UNIVERSITY
OF WOLLONGONG
AUSTRALIA

University of Wollongong
Research Online

Faculty of Science, Medicine and Health - Papers: Part B

Faculty of Science, Medicine and Health

2018

Role of dietary phosphate restriction in chronic kidney disease

Grahame Elder
University of Notre Dame, Garvan Institute Of Medical Research, Westmead Hospital

Avya Malik
University of Notre Dame

Kelly Lambert
University of Wollongong, klambert@uow.edu.au

Publication Details

Elder, G. J., Malik, A. & Lambert, K. (2018). Role of dietary phosphate restriction in chronic kidney disease. Nephrology, 23 (12), 1107-1115.

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au

Role of dietary phosphate restriction in chronic kidney disease

Abstract

Aim: Patients with progressive chronic kidney disease (CKD) develop positive phosphate balance that is associated with increased cardiovascular risk and mortality. Modification of dietary phosphate is a commonly used strategy to improve outcomes but is complicated by the need for adequate dietary protein. Surprisingly, the evidence for patient-level benefits from phosphate restriction is tenuous, and the justification for using any phosphate binder for pre-dialysis patients is questionable.

Methods: The evidence for dietary phosphate modification was reviewed, along with the possible role of a smart phone application (app) that provides information on phosphate, sodium, potassium and nutrients in over 50 000 Australian foods. A pilot study of healthy participants assigned to dietetic advice and standard diet sheets, or dietetic advice, diet sheets and use of the smart phone app was performed.

Results: Following baseline studies, 25 participants commenced the sodium and phosphate restricted diet. After 2 weeks, both groups showed non-significant trends to reduction in urinary phosphate and sodium. App users referred to information on the app more frequently than the control group participants referred to written instructions, found referring to the app more convenient, felt they learned more new information, were more motivated to maintain the diet and were more likely to recommend their information source to family or friends (all $P < 0.05$).

Conclusions: Maintaining phosphate balance remains an important goal of CKD management, although diets incorporating very low phosphate and protein contents may worsen patient outcomes. For selected patients, a smart phone app may improve dietary acceptance and compliance.

Publication Details

Elder, G. J., Malik, A. & Lambert, K. (2018). Role of dietary phosphate restriction in chronic kidney disease. Nephrology, 23 (12), 1107-1115.

This journal article is available at Research Online: https://ro.uow.edu.au/smhpapers1/449

Clean final copy with references, tables and figure.

Title: The role of dietary phosphate restriction in chronic kidney disease.

Authors:

Grahame J Elder PhD[1,2,3], Avya Malik MBBS[3] and Kelly Lambert MSc[4]

[1]Department of Renal Medicine, Westmead Hospital, Westmead, NSW, Australia, [2]Osteoporosis and Bone Biology Division, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia, [3] University of Notre Dame, Sydney, NSW, Australia, [4] School of Medicine, University of Wollongong, NSW, Australia.

Correspondence:

Prof. Grahame Elder,

Department of Renal Medicine, Westmead Hospital,

Westmead, NSW 2145, Australia

g.elder@garvan.org.au

Telephone: +61 2 98456962

Word Count: 2712

Abstract word count: 250

Abstract

Background and objectives

Patients with progressive chronic kidney disease (CKD) develop positive phosphate balance that is associated with increased cardiovascular risk and mortality. Modification of dietary phosphate is a commonly used strategy to improve outcomes but is complicated by the need for adequate dietary protein. Surprisingly, the evidence for patient-level benefits from phosphate restriction is tenuous, and the justification for using any phosphate binder for pre-dialysis patients is questionable.

Design, setting, participants, and measurements

We review the evidence for dietary phosphate modification and the possible role of a smart phone application (app.) that provides information on phosphate, sodium, potassium and nutrients in over 50,000 Australian foods. We performed a pilot study of healthy participants assigned to dietetic advice and standard diet sheets, or dietetic advice, diet sheets and use of the smart phone app.

Results

Following baseline studies, 25 participants commenced the sodium and phosphate restricted diet. After two weeks, both groups showed non-significant trends to reduction in urinary phosphate and sodium. App. users referred to information on the app. more frequently than the control group participants referred to written instructions, found referring to the app. more convenient, felt they learned more new information, were more motivated to maintain the diet and were more likely to recommend their information source to family or friends (all $p<0.05$),

Conclusions

Maintaining phosphate balance remains an important goal of CKD management, although diets incorporating very low phosphate and protein contents may worsen patient outcomes. For selected patients, a smart phone app. may improve dietary acceptance and compliance.

Key words: phosphate, protein, dietary restriction, smart phone application, phosphate binders, cardiovascular risk

Introduction.

Phosphate is a natural component of foods rich in protein and mixed diets usually contain 12-14 mg per gram of protein [1]. The US Institute of Medicine has recommended a dietary intake for maintaining phosphate balance and normal serum phosphate levels of 700 mg/day for healthy adults and up to 1250 mg/day for older children and pregnant women [2], and in Australia and New Zealand, the recommended daily intake for adults is 1000 mg/day [3]. Most studies suggest that protein intakes of 0.6 g/kg per day are adequate, with at least 50% as high biological value protein; containing essential amino acids in a proportion similar to that required by the body, and with a caloric intake sufficient to maintain body weight. However, higher protein intakes of 0.75 g/kg per day have been recommended for active young men and women and for elderly people who use protein less efficiently and have a lower lean mass [4].These recommendations also apply to patients with chronic kidney disease (CKD).

Bioavailable phosphate.

Phosphorus is organically bound and stored as phytate in grains, cereals and seeds. Humans and other non-ruminant animals lack the digestive enzyme phytase that is produced by bacteria in the gut of ruminants, and consequently humans are unable to digest phytate. This results in less than 40% of phosphate from plant sources being bioavailable and the remainder being excreted. By comparison, phosphate derived from animal products such as meat, fish and milk is more readily absorbed [5], and the absorption of phosphate food additives approaches 100%. These additives are frequently used as food processing aids, as colour and flavour enhancers, to alter food texture and to increase shelf life. Sugary carbonated beverages have added phosphoric acid to sharpen flavour and to slow the growth of moulds and bacteria.

The challenges of calculating dietary phosphate.

Depending on the dietary source, around 60% of phosphate undergoes gastrointestinal absorption

and 95% of the absorbed phosphate is renally excreted unless renal function is severely compromised. Intestinal phosphate absorption is responsive to levels of circulating 1,25-dihydroxyvitamin D and prescribed calcitriol or other vitamin D receptor agonists (VDRAs). These drugs can increase active phosphate absorption to around 80% by increasing intestinal type II sodium-dependent phosphate co-transporter 2b (Npt2b) activity. With this in mind, the current Kidney Disease Improving Global Outcomes (KDIGO) CKD-mineral and bone disorder (MBD) guidelines no longer recommend the use of calcitriol/VDRAs for patients with CKD stages 3 to 5 and moderate hyperparathyroidism, instead suggesting that these agents be reserved for severe and progressive hyperparathyroidism[6].

The varying bioavailability of phosphate between food sources and the effect of prescribed drugs on phosphate absorption can lead to the dietetic assessment of phosphate intake being inaccurate. In a study by Oenning *et al. t*hat compared dietary phosphate content using standard food tables and chemical analyses [7], food tables underestimated the phosphate content of diets by approximately 350 mg/day. This inaccuracy was further emphasised in a recent study, which reported that traditional methods of calculating intake from food databases overestimated the true phosphate content of a vegetarian diet by 33%, although a fresh meat and milk product-based diet did match database predictions [5]. For patients with CKD, any reduction of dietary phosphate must be balanced against the maintenance of adequate dietary protein, energy and normal potassium values, which often leads to complex instructions and reduces dietary adherence.

Evidence for restricting phosphate

Restriction of dietary protein, and with it dietary phosphate, slows the progression of renal disease in experimental animal models [8,9]. In humans, elevated phosphate levels are associated with the development and progression of CKD-MBD [10], but the benefits of intervention to restrict dietary protein and phosphate remain unclear. Patients with renal impairment and elevated serum

phosphate values are at greater risk of coronary artery calcification, cardiovascular disease (CVD), progression to end stage renal disease (ESRD), and early mortality [11-13]. However, the Kidney Early Evaluation Program (KEEP) study illustrated that while phosphate levels are associated with these outcomes, they are not necessarily causative and may not be true surrogates [14]. The KEEP nationwide study screened high-risk individuals in the USA with estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73m^2, and analysed risk according to quartiles of serum phosphate. Individuals in the highest serum phosphate quartile had an unadjusted 6.72-fold higher risk of progression to ESRD over a median follow up of 2 years than those with phosphate values of ≤3.3 mg/dl (the reference value). However, this hazard ratio was no longer significant when adjusted for demographic data, other cardiovascular risk factors and severity of CKD. The value of pharmaceutical interventions to reduce serum phosphate is even more controversial. When phosphate binder effects were studied in moderate CKD [15], the risk of developing vascular calcification was greater for patients allocated to any type of phosphate binder (lanthanum, sevelamer and calcium-based) than to placebo.

Another potential benefit of phosphate restriction and/or phosphate binder use is to ameliorate the dramatic rises in FGF23 that occur as CKD progresses. Although early elevations of FGF23 are adaptive to maintain phosphate homeostasis, the extreme values found in patients with CKD are associated with increased cardiac fibrosis, hypertrophy and arrhythmogenic potential [16,17], and with increased progression to dialysis and increased mortality in patients with CKD stages 2-4 [18]. Consequently, recent studies of protein and phosphate restriction, and of interventions using phosphate binding agents, have focussed on FGF23 modulation as a surrogate for the amelioration of CVD.

Evidence for patient-level benefits of protein and phosphate restriction in CKD.

Despite the cost in time and human resources invested in counselling patients on protein and

phosphate restriction, the evidence for dietary intervention is remarkably poor, and even in clinical trials, up to 50% of patients fail to achieve dietary compliance. Table 1 summarises important studies, most of which are randomised, controlled trials, of usual versus reduced dietary phosphate/protein. The table also includes some studies that assessed differing phosphate sources [5,19].

The Modification of Diet in Renal Disease (MDRD) study [20], was a major initiative to assess decline in kidney function in relation to three levels of protein and phosphate intake (normal, low and very low), and two levels of blood pressure management. In the primary analysis, there were no statistically significant differences in progression between low and usual protein diets, or between low and very low protein diets. The authors concluded that the effect of these dietary prescriptions to patients with mild to moderate renal insufficiency remained uncertain. Further analysis suggested that lower protein diets might slow progression in patients with the most rapid decline in GFR [21] and each decrease in protein intake of 0.2 g/kg/day was associated with a slower mean GFR decline [22]. As a result, the authors suggested a prescribed dietary protein intake of 0.8 g/kg/day for patients with GFR < 25 mL/min/1.73 m^2.

Pedrini *et al* [23] performed a systematic review of studies to December 1994 that assessed usual versus low protein dietary restriction in patients with moderate CKD (eGFR <55 ml/min/1.73m^2). That meta-analysis indicated significantly less progression of renal impairment in both non diabetic and type 1 diabetic patients allocated to low protein diets. In five studies of non diabetic renal impairment, the relative risk (RR) for renal failure or death was 0.67 (95% Cl, 0.50 to 0.89), and in the five studies of patients with type-1 diabetes mellitus a low-protein diet significantly slowed increases in urinary albumin and the decline in GFR or creatinine clearance [RR, 0.56 (Cl, 0.40 to 0.77)].
Moe *et al*[5] investigated differences in phosphate absorption between grain-based and meat-based diets that contained equivalent protein and phosphate, and observed higher levels of serum

phosphate and FGF23 and lower PTH levels after one week of the meat-based diet. Most recently, a long term follow up of patients enrolled in the MDRD study [24] reported that pre-randomisation urinary phosphate levels were not associated with long-term outcomes of ESRD or mortality, although in a fully adjusted model a three-day dietary recall for phosphate did show a modest association to all-cause mortality. The authors suggested that until further studies confirmed or refuted their findings, caution should be used in advising reductions in dietary phosphate and protein intake in patients with CKD. The chance of such a study is remote.

Improving the management of phosphate control; 'What you eat today walks and talks tomorrow'.

In 2013, Dr Tonelli writing in Kidney International[25], suggested that a smart phone 'food switch' application (app.) could be developed for patients with CKD to help them control their phosphate levels. After scanning the bar code of a product, the app. would provide information on the phosphate content (inclusive of additives) of the selected and comparable products, so that consumers could make a more informed choice. Of course, this relies on the availability of an extensive, locally germane food database. With this in mind, we approached the developers of the most downloaded, free of charge Australian dietary app. to create a version containing information applicable to patients with CKD. The app. contained information on over 50,000 Australian foods obtained from Australian food databases and food product labels. Patients using the app. could elect to share data collected by the app. with their dietitian or other health professionals, to enable real-time online monitoring of their progress. When released for download, the new renal version (Easy Diet Diary Renal™) included dietary phosphate, sodium, calcium and potassium, in addition to protein, kilojoules and carbohydrate.

Efficacy and acceptance of a renal app. for dietetic monitoring; a pilot study.

To compare the utility of the app. to standard dietetic monitoring, we undertook a pilot study with

approval of the Human Research Ethics Committee of Western Sydney Local Health District and adherence to the Declaration of Helsinki (ACTRN12617000558325).

Methods: After providing volunteers with study information and receiving their informed consent, 25 participants with a normal urinalysis, blood pressure and without a history of kidney disease or use of medications likely to influence urinary sodium or phosphate values were randomly allocated to an intervention or a control group. Next, all participants maintained a food diary for 3 days to assess baseline dietary sodium and phosphate intakes, followed by a 24 hour urine sample for volume, creatinine, sodium and phosphate. Participants were then requested to moderately reduce their sodium and phosphate intake for two weeks, to daily targets often used for people with established renal failure (ERF) of <100 mmol sodium and < 1000 mg phosphate. To achieve this, all participants were provided with a dietary leaflet used in normal clinical care that provided advice on strategies to achieve the reduction. Based on the dietary records, participants were given feedback on their dietary intakes of sodium and phosphate, and provided with individualised advice on reducing that intake to within the target range in a telephone interview of no more than 1 hour with a trained dietician. No additional strategies were used in the control group. However, the intervention group were given approximately 30 minutes instruction by a non-dietician on use of the dietary app. to monitor sodium and phosphate targets.

The primary outcome was to assess within group change in 24 hour urinary phosphate and sodium values between collections at baseline and two weeks after commencement of the diet. The estimated sample size for this was 10 participants per arm. Calculation of between group differences (estimated sample size 123 subjects per arm) was outside the scope of this pilot study. The s**econdary outcome was to compare** ease of dietary compliance between the groups using a questionnaire completed by all participants at the conclusion of the dietary intervention. The questionnaire included 11 questions on acceptability and usability of the food diary, five on compliance, five free text questions and for app. users, 14 questions on ease of use.

Paired t-tests or Wilcoxon signed rank tests were used to test for differences between baseline and

end of the intervention. Independent t-tests or Wilcoxon rank sum tests were used to test for differences between groups. Analyses were conducted by intention to treat and significance was determined by p-values <0.05. Questionnaire responses were recorded by participants using a 5-point Likert scale. Statistical analyses were undertaken using SPSS version 21 (SPSS Inc., Chicago, Illinois, USA).

Results: Participant demographics and clinical details, dietary intakes calculated from the three day food diaries and baseline 24 hour urinary values for sodium, phosphate and creatinine did not differ significantly between groups (Table 2). Baseline sodium and phosphate intakes from the three day dietary assessments were close to the 50^{th} percentile of age adjusted population norms . However, 24 hour urinary values of sodium and phosphate, measured as a single batch after conclusion of the study, were close to the targeted range even before any dietary intervention (Table 2). Comparison of pre and post intervention urinary values indicated trends to reduction in mean sodium and phosphate values that did not reach statistical significance within or between groups (Table 2) or when values for the control and app. group were combined to assess change over the period of dietary intervention. Comparing questionnaire responses, app. users referred to information on the app. more frequently than the control group participants referred to written instructions, app. users found referring to the app. more convenient, felt they learned more new information, were more motivated to maintain the diet and were more likely to recommend their information source to family or friends (all $p<0.05$), with trends to confidence in improving eating habits ($p=0.06$), ease of use ($p=0.07$) and fewer non-compliant days ($p=0.08$) (Table 2) . In the free text section, six control participants felt they lacked access to sufficient information, while no app. users indicated that they lacked information.

Discussion: The pilot study suggested that participants using the app., which gave them immediate access to the sodium, phosphate, potassium and nutrient content of their foods, had a better experience of the restricted diet. Their greater motivation and self assessed increase in knowledge of food sources was encouraging. These results can be contrasted with a study of 279 patients in 14

long-term dialysis facilities with persistently elevated phosphate levels[26]. Patients were allocated to usual care or intervention that included specific instruction, handouts of preferred foods and foods to avoid and additional telephone reinforcement. Serum phosphate levels decreased at three months in the intervention group and food knowledge scores improved in both. However, there was no significant difference in food knowledge between control and interventional groups as noted in our study. Nevertheless, it is important to emphasise that before use of the app. can be endorsed in research or with groups such as patients with CKD, further studies would be required to determine whether the app. assists these patients to achieve their nutrient targets.

The renal app. is now available in Australasia, with approximately 450 downloads in the first six months since its release. A screen shot of a sample breakfast is included (Figure 1). Further modifications will differentiate foods high in organic and inorganic phosphate and provide the 'food switch' capacity suggested by Dr. Tonelli in 2013.

Conclusion.

In ESRD, when phosphate homeostasis is no longer attainable through endogenous responses, a low phosphate, high protein intake has been associated with reduced mortality, but extremely low dietary phosphate combined with a low protein intake may produce worse outcomes. This equipoise is not achieved by many patients. Based on the available evidence, encouragement to eat grain and vegetable-based meals with lower inorganic phosphate, reduced phosphate additives and high-value protein is unlikely to have adverse effects and may have benefits for most people with CKD. Reduced reliance on calcitriol or other VDRAs to suppress PTH, and an acceptance of moderately increased PTH levels in the later stages of CKD, will also lead to reduced intestinal phosphate absorption and may improve phosphate balance. Although based on weak clinical evidence, it appears preferable to target treatment towards *overt* hyperphosphatemia in CKD stages 3-5, rather than targeting values of serum phosphate in the normal range. As well as being more attainable, this would reduce adverse effects of phosphate binder therapy, including hypercalcaemia associated with calcium-

based binders. Public advocacy for the disclosure on packaged food labels of all phosphate additives, which are the source of highly absorbed phosphate, would be a real benefit to consumers. In addition, a renal dietary app. may encourage some users to understand and improve their food choices and dietary compliance.

Disclosures:

Grahame Elder: has acted on the advisory boards and received speakers fees from Shire Australia, Sanofi Australia and Amgen Australia.

Avya Malik: None

Kelly Lambert: None.

Authors' Contributions

Grahame Elder: designed the study, contributed to conducting the research, provided statistical analysis, wrote the paper and had primary responsibility for final content.

Avya Malik: assisted with study design, conducted the research and reviewed the paper.

Kelly Lambert: designed the study, contributed to conducting the research, provided statistical analysis and reviewed the paper.

References

1. Boaz M SS. Regression equation predicts dietary phosphorus intake from estimate of dietary protein intake. *J. Am. Diet. Assoc.* 1996;96(12):1268-1270.
2. Institute of Medicine. Phosphorus. In: Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D,and Fluoride. . Washington,DC: National Academy Press; 1997.
3. Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes. 2006. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n35.pdf.
4. National Research Council (US) Subcommittee on the Tenth Edition of the Recommended Dietary Allowances. Recommended Dietary Allowances: 10th Edition. Protein and Amino Acids. . Washington, DC.: National Academies Press (US). 1989.
5. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* Feb 2011;6(2):257-264.
6. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. *Kidney Int.* Jul 2017;92(1):26-36.
7. Oenning LL, Vogel J, Calvo MS. Accuracy of methods estimating calcium and phosphorus intake in daily diets. *J. Am. Diet. Assoc.* Sep 1988;88(9):1076-1080.
8. Koizumi T, Murakami K, Nakayama H, Kuwahara T, Yoshinari O. Role of dietary phosphorus in the progression of renal failure. *Biochem. Biophys. Res. Commun.* Jul 26 2002;295(4):917-921.
9. Kusano K, Segawa H, Ohnishi R, Fukushima N, Miyamoto K. Role of low protein and low phosphorus diet in the progression of chronic kidney disease in uremic rats. *J. Nutr. Sci. Vitaminol. (Tokyo).* Jun 2008;54(3):237-243.
10. Barsotti G, Giannoni A, Morelli E, et al. The decline of renal function slowed by very low phosphorus intake in chronic renal patients following a low nitrogen diet. *Clin. Nephrol.* Jan 1984;21(1):54-59.
11. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am. J. Kidney Dis.* Apr 1998;31(4):607-617.
12. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J. Am. Soc. Nephrol.* Oct 2001;12(10):2131-2138.
13. Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA.* Mar 16 2011;305(11):1119-1127.
14. Mehrotra R, Peralta CA, Chen SC, et al. No independent association of serum phosphorus with risk for death or progression to end-stage renal disease in a large screen for chronic kidney disease. *Kidney Int.* Nov 2013;84(5):989-997.
15. Block GA, Wheeler DC, Persky MS, et al. Effects of phosphate binders in moderate CKD. *J. Am. Soc. Nephrol.* Aug 2012;23(8):1407-1415.
16. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J. Clin. Invest.* Nov 2011;121(11):4393-4408.
17. Kao YH, Chen YC, Lin YK, et al. FGF-23 dysregulates calcium homeostasis and electrophysiological properties in HL-1 atrial cells. *Eur. J. Clin. Invest.* Aug 2014;44(8):795-801.
18. Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA.* Jun 15 2011;305(23):2432-2439.
19. Mircescu G, Garneata L, Stancu SH, Capusa C. Effects of a supplemented hypoproteic diet in

chronic kidney disease. *J. Ren. Nutr.* May 2007;17(3):179-188.

20. Klahr S, Levey AS, Beck GJ. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. modification of diet in renal disease study group. *N. Engl. J. Med.* 1994;330.

21. No author. Effects of dietary protein restriction on the progression of moderate renal disease in the Modification of Diet in Renal Disease Study. *J. Am. Soc. Nephrol.* Dec 1996;7(12):2616-2626.

22. Levey AS, Adler S, Caggiula AW, et al. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am. J. Kidney Dis.* May 1996;27(5):652-663.

23. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann. Intern. Med.* Apr 01 1996;124(7):627-632.

24. Selamet U, Tighiouart H, Sarnak MJ, et al. Relationship of dietary phosphate intake with risk of end-stage renal disease and mortality in chronic kidney disease stages 3-5: The Modification of Diet in Renal Disease Study. *Kidney Int.* Jan 2016;89(1):176-184.

25. Tonelli M. Serum phosphorus in people with chronic kidney disease: you are what you eat. *Kidney Int.* 2013;84(5):871-873.

26. Sullivan C, Sayre SS, Leon JB, et al. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. *JAMA.* Feb 11 2009;301(6):629-635.

27. Menon V, Wang X, Greene T, et al. Homocysteine in chronic kidney disease: Effect of low protein diet and repletion with B vitamins. *Kidney Int.* Apr 2005;67(4):1539-1546.

28. Cianciaruso B, Pota A, Pisani A. Metabolic effects of two low protein diets in chronic kidney disease stage 4–5--a randomized controlled trial. *Nephrol. Dial. Transplant.* 2008;23.

29. Di Iorio B, Di Micco L, Torraca S, et al. Acute effects of very-low-protein diet on FGF23 levels: a randomized study. *Clin. J. Am. Soc. Nephrol.* Apr 2012;7(4):581-587.

30. Sigrist M, Tang M, Beaulieu M, et al. Responsiveness of FGF-23 and mineral metabolism to altered dietary phosphate intake in chronic kidney disease (CKD): results of a randomized trial. *Nephrology Dialysis Transplantation.* 2013;28(1):161-169.

31. Isakova T, Barchi-Chung A, Enfield G, et al. Effects of dietary phosphate restriction and phosphate binders on FGF23 levels in CKD. *Clin. J. Am. Soc. Nephrol.* Jun 2013;8(6):1009-1018.

32. Goto S, Nakai K, Kono K, et al. Dietary phosphorus restriction by a standard low-protein diet decreased serum fibroblast growth factor 23 levels in patients with early and advanced stage chronic kidney disease. *Clin. Exp. Nephrol.* Dec 2014;18(6):925-931.

Legend to tables 1 and 2 and to figure 1.

Table 1. Studies comparing diets containing usual versus reduced phosphate and protein. Abbreviations; CKD: chronic kidney disease, DM: diabetes mellitus, P: phosphate, BP: blood pressure, tHcy: total homocysteine, Na: sodium, PTH: parathyroid hormone, BMI: body mass index, FGF23: fibroblast growth factor 23, 25OHD: 25-hydroxyvitamin D, $1,25(OH)_2D$: 1,25-dihydroxyvitamin D, Ca: calcium, ESRD: end-stage kidney disease, CV: cardiovascular, HR: hazard ratio, SD: standard deviation, CI: confidence interval.

Table 2. Participant demographics, dietary intakes calculated from three-day food records, pre and post study values for 24 hour urine biochemistry and selected questionnaire responses. * $p<0.05$ for between group differences.
For the general population aged 19 to 30 years, the 50^{th} percentile for usual daily sodium intake, excluding discretionally added salt, is 2247 mg for females and 2965 mg for males and for phosphorus is 1228 mg for females and 1695 mg for males (http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.008~2011-12~Main%20Features~Essential%20minerals~400; accessed September 2017). Based on the three day food diary prior to dietary intervention, 33 % of participants had sodium intakes within the target range, while 33% of control group participants had phosphate intakes within the target range. However, based on urinary sodium and phosphate values, 33% and 54% of participants had baseline sodium values within the target range and 92% and100% had baseline phosphate values within the target range before dietary intervention. Baseline and end of study urinary values were determined after study completion.

Figure 1. Screenshot of a sample breakfast using the app.

Table 1.

Author and year Hypothesis	**Number available for analysis**	**Study duration**	**GFR / eGFR ml/min/1.73m^2**	**Active intervention**	**Primary outcome**	**Secondary outcomes**
Pedrini et al [23], 1996 (Meta analysis January 1966-December 1994; included MDRD) Protein and P restriction may prevent or delay worsening of CKD	1413 non diabetic patients (5 studies) 108 patients with type 1 DM (5 studies)	18-36 months 9-33 months	<55	Low protein: 0.4-0.6 g/kg/day *vs.* usual protein Low protein 0.50 g/kg/ day - 0.85 g/kg/day	Progression of renal disease 27% lower in patients on low protein diet	Benefit of low protein diet not related to BP lowering
Klahr et al [20], 1994 (MDRD 1989-93) Rate of decline in kidney function will be modified by protein, P restriction and BP control	Study A: 574 Study B: 252	3 years Mean 2.2 years	Study A: 25-55 Study B: 13-24	Study A: usual-protein (1.3 g/kg day) *vs.* low-protein (0.58 g/kg/day}, P 5-10 mg/kg/day Study B: Low-protein 0.58 g/kg/day, P: 5-10 mg/kg/day *vs.* very low-protein 0.28 g/kg/day + keto acids-amino acids 0.28 g/kg/day and P 4-9 mg/kg/day	Study A: Projected decline in GFR at 3 years did not differ between diet groups Study B: Trend (p = 0.07) toward slower mean decline in GFR with very low-protein diet. No significant effect on time to renal failure / death.	
Levey et al [21], 1996 (MDRD) Rate of decline in kidney function will be modified by protein and P restriction and BP control	574	3 years	Study A: 25-55	Three levels of protein and P intake and two levels of BP management Low-protein: 0.58 g/kg per day Usual protein: 1.3 g/kg day	Effect of low-protein diet inconclusive due to nonlinear GFR decline and limited duration of follow-up	Faster GFR decline on low-protein diet in 1st 4 months, then slower decline No difference between dietary groups over 3 years Possible beneficial effect of low- protein diet to

						slow GFR decline in patients with the most rapidly declining GFR, and to reduce urine protein excretion
Levey [22], 1996 (MDRD 1989-93) Rate of decline in kidney function will be modified by protein restriction and BP control	252	Mean 2.2 years	Study B: 13-24	Prescribed diets for Study B as above Reanalysis using *achieved* protein intake calculated from average of monthly urea nitrogen excretion levels: Low 0.73 g/kg/day Very low 0.66 g/kg/day	The *achieved* lower protein intake retarded CKD progression	Risk of developing end stage renal disease or death within 3 years of follow-up: 51% for 0.8 g/kg/day *vs.*30% for 0.6 g/kg/day (a 40% reduction) No relationship of protein intake to change in urine protein excretion Keto acid-amino acid supplements did not influence progression
Menon [27], 2005 (MDRD 1989-93) High protein intake will be associated with higher tHcy	678	1 year	13-24 25-55	Dietary protein low *vs.* usual Dietary protein low *vs.* very low + amino acids and ketoacids	No association of protein intake to tHcy values.	Vitamin supplementation reduces tHcy levels in some patients
Mircescu [19], 2007 Low protein intake will improve nitrogen waste products retention and calcium, P and acid-base disturbances	53	48 weeks	<30	Very low 0.3 g/kg/day vegetable protein + keto-analogues *vs.* conventional low mixed protein diet 0.6 g/kg/day	Significantly higher serum bicarbonate and lower serum P in the very low group	No death in either group No significant change in eGFR for very low group Fewer patients in the very low group progressed to dialysis; 4% *vs.* 27% Limitations; small numbers and relatively short duration
Cianciaruso [28], 2008 (Patients screened 1999-2003)	392	6-18 months	18±7 CKD stages 4-5	Usual and low protein diets: 0.80 *vs.* 0.55 g/kg/day +	Significant between-group difference in protein intake	Compliance: 27% for 0.55g and 53% for 0.8g No significant differences

Low protein will modify serum urea nitrogen concentration				multivitamin and mineral tablet daily + calcium and iron supplements. Calcium, sevelamer and bicarbonate were used to achieve K/DOQI targets	No significant difference in blood urea for intention to treat Increased urea with higher protein in *per protocol* analysis	in serum P/PTH/ bicarbonate or progression of renal failure in intention to treat or *per protocol* analyses Lower urinary P and Na and less P binder use in low protein group No change in BMI or body weight over time, including patients strictly adhering to 0.55 g diet
Moe [5], 2011 Vegetarian or meat protein sources affect levels of serum P and FGF23	8 (crossover)	1 week then 2 -4 week washout then crossover 1 week	25-40	Grain/soy (vegetarian) or meat/dairy (meat); equivalent content of protein and P 800 mg/day No preservative	After 1 week meat *vs.* vegetable diet, higher P, FGF23, and trend to urinary P and lower PTH	Correlation of change in plasma P and FGF23. No relationship to 25OHD, $1,25(OH)_2D$ or PTH
Isakova [18], 2011 Dietary P restriction, the P binder lanthanum or both will reduce levels of FGF23	16 (2 by 2 factorial)	2 weeks	15-60	750 or 1500 mg dietary P daily and lanthanum 1g or placebo with meals. 750 mg P added to meals 3 times daily	Neither group had lower FGF23	Lower urinary P with lower P diet and rise in FGF23 with higher P and placebo No significant changes in serum P levels between or within the diet or binder groups Limitation: short duration
Di Iorio [29], 2012 (Study 2008-2010) Low protein and P will reduce levels of FGF23	32 (crossover)	2 weeks	21-54	Very-low-protein (0.3 g/kg per day; 350-420 mg/day P) *vs.* conventional low protein (0.6 g/kg per day; 600-700 mg/day P) + ketoanalogues	FGF23 fell significantly by 33.5% in the very low protein/P group	Lower serum and urine P and increased urinary P reabsorption. Limitation: short duration

				and amino acids		
Sigrist [30], 2013 Altered dietary protein influences FGF23 levels	18 patients with CKD and 12 healthy controls (crossover)	3 weeks	15-60 (CKD group)	High P: 2000 mg/day, low P: 750 mg/day, low P + 500 mg aluminium hydroxide three times daily Low protein:76 ± 3 g/day, high protein: 82 ± 5 g/day	FGF23 levels respond to dietary change in CKD patients and controls	In patients with CKD and controls, higher dietary P is associated with lower serum $1,25(OH)_2D$ and higher serum P values Limitation: short duration
Isakova [31], 2013 Reduced dietary P plus lanthanum carbonate will reduce FGF23 from baseline	39: 4 groups of 8-10 patients at study completion	12 weeks	15-60	*Ad libitum* diet or 900 mg P diet ± three times daily lanthanum 1000 mg or placebo	P-restricted diet + lanthanum reduced FGF23 P-restricted diet had borderline effect	No between group differences in serum P, Ca, PTH, $1,25(OH)_2D$, urinary P Urinary P might not be useful for monitoring adherence or titrating interventions aimed at reducing FGF23 No differences in cardiac echo parameters PTH rose in patients on *ad libitum* diet
Goto [32], 2014 A standard low-protein diet reduces FGF23 in CKD	15 (Early CKD) 20 (Advanced CKD)	<1 week	>60 <30	Regular protein; 1.1-1.4 g/kg/day and 15-20 mg/kg/day P *vs.* low protein; 0.6-0.8 g/kg/day and 10-15 mg/kg/day P	FGF23 was lower in both groups on low protein diet FGF23 correlated to urinary P excretion only in patients with advanced CKD	With lower protein diet; PTH and P levels fell in advanced CKD $1,25(OH)_2D$ levels increased in early CKD Urine P decreased in both groups Limitation: short duration
Selamet [24], 2016 (MDRD 1989-93) A relationship exists of pre-randomisation dietary P, evaluated by	795	Mean follow up 16 years (0.25-22)	33±12 CKD stages 3-5	Comparison of baseline urinary P quartiles and outcomes; 589 progressed to ESRD, 191 died of CV and	No statistically significant associations of 24hr urinary P and ESRD, CV, non-CV and all cause	A direct association of 3 day dietary P recall and all-cause mortality (HR per SD higher 1.19 [95% CI 1.03, 1.37], p=0.02) in the fully adjusted model

24 hour urine P, to risks of ESRD and mortality				228 of non-CV causes	mortality in minimally or fully adjusted models.	Limitation: baseline urinary P may not reflect long term values

Table 2.

	Baseline		2 weeks	
	Intervention group n=13	Control Group n=12	Intervention group n=13	Control Group n=12
Baseline demographic and clinical details				
Age median (IQR)	26 (25.5-29.5)	26 (24.5-28.75)	-	-
Male sex (n)	4	5	-	-
Weight (kg) median (IQR)	64.4 (55.2-72.5)	59.5 (54.8-66.1)	-	-
BMI kg/m2, mean SD	22.56 (2.52)	23.58 (3.06)	-	-
Systolic BP mean SD	111 (12)	111 (11)	-	-
Diastolic BP mean SD	74 (9)	69 (10)	-	-
Daily intakes calculated from 3 day dietary analyses (mean±SD) *Baseline vales are prior to dietary interventions*				
Dietary sodium (1 mmol sodium=23 mg)	119 (41) mmol 2734 (941) mg	116 (32) mmol 2665 (732) mg	-	-
Participants (%) with dietary sodium estimation <100 mmol/day (2300 mg/day)	33	33		
Dietary phosphate (1 mmol phosphorus=31 mg)	50 (14) mmol 1554 (430) mg	42 (13) mmol 1305 (412) mg	-	-
Participants (%) with dietary phosphate estimation <1000 mg/day (32.3 mmol/day)	0	33		
Protein g/day	100 (26)	88 (30)	-	-
Energy kJ/day	9306 (2092)	8714 (2343)	-	-
24 hour urine biochemistry (mean±SD) *Baseline values are prior to dietary intervention*				
Urinary sodium	134 (62) mmol 3082 (1426) mg	126 (37) mmol 2898 (851) mg	114 (62) mmol 2622 (1426) mg	123 (38) mmol 2829 (874) mg
Participants (%) with urinary sodium <100 mmol/day (2300 mg/day)	54%	33%	75%	33%
Urinary phosphate	27 (11) mmol 837 (326) mg	24 (5) mmol 744 (155) mg	25 (12) mmol	20 (6)mmol
Participants (%) with urinary phosphate <1000 mg/day (32.3 mmol/day)	92	100	83	100
Urinary calcium	4.2 (1.7) mmol	3.4 (1.5) mmol	3.4 (2.5) mmol	3.4 (1.4) mmol

	168 (68) mg	136 (45) mg	136 (100) mg	136 (56) mg
Urinary creatinine	13.1 (6.6) mmol	11.1 (3.0)		
Post study evaluation questionnaire responses				
Number of days of non-compliance to the diet over the past 2 weeks (Mean±SD)	-	-	2.6 (1.7)	4.9 (4.1)
Proportion (%) who agreed the supplementary information/app. increased their motivation to adhere to the diet	-	-	50*	25
Number of times referring to supplementary diet information/app. [Median (IQR]	-	-	3.5 (2-3)*	2 (1.3-3)
Proportion (%) who agreed the supplementary information/app. increased their knowledge	-	-	92*	54
Proportion (%) who agreed the supplementary information/app. increased their confidence about following the diet	-	-	50*	25

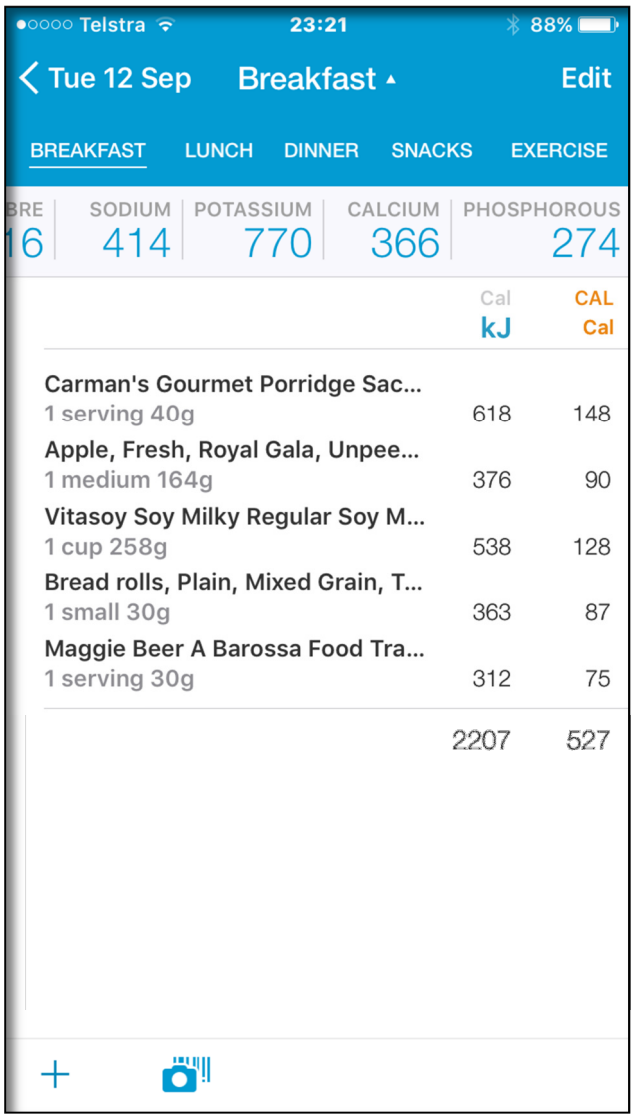
Telstra
23:21
88%
Tue 12 Sep
Breakfast
Edit
BREAKFAST
LUNCH
DINNER
SNACKS
EXERCISE
BRE
16
SODIUM
414
POTASSIUM
770
CALCIUM
366
PHOSPHOROUS
274
Cal
kJ
CAL
Cal
Carman's Gourmet Porridge Sac...
1 serving 40g
618
148
Apple, Fresh, Royal Gala, Unpee...
1 medium 164g
376
90
Vitasoy Soy Milky Regular Soy M...
1 cup 258g
538
128
Bread rolls, Plain, Mixed Grain, T...
1 small 30g
363
87
Maggie Beer A Barossa Food Tra...
1 serving 30g
312
75
2207
527

Figure 1.