium excretion as dependent and phosphate excretion as independent covariate in a first model. Than we constructed the second model together with covariates that may confound the relation: age, gender and BMI to adjust for overt differences in body composition, and eGFR to adjust for differences in solute clearance

capacity. In the third model, we introduced urea excretion to reflect differences in dietary intake of protein. In the fourth model, calcium excretion was added to account for intestinal calcium absorption as a proxy for calcium intake. Interactions were assessed by invoking multiplicative interaction terms.

In the intervention trials we assessed the effect of dietary sodium restriction on phosphate excretion in patients that had complete 24h urinary collections by paired t-tests per study or Wilcoxon Signed Rank test as appropriate, and analyzed the associations between the percent change in sodium and phosphate excretion with Pearson's correlation test. Relative changes in excretion between treatment periods were calculated as follows: relative change = (excretion at regular sodium – excretion at low sodium) / excretion at regular sodium × 100%.

Results

Study Populations

We investigated three independent observational cohorts recruited in two different centers in the Netherlands (Table 1). The first consisted of 252 healthy controls (HC), aged 53± 10.6 years with an eGFR of 91.1±14.0 mL/min/1.73m^2, the second of 255 patients with diabetes that were 63.2±8.9 years old with an eGFR of 72.3±24.4 mL/min/1.73m^2, and the third of 705 renal transplant recipients (RTR) aged 53.0±12.8 years with an eGFR of 52.2±20.1 mL/min/1.73m^2 on median 5.4 (interquartile range 1.9-12.2) years after transplantation (17). We also included cross-sectional analyses of two patient cohorts derived from randomized controlled trials, both during regular sodium intake and during low sodium intake (Table 2). The ND-CKD patients were 51.3±13.9 years old and had an eGFR of 59.3±29.1 mL/min/1.73m^2 during regular sodium intake. The D-CKD patients were 64.0±8.6 years old, had an eGFR of 66.5±25.2 mL/min/1.73m^2 during regular sodium intake, and had a HbA1c of 7.1±0.8%.

Sodium and phosphate excretion

Sodium excretion was similar among patients and healthy controls (Table 1). Mean 24h phosphate excretion was between 25-31 mmol per day. The 24-hour phosphate and sodium excretion correlated strongly in all groups (R=0.386, *P*<0.001 in healthy controls, R=0.490, *P*<0.001 in diabetic patients and R=0.519, *P*<0.001 in RTR (Figure 1). In multivariable regression analysis sodium excretion remained significantly correlated with phosphate excretion after adjustment for age, gender, BMI and eGFR in healthy controls (Standardized beta [St. β]= 0.252, *P*<0.001, R^2=0.30), DM (St. β=0.386, *P*<0.001, R^2=0.35) and RTR (St. β=0.391, *P*<0.001, R^2=0.38, table 3 model 2). Additional adjustment for urea excretion – reflecting protein intake–did not influence the association between sodium and phosphate

excretion (Table 3, model 3). In healthy controls however, significance for sodium excretion was lost after addition of urea excretion. This may suggest an interaction between sodium excretion and urea excretion, i.e. concomitant intake food high in sodium and protein, that explains the variability in phosphate excretion. Indeed, the standardized regression coefficient of sodium excretion also decreased in RTR from 0.391 to 0.11 after introduction of urea in model 3. We found no significant interaction between sodium excretion and urea excretion in its relation to phosphate excretion (*P*- interaction 0.7 in healthy controls and P-interaction=0.3 in RTR). Introduction of calcium excretion improved all models but did not influence the association between sodium and phosphate excretion (Table 3, model 4). One healthy control (pH 7.16) and six RTRs had urine pH >7.0 (maximum pH=7.68). Exclusion of these individuals did not alter conclusions of our analysis. Vitamin D use was only common in the RTR cohort (Tables 1 and 2) and did not materially influence our results. Sodium excretion correlated with phosphate excretion in the vitamin D users (n = 174, St. β=0.485, *P*<0.001) and non-vitamin D users (n=531, (St. β=0.528, *P*<0.001). Vitamin D use did not attenuate our regression models, e.g. when introduced to model 1 of table 3 (R^2 increased from 0.27 to 0.29; coefficient for vitamin D use, St. β= –0.150, *P*<0.001; coefficient for sodium excretion, St. β= 0.508, *P*<0.001).

Intervention studies

We subsequently studied the effect of an intervention in sodium intake, namely moderate sodium restriction, on phosphate intake as reflected by urinary phosphate excretion. In ND-CKD, sodium restriction from 189±56 to 106±48 mmol/d was accompanied by a reduction in phosphate excretion from 31±10 to 28±10 mmol/d (*P*=0.04). In D-CKD, even a moderate sodium restriction from 224±76 to 148±65 mmol/d led to a concomitant reduction of phosphate excretion from 26±11 to 23±9 mmol/d (*P*=0.02, Figure 2). Urinary phosphate and sodium excretion during regular sodium intake correlated strongly in ND-CKD (R=0.491)

and in D-CKD (R=0.729, both P<0.001). The relative reduction in urinary sodium excretion and phosphate excretion correlated poorly (ND-CKD: R=0.248, *P*=0.11, and D-CKD: R=0.065, *P*=0.7).

To investigate whether the change in phosphate excretion in response to dietary sodium restriction was driven by changes in protein intake, we subsequently adjusted our analyses for the change in 24-hour urinary urea excretion. This further weakened the association between the change in sodium and phosphate excretion (ND-CKD: St. β= –0.047, *P*=0.7, D-CKD St. β=0.107, *P*=0.7). Although sodium restriction did not lower urea excretion significantly (Figure 2), the percent change in urea excretion correlated in itself strongly with percent phosphate reduction in ND-CKD (St. β =0.634, *P*<0.001) and correlated borderline-significantly in D-CKD (St. β=0.439, *P*=0.08).

Discussion

In this analysis we confirm that sodium and phosphate intake are strongly correlated across different stages of chronic kidney disease and in healthy controls. Moreover, a dietary intervention aimed solely at sodium restriction achieved a mild but significant concomitant, off-target reduction in phosphate load.

The sodium intake of 10-12 grams of sodium chloride a day in this study equals or is even higher than the already superfluous sodium intake of the general Dutch population of 8.5 grams a day (4). This is far more than the maximum of 5 grams per day as recommended by chronic kidney disease guideline (20). Also for the general population, the WHO recommends to reduce worldwide sodium intake to less than 5 grams per day for every person (21). The phosphate intake can be estimated from the 24-hourly phosphate excretion. The phosphate excretion of our patients was 25-30 mmol per day [~800-1000 mg/day], which is comparable with the mean excretion of 1008 mg/day in 481 patients with normal renal function in the PREMIER study (22). This corresponds with an estimated intake by dietary recall of around 43 mmol/day [~1400 mg/day] (23), assuming that 70% of all phosphorus intake is absorbed in the intestine. As of yet, there is no target value for phosphate intake for the healthy population. A phosphate-restricted diet in the setting of ESRD would target a phosphate intake of 700 mg per day, i.e. roughly half of 'normal' dietary intake.

The coincidence of high sodium load with a high phosphate load is in line with our hypothesis. Food additives contribute substantially to both sodium and phosphate intake (16). Many phosphate-based food additives also contain sodium. For example the mono-, di- and trisodiumphosphates that are used ubiquitously in baking products, beverages, processed cheeses and the sodiumtripolyphosphates used for conservation and stabilizing of meat and fish products (13). Although sodium content is routinely expressed on labels on food

products, its phosphate content is not quantified nor clearly mentioned. The high concurrent sodium and phosphate load in our Western patients is at striking variance with the low sodium and phosphate excretion rates in individuals of African ancestry living in Africa (24), quantifying the effect of the superfluous, additive-rich Western diet. Furthermore, the correlation between sodium excretion and phosphate excretion was independent from urea excretion in RTR, but not in the healthy controls. This may suggest that RTR are particularly susceptible for the contribution of phosphate-rich additives to their sodium/phosphate load , whereas the correlation of sodium and phosphate in healthy controls appears to be mainly protein-driven. As the correlation was attenuated in RTR, of course protein intake played a large role in the RTR population too. Alternatively, the sodium-phosphate excretion association in healthy controls may have become insignificant because of the smaller size of this cohort.

We report that an intervention targeting solely sodium intake, also achieves a reduction in phosphate excretion. The 10% reduction of 3 mmol/day [~ 92 mg/day] is subtle, however, in perspective of the 5.6 mmol/day [173 mg/day, 23%] reduction achieved by a trial that actively targeted phosphate intake it should not be discarded as trivial (23). Also in ten healthy controls, the change from one week on a low-additive diet to one week on an additive-enhanced diet increased phosphate excretion by 4.0 mmol/day [124 mg/day, 20%] (25). Most sodium restriction trials tend to not report urinary phosphate excretion, and vice versa. Thus, it is not surprising yet often overlooked that an intervention aimed at sodium restriction may also exerts effects on other nutrients. It is well-known that dietary sodium restriction leads to a lower protein intake determined by urea excretion (5). This was not significant in our diabetic CKD intervention study, maybe because this population had a different dietary pattern (e.g. a bit more meat, and far more added salt or salty snacks), as reflected by higher urea excretion compared with the nondiabetic CKD intervention study.

Consequently, the D-CKD patients may strongly reduce sodium intake by reducing added salt, without changing protein intake. Because food frequency questionnaires were not available, we could not identify differences in dietary pattern. Alternatively, the effect may have been absent due to a too small sample size. In line, in 22 RTR sodium restriction did not significantly reduce urea excretion (26). Nevertheless, the relative reduction of urea correlated with the reduction of phosphate excretion levels and obliterated the contribution of the reduction in sodium excretion in the intervention studies. This suggests that although sodium restriction may partly reduce protein-associated phosphate, the main effect may be reduction of non-organic phosphate intake, i.e. additives.

From a scientific point-of-view this non-specificity of sodium restriction, i.e. off-target effects on phosphate intake, may be bothersome. On the other hand, this reflects the real-life situation and simply emphasizes that sodium, protein and phosphate are overly represented in the Western diet. Whilst this technically confounds dietary sodium intervention studies, this may offer at the same time an additional clinical benefit: a double-edged sword. One explanation may be that improved adherence to sodium restriction (i.e. avoiding processed foods, additives) concomitantly reduces phosphate load, although this did not translate to a marked correlation between relative change in sodium excretion and phosphate excretion in our study. Also, recent concerns about adverse effects of an overzealous sodium restriction may be influenced by effects on other particular nutrients or malnutrition in general. This serves as an example of the effect of sodium restriction on other nutrients.

. The strength of this study is that we could combine data from observational studies with the effects of sodium-based interventions in randomized clinical trials. Moreover, our populations cover a broad spectrum of the nephrology outpatient clinic, allowing for generalization of our data. For this study, we could rely on 24-hourly urinary excretions as an estimate for sodium and phosphate intake in a stable outpatient setting. No food frequency

questionnaires were available in all cohorts. Also in the trial conditions of the dietary intervention studies, due to the relative long intervention period there are no detailed data on the actual intake. This reflects real-life outpatient conditions, but may be considered a limitation. Our observations thus rely on the premise that 24-hourly urinary excretion reflects intake. Taking into account that there are also non-osmotic buffering capacities for sodium (27) and changes in bone-metabolism for phosphate were not assessed, one cannot state that every mmol of sodium eaten is eventually excreted in the steady state. Notwithstanding, a 24-hourly urinary collection remains the gold standard for dietary intake of the electrolytes sodium and phosphate. Indeed, dietary recall consistently underestimates sodium intake (28), and aforementioned mechanisms would only serve to attenuate the found association rather than confound it.

In conclusion, we found that across different patient populations sodium and phosphate intake are closely related, and that intervention aimed at reduction of sodium also reduces phosphate. Future studies should explore the interaction between sodium and phosphate handling thoroughly. In the meantime, moderate reduction of sodium intake appears to have beneficial effects on phosphate load. This “off-target” effect supports dietary prescriptions aimed at avoidance of processed foods, which should be enforced by dietitians and physicians.

Acknowledgements

C.A.K. and M.H.d.B are partly supported by a consortium grant from the Dutch Kidney Foundation (NIGRAM consortium, grant no CP10.11). The NIGRAM consortium consists of the following principal investigators: Pieter M. ter Wee, Marc G. Vervloet (VU University Medical Center, Amsterdam, the Netherlands), René J. Bindels, Joost G. Hoenderop (Radboud University Medical Center Nijmegen, the Netherlands), Gerjan Navis, Jan-Luuk Hillebrands and Martin H. de Borst (University Medical Center Groningen, the Netherlands). M.H.d.B. is supported by a grant from the Netherlands Organization for Scientific Research (Veni grant no 016.146.014).

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Table 1: Clinical and Biochemical Parameters of the Observational Cohorts.

	HC n= 252	DM n= 255	RTR n= 705
Age, years	53.3±10.6	63.2±8.9	53.0±12.8
Male, n(%)	116 (46)	137 (54)	401 (57)
Weight, kg	79.4±13.8	96.7±18.9	80.4±16.6
BMI	26.0±3.4	33.1±6.0	26.7±4.8
Vitamin D use, n (%)	0	8 (3)	174 (25)
eGFR, ml/min	91.1±14.0	72.3±24.4	52.2±20.1
Systolic blood pressure	125±14	141±16	136±18
Diastolic blood pressure	76±9	76±10	83±11
Serum sodium (mmol/L)	142±1.9	138±3.0	141±3
serum phosphate (mmol/L)	1.07±0.18	0.99±0.18	0.96±0.21
Urinary sodium, mmol/day	194.2±71.6	189.6±79.4	157.1±62.0
Urinary phosphate, mmol/day	28.1±9.6	26.4±10.9	25.0±8.9
Urinary calcium, mmol/day	5.0 (3.4-6.8)	3.2 (1.5-5.2)	2.4 (1.1-3.9)
Proteinuria, g/day	0.0 (0.0-0.2)	0.2 (0.1-0.4)	0.2 (0.0-0.4)
Urea excretion (mmol/day)	404±119	N/A	388±114
Creatinine excretion, mmol/day)	13.2±4.2	13.3±4.3	11.6±3.5

Abbreviations: HC, healthy controls, DM, diabetes mellitus patients; RTR, renal transplant recipients; BMI, Body Mass Index; BSA, Body Surface Area; eGFR, estimated Glomerular Filtration Rate; N/A, not available.

Table 2: Clinical and Biochemical Parameters of the Intervention Studies after Regular Sodium Treatment Period

	ND-CKD, n=43			D-CKD, n=39		
	Regular Sodium	**Low Sodium**	***P*-value**	**Regular sodium**	**Low Sodium**	***P*-value**
Age, years	51.3±13.9	-		64.0±8.6	-	
Male, n(%)	36 (84)	-		33 (85)	-	
BMI	27.5±4.2	-		32.4±5.1	-	
Vitamin D use, n(%)	4 (9)			2 (5)		
Weight, kg	88.9±17.1	86.3±16.3	<0.001	102.3±18.6	100.7±18.7	<0.001
eGFR, ml/min	59.3±29.1	54.6±26.7	0.05	66.5±25.2	66.7±26	0.6
Systolic blood pressure	135±20	125±18	<0.001	146±16	140±16	0.008
Diastolic blood pressure	81±14	73±12	<0.001	82±10	78±10	0.007
Serum sodium (mmol/L)	141±3	139±3	0.003	140±3	140±3	0.06
Serum phosphate (mmol/L)	1.06±0.21	1.11±0.18	0.1	0.99±0.15	1.01±0.14	0.4
Urinary sodium, mmol/day	188.7±58.8	104.4±40.9	<0.001	232.5±72.2	150±69	<0.001
Urinary phosphate, mmol/day	30.7±9.9	28.3±10.1	0.04	26.5±11.5	23.4±9.0	0.02

Urinary urea, mmol/day	386±119	353±109	0.06	422±137	449±197	0.5
Urinary potassium, mmol/day	76±23	75±24	0.3	78±26	83±34	0.3
Urinary creatinine, mmol/day	13.8± 4.1	13.5±4.1	0.2	14.3±4.2	13.8±4.0	0.3
Proteinuria, g/day	2.0 (0.9-3.5)	0.9 (0.5-1.7)	<0.001	1.1 (0.5-3.2)	0.6 (0.4-2.1)	<0.001

Abbreviations: CKD, Chronic Kidney Disease patients without diabetes; D-CKD, CKD patients with diabetes; BMI, Body Mass Index; BSA, Body Surface Area; eGFR, estimated Glomerular Filtration Rate.

Table 3: Multivariate Linear Regression Analysis of Determinants of Phosphate Excretion in Observational Cohorts.

		HC			DM*			RTR		
Model	**Variable**	**St. Beta**	***P*-value**	**R^2**	**St. Beta**	***P*-value**	**R^2**	**St. Beta**	***P*-value**	**R^2**
1	Sodium excretion	0.386	<0.001	0.15	0.490	<0.001	0.24	0.519	<0.001	0.27
2	Sodium excretion	0.252	<0.001	0.30	0.389	<0.001	0.35	0.391	<0.001	0.38
	BMI	0.203	<0.001		–0.065	0.2		0.163	<0.001	
	Gender	–0.316	<0.001		–0.285	<0.001		–0.245	<0.001	
	Age	–0.120	0.10		–0.250	<0.001		–0.028	0.4	
	eGFR (CKD-EPI)	0.010	0.9		–0.002	0.9		0.200	<0.001	
3	Sodium excretion	0.099	0.07	0.49	0.389	<0.001	0.35	0.111	<0.001	0.58
	BMI	0.082	0.10		–0.065	0.2		0.125	<0.001	
	Gender	–0.194	<0.001		–0.285	<0.001		–0.154	<0.001	
	Age	–0.095	0.13		–0.250	<0.001		–0.061	0.02	
	eGFR (CKD-EPI)	–0.026	0.7		–0.002	0.9		0.156	0.001	
	Urea excretion	0.518	<0.001		N/A	N/A		0.554	<0.001	
4	Sodium excretion	0.054	0.295	0.54	0.337	<0.001	0.40	0.097	0.002	0.60
	BMI	0.091	0.056		–0.047	0.4		0.108	<0.001	
	Gender	–0.217	<0.001		–0.274	<0.001		–0.180	<0.001	
	Age	–0.102	0.084		–0.224	<0.001		–0.079	<0.001	

eGFR (CKD-EPI)	–0.039	0.5	–0.121	0.05	0.085	0.001
Urea excretion	0.454	<0.001	N/A	N/A	0.509	<0.001
Calcium excretion	0.242	<0.001	0.265	<0.001	0.188	<0.001

Abbreviations: HC, healthy controls, DM, diabetes mellitus patients; RTR, renal transplant recipients; St. Beta, standardized beta; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; *Urea excretion measurements were not available (N/A) for the DM cohort.

Figure Legends

Figure 1: Correlation of 24-hourly Sodium Excretion and Phosphate Excretion in the three Observational Cohorts.

Figure 2: Concomitant Effects of a Low Sodium Diet on Phosphate and Urea Excretion.

24-hourly excretion of phosphate (left Y-axis) and urea (right Y-axis) under regular and low sodium diet in ND-CKD (upper panel) and D-CKD (lower panel). *P*-value reflects paired t-test. ND-CKD, nondiabetic chronic kidney disease; D-CKD, diabetic chronic kidney disease; NS, not-significant.

Figure 1

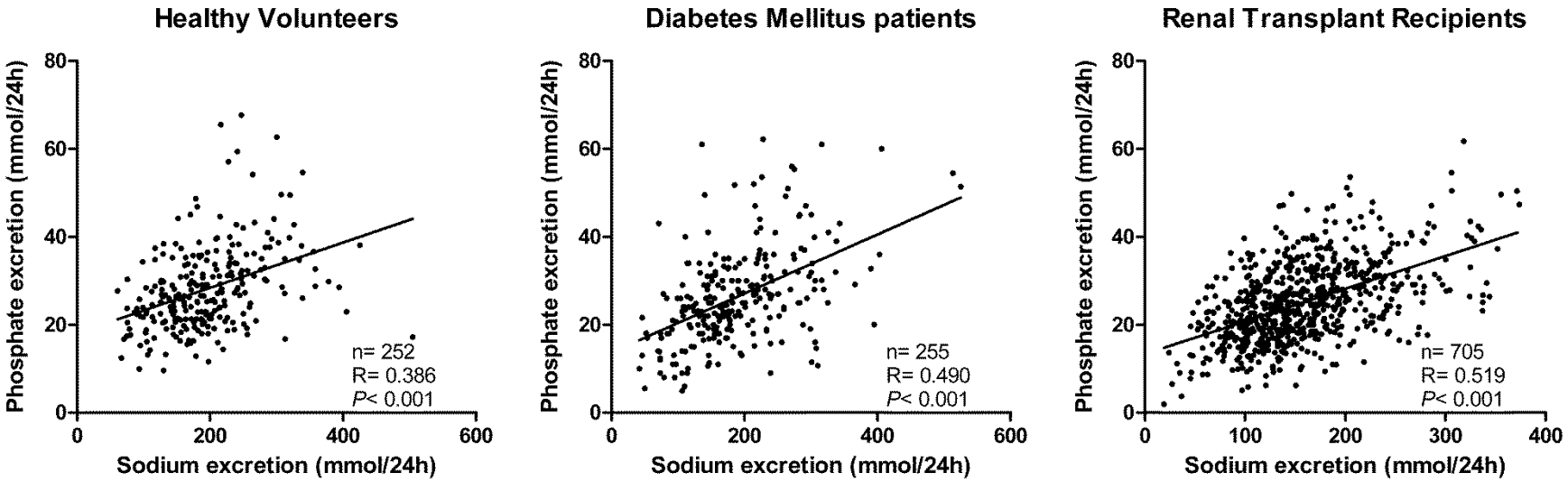
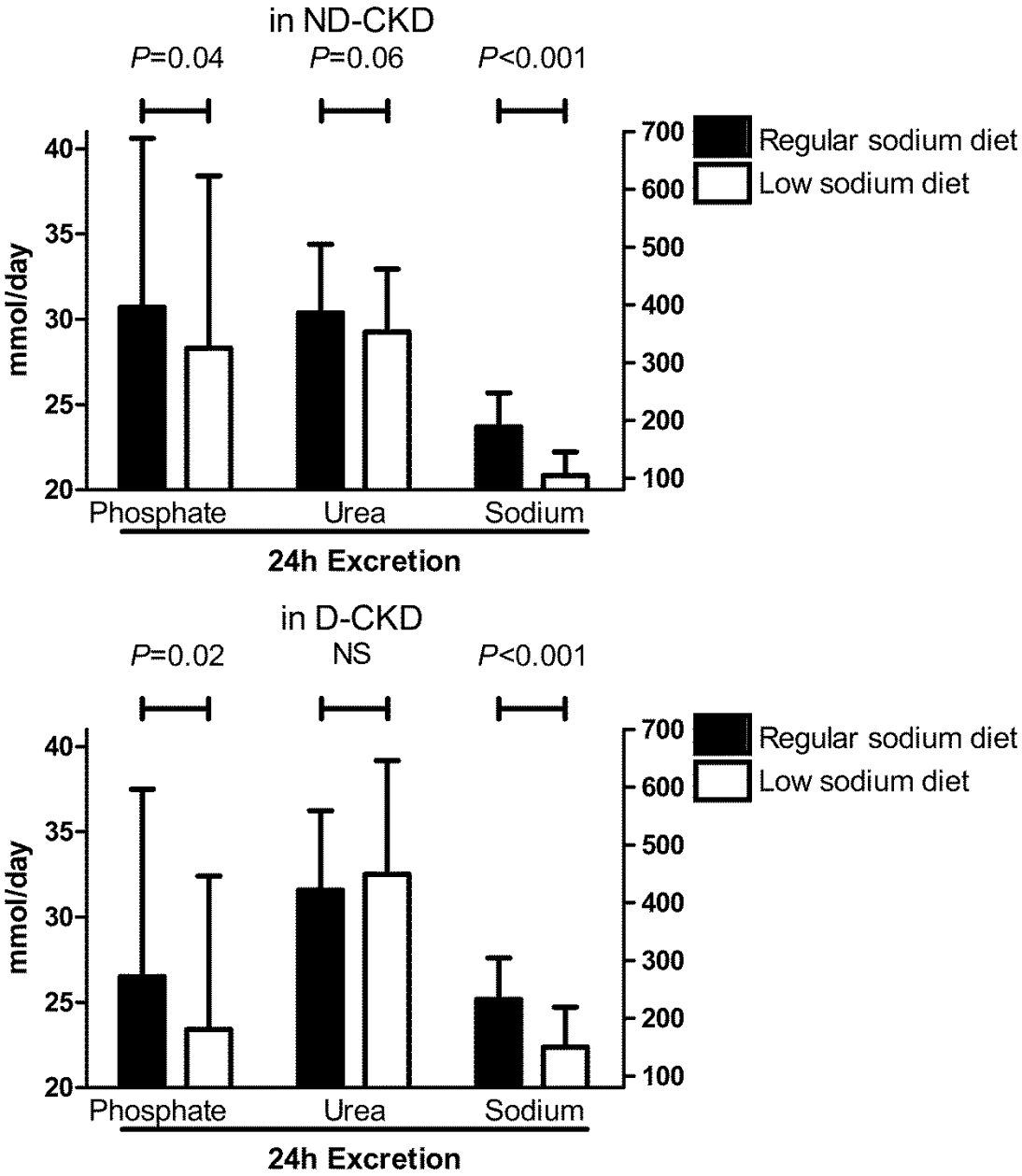


Figure 2


in ND-CKD
P=0.04
P=0.06
P<0.001
mmol/day
40
35
30
25
20
700
600
500
400
300
200
100
Regular sodium diet
Low sodium diet
Phosphate
Urea
Sodium
24h Excretion
in D-CKD
P=0.02
NS
P<0.001
mmol/day
40
35
30
25
20
700
600
500
400
300
200
100
Regular sodium diet
Low sodium diet
Phosphate
Urea
Sodium
24h Excretion

Highlights

- **A high intake of sodium and phosphorus may be harmful, particularly for CKD patients.**
- **Sodium and phosphorus are ubiquitously present in additive-rich, processed foods.**
- **24-hourly urinary excretion of sodium and phosphorus are strongly correlated across different populations.**
- **Dietary counseling to reduce sodium intake concomitantly reduces phosphate intake.**
- **Studies aimed at reducing one food component should assess changes in other nutrients.**