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Title	Dietary phosphorus in chronic kidney disease
Authors	Byrne, Fiona Nora
Publication date	2020
Original Citation	Byrne, F. N. 2020. Dietary phosphorus in chronic kidney disease. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
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Download date	2026-11-07 10:31:32
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Dietary Phosphorus in Chronic Kidney Disease

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This thesis is being submitted for the award of PhD to the HRB Clinical Research Facility in the School of Public Health, at University College Cork.

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2020

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere.

All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

Parts of this work have appeared in the following peer reviewed publications:

Byrne F, Gillman B, Gleeson B, Scannell G, Long E, Eustace J. Comparison of Two Diets with Different Phosphorus Contents and Bioavailability on Serum Phosphate Levels in Haemodialysis Patients. Nephrology Dialysis Transplantation. 2017;32 (suppl_3):iii683-iii.
Also presented as a poster at European Renal Association, European Dialysis and Transplant Association (ERA EDT)A Madrid 2017, at the Irish Nephrology Society (INS) Annual Scientific Meeting Kildare 2018 and at the Irish Nutrition & Dietetic Institute (INDI) Research Symposium, Dublin, 2018.

Byrne F, Gillman B, Renal Interest Group of INDI, Eustace J. Multicentre Randomised Control Trial of Phosphate Control with a Modified as Compared to Standard Renal Diet FO046. Nephrology Dialysis Transplantation. 2018;33(suppl_1):i37-i.
Presented as an oral presentation at ERA EDTA Copenhagen, 2018.

Byrne F, Gillman B, Renal Interest Group INDI, Eustace J. Multicentre Randomized Control Trial of Phosphate Control with a Modified as Compared to Standard Renal Diet TH-OR030. J Am Soc Nephrol 2018;29:8.
Presented as an oral presentation at the American Society Nephrology (ASN) Kidney Week San Diego, 2018.

Byrne FN, Calvo MS. Pulses and Chronic Kidney Disease: Potential Health Benefits from a Once Forbidden Food. In: Dahl JD, editor. Health Benefits of Pulses. Switzerland: Springer; 2019. p. 73 - 90.

Parts of this work have been submitted for peer review in the following publications:

Chapter 2 was submitted to the Journal of Renal Nutrition in December, 2019.

Chapter 4 has been submitted to Nephrology Dialysis and Transplantation in December, 2019.

Chapter 5 has been submitted to Clinical Journal of the American Society of Nephrology in December, 2019.



_____

Fiona Byrne
December 2019

Acknowledgements

I would like to thank Professor Joseph A. Eustace, for supervising, mentoring and supporting me. Thank you for your constant good humour and excellent instruction. Thank you also, Professor Mairead Kiely, Dr. Frances Shiely and Professor Patricia Kearney and my statistician Dr. Brendan Palmer for your insightful comments, feedback and encouragement.

I am indebted to the dialysis patients who graciously and generously participated in this study.

To Barbara Gillman, who has been a fountain of knowledge and an excellent person with whom to debate. Thank you for your support, advice, friendship and unsurpassed attention to detail and commas.

To my co-researchers, Fiona Keohane, Oonagh Smith, Bernice Curtis, Pauline Connolly, Denise McCarthy, Karina Brennan, Joyce Earlie, Sarah Wade, Barbara Gillman, Halóg Mellett, Theresa Rennick, Maria Bowles, Celene Sands and Orla Slevin. Thank you so much for your support. This project would not have been possible without you.

The friendship and unwavering support provided by Irene Cronin, Abina Harrington, Phil O Driscoll and Teresa O'Neill was essential. A special thanks to my running partner and my mindfulness guru and story writer. To Dr. Sinead Kinsella, you were

inspiring me in spirit. You would absolutely have been centre stage, were you still with us.

To Annemarie Fanning, my manager, for her support and to my dietetic colleagues, especially in renals, who supported and encouraged me all the way.

I am grateful to my Mum, Eileen and Dad, Vincent, my sisters Niamh, Orla and Elaine and brothers Dan and Vincent. Thanks for your help support and encouragement.

Finally, thank you to my family, Stephen and my sons Padraic, James and Darragh. Thank you for all the shopping and cooking and tasting of chickpea soup. Thank you Steve, for your unwavering support, help, patience and technical support. I could not have done it without you.

I am indebted for the support and kindness shown to me by all of the above and the many others not acknowledged here.

Dedication

To all the people with CKD and ESKD, whom I have had the honour of caring for, this is dedicated to you.

Abstract

Hyperphosphataemia is common in the later stages of chronic kidney disease and is a universal problem in end stage kidney disease, where it is associated with increased morbidity and mortality. Treatment includes a low phosphorus diet, that imposes numerous dietary restrictions, lacks a robust evidence base and in current practice fails to distinguish between phytate and non phytate bound phosphorus. The overall aim of this PhD was to provide the evidence basis for a revised low phosphorus diet, and to assess its effectiveness, safety and tolerability. Specific aims were 1) to define revised dietary recommendations for phosphorus in chronic kidney disease and to translate these recommendations into food based advice, 2) to conduct a proof of concept acute feeding study in prevalent haemodialysis patients using the modified diet and 3) to investigate the effectiveness of the modified diet in a multicentre randomised controlled trial in prevalent haemodialysis patients.

To update the traditional low phosphorus diet, as chair of a national working group of Irish renal dietitians, I undertook a narrative review of the available renal nutrition literature. We combined the evidence with clinical experience and expertise to update the traditional low phosphorus diet.

The modified diet, agreed by consensus, relaxed the restrictions of phytate bound phosphorus, and introduced previously disallowed foods such as pulses, peas, nuts and more whole grains. To ensure adequate but not excessive protein intake, we introduced guidance on bread and cereal intakes and included some advice based

on phosphorus to protein ratios. Finally we increased the focus on avoiding phosphate additives. These changes were incorporated into a modified renal diet. The modified diet was initially evaluated against the standard low phosphorus diet in an in-centre, directly observed, one day, cross-over feeding study in order to examine the immediate postprandial effects of the modified diet. We demonstrated that the modified diet blunted post-prandial hyperphosphataemia, was not associated with increased hyperkalaemia and was well tolerated.

Given the results of the acute feeding study, we conducted a national multicentre randomised controlled trial, comparing the modified low phosphorus diet with the standard low phosphorus diet in 74 prevalent patients treated with maintenance haemodialysis. The modified renal diet, with its broader food choice, achieved a significantly higher fibre intake, was well tolerated and provided comparable serum phosphate and potassium control as the standard renal diet. Based on the evidence from this project, a decision was taken by the Irish Renal Interest Group of the Irish and Dietetic Institute in January 2019, to endorse the modified low phosphorus diet and to implement it nationally.

Chapter 1: Introduction

1.1 Background

Chronic kidney disease (CKD) is common, expensive to treat and substantially reduces the health related quality of life of those affected by it. Disturbances in bone and mineral metabolism, which begin early in CKD, get progressively worse as the condition progresses and are central to the development of both bone and vascular complications. One of these disturbances, hyperphosphataemia is almost universally in end stage kidney disease (ESKD). The management of dietary phosphate is central to the management of hyperphosphataemia. This body of work looks at the evidence for dietary phosphate restriction, revises current dietary advice and tests the immediate and short-term (one month) safety, tolerance and efficacy of the modified as compared to the traditional standard diet.

1.2 Definition and Classification of CKD and ESKD

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines on Chronic Kidney Disease in 2002 provided the first standardised definition of CKD. The definition was independent of cause and introduced standardisation of terminology and a classification system of severity based on the glomerular filtration rate (GFR) level.[1] After a decade the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of CKD updated these guidelines and provides a uniform terminology and standardised diagnostic classification system (Figure 1-1).

Figure 1-1 CKD Definition and Prognosis

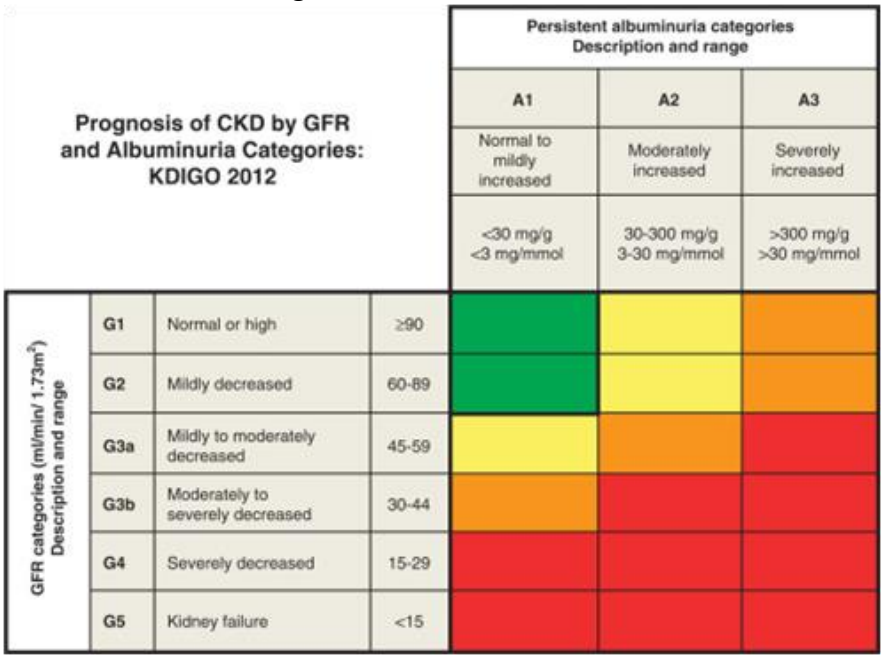


Figure 1-1:"CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA)."

1.3 Burden of CKD and ESKD

On a world scale the total number of individuals with CKD, acute kidney injury and those on renal replacement therapy exceeds 850 million.[2] A recent systematic review quotes a consistent estimated global CKD prevalence of between 11 - 13% with the majority being in stage 3.[3] A small but significant minority of patients with CKD go on to develop ESKD. In 2010, 2.62 million people received dialysis worldwide and the need for dialysis was projected to double by 2030.[4] The US expects the number of patients with ESKD to increase by 29–68% between 2015 and 2030.[5]

Kidney disease significantly increases mortality and equally important, it increases morbidity. The global burden of disease 2015 study, reported that total mortality for CKD, rose by 31.7% to 1.2 million deaths from 2005 to 2015.[6] The disability-

adjusted life-year (DALY) measures health loss due to both fatal and non-fatal disease burden. In the 26 year time period from 1990 to 2016, DALYs due to all causes decreased by 2% whereas DALYs due to CKD increased by 62%, from 22 million to 35 million.[7]

Kidney disease is associated with a tremendous economic burden. In 2015, in the United States of America, for example, Medicare expenditures on CKD exceeded 64 billion dollars and with expenditures on end-stage kidney disease of more than 34 billion dollars, the total expenditure was over $98 billion.[8]

High income countries typically spend more than 2–3% of their annual health-care budget on the treatment of ESKD, even though those receiving such treatment represent under 0.03% of the total population.[9] Chronic Kidney Disease, Mineral Bone Disorder (CKD MBD) is a major complication of CKD and ESKD which is suggested to substantially contribute to the increased morbidity and mortality seen in these conditions.

1.4 Pathophysiology of CKD MBD

As kidney function declines, there is a progressive deterioration in mineral homeostasis, a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These hormones include parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), other vitamin D metabolites, fibroblast growth factor-23 (FGF-23), and growth hormone. Collectively these abnormalities and their complications are referred to as Chronic Kidney Disease, Mineral & Bone Disorder (CKD MBD).[10]

The development of secondary hyperparathyroidism is central to the pathophysiology of CKD MBD. The aetiology of secondary hyperparathyroidism is complex and multifactorial. The main drivers for continued PTH secretion in CKD are hypocalcaemia, decreased 1,25 dihydroxy vitamin D and hyperphosphatemia. Calcium and phosphate levels remain within the normal range until the later stage CKD, [11] while elevations in PTH levels and vitamin D deficiency develop early in the course of the disease.[11] FGF 23 also plays a role and increases progressively beginning in early CKD, promoting phosphaturia and decreased production of 1, 25 dihydroxy vitamin D.[12] These mechanisms are initially compensatory, serving to maintain a normal serum calcium and phosphate, however as CKD progresses, these mechanisms become overwhelmed and maladaptive.

Phosphorus load and hyperphosphataemia are considered driver of CKD MBD.[10,13] The use of phosphorus restricted diets in combination with oral phosphate binders, which reduce gastrointestinal absorption are well established treatments of hyperphosphataemia.[14]

1.5 Phosphate Toxicity

Hyperphosphataemia is associated with increased mortality in ESKD.[15,16] Elevated phosphate levels, even within normal range, are associated with increased mortality in those in the earlier stages of CKD, and in patients with normal renal function.[17-22]

Hyperphosphataemia has also been implicated with a more rapid rate of progression of CKD.[23]

High dietary phosphorus intake has also been associated with coronary artery calcification in patients with CKD[24] and with increased mortality in healthy populations.[20] In a review "Phosphate - a poison for humans?", Komaba & Fukagawa summarise the toxic effects of hyperphosphataemia as vascular calcification, endothelial dysfunction, left ventricular hypertrophy, bone disease, ageing and cytotoxicity.[25] Figure 1-2 provides a schematic representation of this toxicity. While we have extensive associative data linking hyperphosphataemia to poor outcome, we lack definitive hard outcome data.

Figure 1-2 Schematic Representation of Phosphate Toxicity

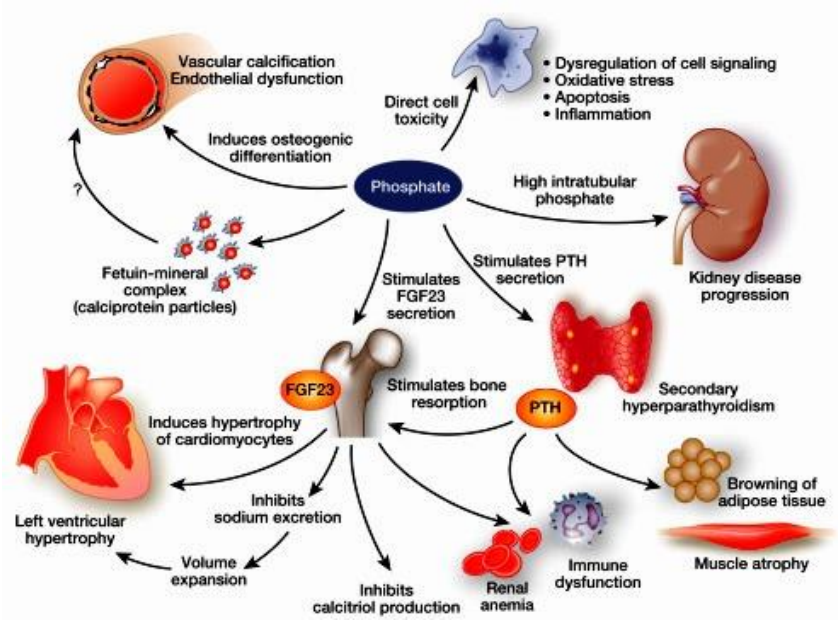


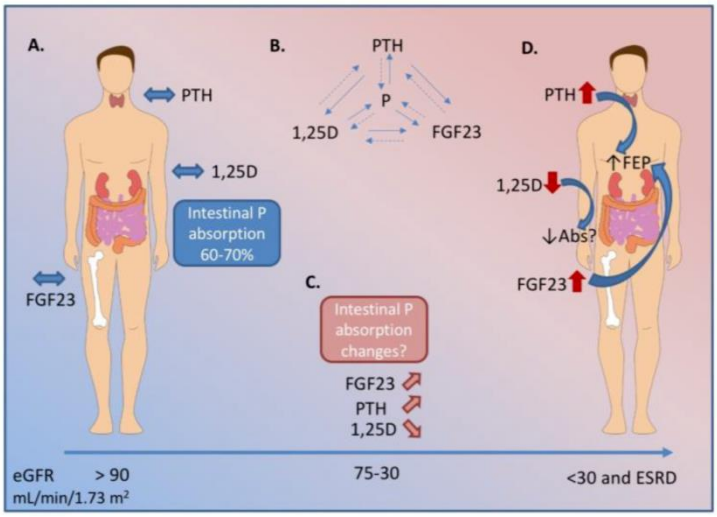
Figure 1.2: "Excess phosphate exerts toxic effects through a variety of pathways. High phosphate levels directly potentiate vascular calcification and endothelial dysfunction, promote the progression of kidney disease, and induce cell stress and apoptosis. High phosphate levels also contribute to adverse outcomes through increases in the levels of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH), including left ventricular hypertrophy, renal anemia, immune dysfunction, adipose tissue browning, and skeletal muscle atrophy."[25] Figure reprinted with permission.

1.6 Regulators of Phosphorus

Phosphorus has multiple regulators. Hormones from the kidneys, intestine, parathyroid glands, and bone are involved in maintaining homeostasis.

The major hormones are parathyroid hormone, 1,25-dihyxdroxyvitamin D (1,25 D), and fibroblast growth factor 23 (FGF23). Figure 1-3 summaries the complex systems which maintain homeostasis.

Figure 1-3 Regulators of Phosphorus throughout the Course of CKD



"Biochemical changes in hormonal regulators of P (phosphorus) throughout the course of chronic kidney disease (CKD).
***A.** In health, fibroblast growth factor 23 (FGF23) from osteocytes, parathyroid hormone (PTH) from the parathyroid gland, and 1,25-dihyxdroxyvitamin D (1,25D) work together to keep serum P within a tight range. A healthy person absorbs 60–70% of P in a mixed diet.*
***B.** PTH, 1,25D, and FGF23 also regulate each other in a series of feedback loops.*
***C.** As renal decline progresses, the kidney loses its ability to excrete excess P. FGF23 begins to rise earlier in the disease course, followed by a decline in 1,25D, and a rise in PTH.*
***D.** In end stage renal disease, the hormonal regulation is unable to maintain serum P within a normal range. At this stage, patients have very high FGF23, PTH, and low 1,25D. The biochemical profile in early and moderate stage CKD indicate intestinal P absorption should be decreased. However, literature suggests P absorption may be inappropriately maintained and, therefore, contributes to overall P burden in CKD. Dashed lines indicate negative feedback. Abs indicates intestinal P absorption; FEP indicates fractional excretion of P from the kidney; eGFR indicates estimated glomerular filtration rate. ESRD indicates end stage renal disease."*[26] Reprinted with open access permission

Much research in recent years has focused on FGF23. While FGF23 is involved in phosphate homeostasis, it is also involved in sodium and calcium metabolism, in bone mineralisation and the development of cardiac hypertrophy. These findings

have linked phosphate with volume homeostasis, and may have major implications for CKD, CKD MBD and cardiovascular disease.[27] While the effects and regulators of FGF23 are still being elucidated, phosphate excess is still recognised as a primary stimulator.[28] Short-term dietary phosphate restriction tends to reduce FGF23 levels in patients with moderately decreased kidney function, and the FGF23-lowering effects tend to be more prominent when measured with the intact assay.[29] Limiting dietary phosphorus intake and intestinal absorption is a central strategy to reduce the serum phosphate in CKD and ESKD and to attenuate its proposed complications.[14]

1.7 Dietary Phosphorus Intake and Absorption

Phosphate is abundant in the human diet; mean (SD) dietary phosphate intake for Irish men and women was estimated at 1645 (463) mg and 1161 (318) mg per day respectively.[30] Dietary intake has a considerable impact on intestinal phosphate absorption and this will be reviewed in more detail in chapter 2.

In the gut, dietary phosphate is absorbed through passive paracellular diffusion (driven by high luminal phosphate concentration) and by active cell–mediated transport of phosphate via the NaPi-2b co transporter on the luminal side of the enterocyte (regulated by dietary phosphate, calcitriol, and FGF23).[31] NaPi-2b is estimated to contribute >90% of sodium-dependent transport based on a mouse NaPi-2b knockout model.[32] In rats considered most similar to humans, the highest rates of phosphate transport occur in the duodenum and jejunum, whilst in mice maximal absorption occurs in the ileum.[33] A low phosphorus diet may lead to increased absorption as evidenced by a study where animals receiving a low-Pi diet,

had elevated expression of co-transporters NaPi-IIb and PiT-1/2 in the jejunum.[34] New drugs designed to bind potassium, may reduce paracellular phosphate permeability.[35] Knowledge of the factors that influence dietary phosphorus absorption is improving but remains poorly understood.[26,36,37]

1.8 Dietary Phosphorus and the Renal-Gastrointestinal Axis

It has been suggested that the small intestine mucosa senses an increase in phosphate concentrations and secretes a circulating substance that exerts a phosphaturic effect in the kidney.[38,39] However a recent study of phosphate loading in 12 healthy volunteers found no evidence for a quantitatively important intestinal sensing and effector mechanism that would elicit renal phosphaturia independent of changes in plasma phosphate concentration.[40]

Given the strong association of hyperphosphataemia with morbidity and mortality and given there is a limited understanding of the impact of dietary phosphorus on hyperphosphataemia, we designed a dietary intervention to control hyperphosphataemia while increasing food choice for patients.

1.9 Target Serum Phosphate

The optimal serum phosphate level is not known and to date we have used association data to define target serum phosphate levels. While large multicentre observational studies such as COSMOS[41] provide useful data, we need adequately powered trials to define the appropriate serum phosphate target range. Two feasibility studies in dialysis populations, one using calcium based binders[42] and the other using non calcium based binders[43] have established the feasibility of achieving and maintaining a difference in serum phosphate concentrations in

haemodialysis recipients over time. However no adequately powered randomised trials have yet reported on whether the management of serum phosphate actually improves hard clinical outcomes.[25]

One planned study, the HiLo study, may address this issue. HiLo is a 45 month pragmatic, multicenter outcomes trial that will compare outcomes at higher phosphate targets (6-7 mg/dl) to lower serum phosphate targets (5 mg/dl).[44] The primary outcome will be all-cause hospitalisation rates. Key secondary analyses will compare all-cause mortality and patient-reported outcomes.

In summary, our understanding of the risks and the effectiveness of the current management of hyperphosphataemia is poor. The evidence base, particularly in relation to the dietary management of hyperphosphataemia is lacking. We sought to improve the nutritional care of our renal patients by undertaking a pragmatic dietitian-led study on the renal low phosphorus diet.

1.10 Study Aims

1. To conduct a narrative review of the published literature regarding renal dietary interventions in order to define revised dietary recommendations for phosphorus in CKD G3 - 5D and to translate these nutrient based recommendations into practical dietary advice for patients in the form of a diet sheet (Chapter 2).

2. To conduct a proof of concept and safety acute feeding study in prevalent haemodialysis patients using the developed modified diet compared to

standard diet in order to assess the tolerance and effect of diet on the immediate post-prandial biochemistry (Chapter 4).

3. To establish the effectiveness of the modified diet by conducting a national multicentre parallel arm randomised controlled trial in maintenance haemodialysis patients (Chapter 5).

Chapter 2: Revision of the Renal Low Phosphorus Diet in CKD

2.1 Revising Dietary Recommendations for Phosphorus in Chronic Kidney Disease G3- 5D

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5 Key Words: Hyperphosphataemia, Phosphorus, Potassium, Diet, Phytate

This paper was submitted to the US Journal of Renal Nutrition on 16-12-19.

Abstract

We summarize how practicing dietitians combined available evidence with clinical experience, to define revised dietary recommendations for phosphorus in chronic kidney disease (CKD) G3 - 5D. As well as a review of the evidence base, four priority topics were reviewed. These were translated into three nutrient level recommendations; the introduction of some plant protein where phosphorus is largely bound by phytate; consideration of protein intake in terms of phosphorus load and the phosphorus to protein ratio; and an increased focus on avoiding phosphate additives. We provide a scientific rationale to guide and support the development of practical food based advice for patients with CKD.

Introduction

Dietary phosphorus restriction remains a cornerstone of the dietary management of patients with chronic kidney disease and hyperphosphatemia. However, despite its long standing and widespread adoption, the underlying evidence is weak,[45] and largely justified based on clinical experience, a preponderance of observational findings and the suspected underlying pathophysiological mechanisms. Recently a number of experts have suggested the need to revise and update how we manage dietary phosphorus.[46-48] The Irish Nutrition & Dietetic Institute (INDI) renal dietitians, formally decided to update the phosphorus section of the Irish Renal Diet Sheet, a national reference used to educate patients throughout the country, which had remained largely unchanged for the previous two decades. The current diet sheet moderates protein intake, restricts dairy and foods with a high total

phosphorus content and provides some advice regarding the avoidance of phosphate additives.

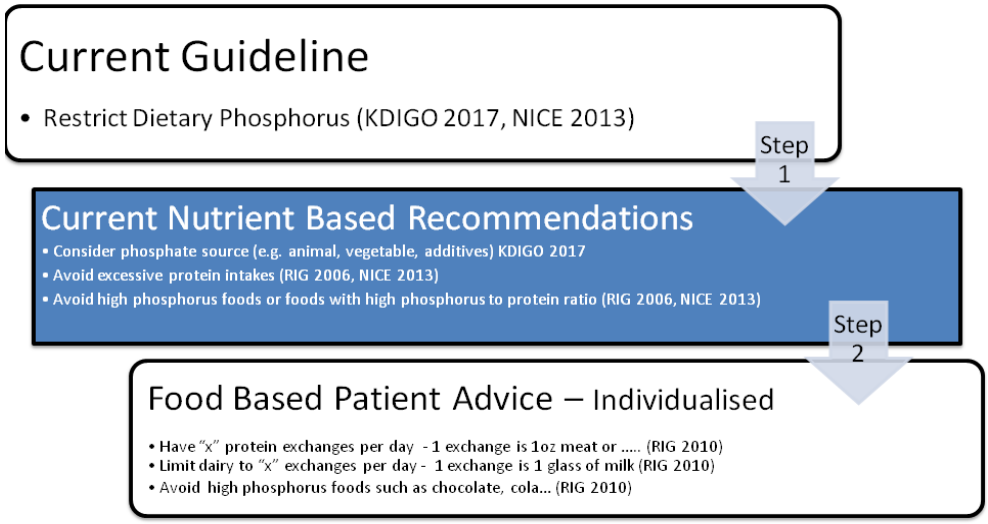
A challenge in updating the diet sheet was readily accessing the relevant information from the scientific literature. Existing international clinical practice guidelines such as Kidney Disease Improving Global Outcomes (KDIGO) are not intended and are not sufficiently detailed to facilitate the development of specific dietary interventions. Thus, whilst the 2009 Kidney KDIGO guidelines, recommended that dietary phosphorus should be limited to treat hyperphosphataemia, they did not provide any specific food based recommendations.[10] The updated 2017 KDIGO guidelines added an ungraded recommendation "to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations".[49] This was added on the basis of differing bioavailability of dietary phosphorus from different food choices,[50] but this generic advice does little to help formulate dietary advice.

Process

A one day national conference was held in 2015 to summarize the recent advances and challenges in dietary phosphorus management. The purpose of the meeting was to examine recent advances in the understanding of phosphorus bioavailability, nutrient analysis data and current European legislation on the use of phosphate additives. This brought together both scientific and clinical experts from Ireland and the United Kingdom as well as national stakeholders including the Food Safety Authority of Ireland, Teagasc- the Agriculture and Food Development Authority in Ireland and the Public Analyst Laboratory. It was attended by 28 renal dietitians

from renal units facilities across the country. Workshops were used to identify which topics were clinically relevant and which should be prioritised for review. A working group of seven senior renal dietitians conducted the review and dietary management update in two steps. In the first step, described in this paper, we developed updated nutrient level recommendations by pragmatically combining clinical experience and expertise with available research evidence. In the second step, also reported in this chapter, these updated nutrient level recommendations were used to develop a national modified diet sheet, that could be individualized to the needs of each patient. Figure 2-1 summarizes current nutrient level recommendations and approaches to food based advice.

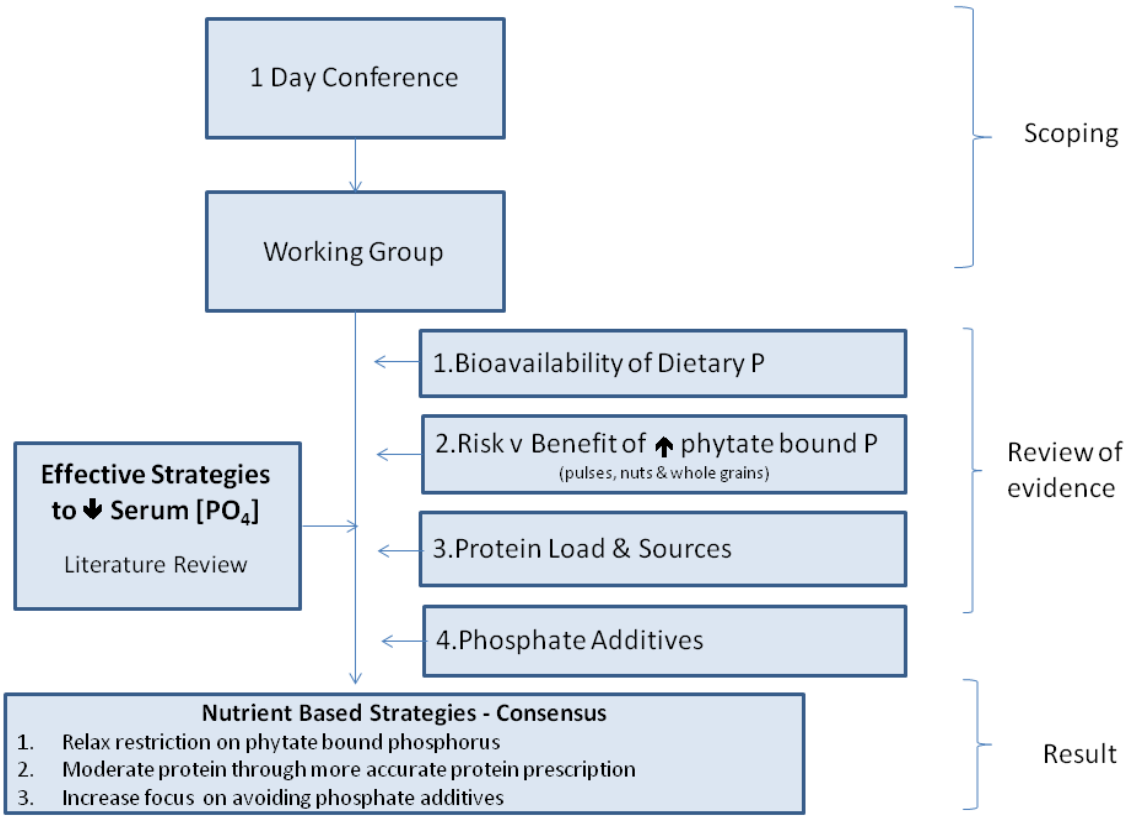
Figure 2-1 Current Guidelines, Recommendations and Food Based Advice



KDIGO. Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD). Kidney International Supplements. 2017;7(1):1-59.
NICE. Chronic kidney disease (stage 4 or 5):management of hyperphosphataemia. National Institute for Health and Clinical Excellence Guidelines. 2013.
Renal Interest Group Irish Nutrition & Dietetic Institute. Renal Nutrition Guidelines. 2006.
Renal Interest Group Irish Nutrition & Dietetic Institute Eating Well with Kidney Disease. 2010

We began by conducting a literature review to identify dietary strategies effective in lowering serum phosphorus. Based on the scoping meeting and subsequent discussions, four additional topics were identified to be reviewed in light of recent scientific progress, 1) phosphorus absorption and bioavailability; 2) safety and benefit of increasing plant protein; 3) protein prescription and phosphorus to protein ratio; 4) phosphate additives. Figure 2-2 summarises the scoping, review and outcomes of this process.

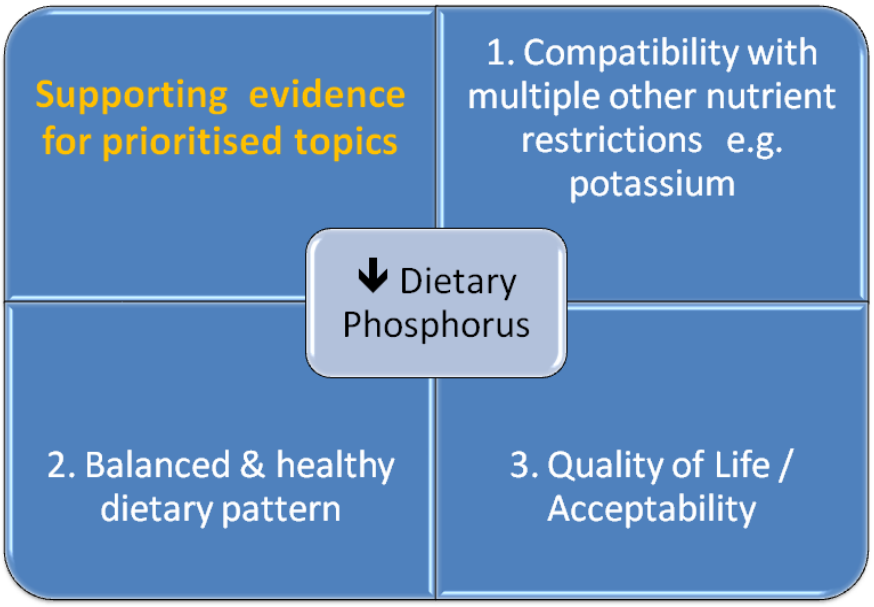
Figure 2-2 Process of Reviewing Dietary Phosphorus Advice



This figure describes how practicing Irish renal dietitians scoped the review of dietary phosphorus advice through a conference and a working group. As well as a review of the evidence base for effective strategies to reduce serum phosphate, four priority topics were reviewed. This process resulted in agreement to relax restriction on phytate bound phosphorus, to moderate protein intakes and to increased focus on avoiding phosphate additives. P Phosphorus. [PO_4] Serum phosphate.

Additional considerations, that influenced deliberations included, ensuring compatibility with other concurrent nutrient restrictions, acceptability to patients and ensuring a balanced and healthy dietary pattern (Figure 2-3).

Figure 2-3 Additional Considerations



Combined with the evidence to support the prioritised topics, dietitians also incorporated 3 other considerations in reaching consensus on what changes to nutrient based recommendations to reduce dietary phosphorus should be made.

To conduct the review, the working group held two face-to-face meetings and 36 telephone conference calls, over a nine month period. Whilst our approach to reaching consensus included all the recommended components,[51] we did not employ a formal consensus building framework.

Literature Search: Strategies which may improve serum phosphate

Initial review identified a substantial volume of trial literature for the effectiveness of dietary intervention in reducing serum phosphate. However a Cochrane review by Liu *et al* published in 2015 established that there was limited low quality evidence to indicate that dietary interventions may positively affect hyperphosphataemia.[45] Despite the low quality evidence available, there remained a clinical responsibility to review and update dietary advice, using a pragmatic approach that combined the available evidence and professional expertise. The working group therefore decided to undertake a narrative review describing the range of dietary interventions that have been trialled in the research setting and to interpret this available literature.

The detailed search strategy, inclusion criteria and methodology for the narrative review of effective strategies for dietary phosphorus restriction is outlined in appendix 1. We focused on non pharmacological strategies identified from the literature search, which may improve serum phosphate control. Trials deemed relevant to the revision of dietary recommendations for phosphorus are summarised below and in table 2-1.

The strategies identified were, consumption of vegetarian protein,[52-58] the use of lower protein diets, [13,45,59-67] low phosphorus diets, [45,68-72] avoidance of phosphate additives,[73-80] the inclusion of egg whites[81] and low phosphorus milks.[82]

The use of vegetarian sources of protein including soya led to a reduction in serum phosphate in some[52,56,58] but not all studies.[53-55,57] Liu *et al*.'s systematic review concluded that a very low protein intake was not superior to conventional low

protein intake in terms of effect on serum phosphate.[45] While lower protein diets have been shown to reduce serum phosphate,[13,59,61-63] not all studies demonstrated a significant reduction in serum phosphate.[64,65] The Modification of Diet in Renal Disease (MDRD) study showed that fewer patients on the low-protein diet than in the usual-protein diet group required dietary modification for high serum phosphorus (12% vs. 26%).[83]

Table 2-1 Clinical Trials of Dietary Strategies which may Improve Serum Phosphate

Intervention	Population	Design	Randomized	Details	Interventions N	Subjects N	Duration	Reference	*Outcome
Vegetarian Protein	CKD	Trial	Yes	Crossover	2	9	14 Days	Moe 2011 [52]	Positive
	CKD	Trial	Yes	Crossover	2	15	12 Mos	Soroka 1998 [53]	Negative
	CKD	Trial	No	-	3	62	6 Mos	Barsotti 1996 [54]	Negative
	Dialysis	Trial	Yes	-	2	40	8 Wks	Imani 2009 [55]	Negative
	Dialysis	Observational	N/A	Cross-sectional	2	63	N/A	Ou 2016 [56]	Positive
	CKD	Observational	N/A	Cross-sectional	1	2938	N/A	Scialla 2012 [57]	Negative
Lower Protein Diets	CKD	Trial	No	-	1	16	16 Mos	Lai 2015 [59]	Positive
	CKD	Trial	Yes	-	2	585	3 Yrs	Newsome 2013 [60]	Negative
	CKD [a]	Trial	No	-	2	15	8 Days	Goto 2014 [61]	Negative
	CKD [b]	Trial	No	-	2	20	8 Days	Goto 2014 [61]	Positive
	CKD	Trial	No	-	2	157	20 Days	Martinez 1997 [13]	Positive
	CKD	Trial	Yes	-	4	228	18 Mos	Rosman 1984 [62]	Positive
	CKD	Trial	No	-	2	39	11 Mos	Barsotti 1983 [63]	Positive
	CKD	Trial	Yes	-	2	423	18 Mos	Cianciaruso2008 [64]	Negative
	CAPD	Trial	No	Crossover	2	8	14-33 Days	Blumenkrantz1982[65]	Negative
	HD	Observational	N/A	Retrospective	N/A	69,355	N/A	Streja 2013 [66]	Positive
	CAPD	Observational	N/A	Cross-sectional	N/A	205	N/A	Dong 2007 [67]	Positive

Table 2-1. Clinical Trials of Dietary Strategies which may Improve Serum Phosphate continued

Intervention	Population	Design	Randomized	Details	Interventions N	Subjects N	Duration	Reference	*Outcome
Low Phosphorus Diet	CKD	Trial	Yes	Crossover	3	18	21 Days	Sigrist 2013 [68]	Positive
	CKD	Trial	Yes	-	2	16	14 Days	Isakova 2011 [69]	Negative
	CKD	Trial	Yes	-	4	39	3 Mos	Isakova 2013 [70]	Negative
	CKD	Trial	No	-	1	26	7 Days	Muras 2013 [71]	Positive
	Dialysis	Trial	No	-	1	20	8 Wks	Cupusti 2004 [72]	Negative
Additives	CKD	Trial	Yes	Cluster	2	279	3 Mos	Sullivan 2009 [73]	Positive
	Healthy	Trial	No	Crossover	2	8	8 Wks	Bell 1977 [74]	Positive
	Healthy	Trial	No	Crossover	2	10	2 Wks	Gutiérrez 2015 [75]	Negative
	Healthy	Trial	Yes	Crossover	5	16	5 Days	Karp [76]	Negative
	Healthy	Trial	Yes	Parallel arm	4	62	10 Wks	Trautvetter [77]	Positive
	Dialysis	Observational	N/A	Retrospective	N/A	100	N/A	Santoro 2015 [79]	Positive
	Healthy	Observational	N/A	Cross-sectional	N/A	2664	N/A	Gutiérrez 2012 [80]	Negative
Egg Whites	Dialysis	Trial	No	-	1	13	6 Wks	Taylor 2011 [81]	Positive
Low P Milk	Dialysis	Trial	No	-	1	20	28 Days	Oliverio 2006 [82]	Negative

Table 2-1 details the relevant clinical trials or observational studies which examined strategies which may improve serum phosphate control, and whether the trial outcome was positive or negative in terms of reducing serum phosphate. *Outcome positive or negative based on the effectiveness of the strategy to lower serum phosphate. CKD Chronic Kidney Disease CKD; End Stage Kidney Disease ESKD; number N; Months Mos; Weeks Wks; Phosphorus P; [a] early CKD; [b] advanced CKD;

Peritoneal dialysis patient's protein intake were significantly lower in those who achieved a serum phosphate of < 1.78mmoles/l but malnutrition was higher.[67]

In CKD, a low phosphorus diet decreased fasting serum phosphate,[68] although the phosphate load did not affect serum phosphate in another study.[69] Serum phosphorus increased significantly in non diabetic chronic kidney disease (CKD) patients when fed a high phosphorus diet for 6 days.[71]

A seminal paper showed that the avoidance of foods high in phosphate additives was effective in lowering serum phosphate in a cluster randomized trial of 279 dialysis patients.[73] Egg whites may be an effective diet component to lower serum phosphate.[81]

The introduction of a low phosphorus milk, improved satisfaction without adversely affecting phosphate levels.[82] Dietary interventions that improved survival based on observational studies include vegetarian diets,[84,85] a lower dietary phosphorus intake and a dietary phosphorus to protein ratio of 12-14mg/g. [86] We did not include very low protein diets (VLPD) supplemented with ketoacid analogues (KA)[87-93] in our review because VLPD are not currently in use in Ireland and KAs may contain significant calcium which may act as a binder.

Based on this literature review, the working group agreed that the inclusion of vegetarian protein, moderation of protein intakes, low phosphorus intakes, a focus on phosphate additives, and the inclusion of egg whites and milk replacers approaches were appropriate for the Irish renal patients and should be included in the revised advice.

Topic 1: Bioavailability of Dietary Phosphorus

The literature available for review on the bioavailability of dietary phosphorus is limited and the mechanism of phosphorus absorption is poorly understood. Evidence from faecal studies of gastrointestinal absorption of phosphorus range from approximately 53-60% in CKD and end stage kidney disease (ESKD) populations.[65,94-96] Active vitamin D significantly increased phosphorus absorption to 86%.[96] This is similar to gastrointestinal absorption of 50-80% in non CKD populations.[96-105]

In reviewing topic 1, we focused on the absorption of phosphate additives, how the food matrix affects absorption and how food processes alter absorption of phosphorus**.**

Absorption of Phosphorus from Additives and Food

Whilst additive consumption has also been associated with hyperphosphataemia,[78,79] original studies on the absorption of additives are extremely limited. The evidence largely comes from healthy populations and in-vitro studies. In a small but widely referenced study, conducted in 8 subjects with normal kidney function, a high additive diet increased serum phosphate (non fasting).[74] The authors surmise that phosphorus absorption from additives averaged at least 51%. In healthy young women, three different foods and a phosphate supplement significantly increased postprandial serum phosphate. Cheese had the greatest effect followed by supplements, meat and whole grains.[76] With the exception of cheese, fasting phosphate levels the following day were not different. In the same study, phosphorus absorption as indicated by urinary phosphorus was

significantly higher with the phosphate supplements and meat than with cheese and whole grains.[76] In a wartime study where inorganic phosphorus was added to the diets, the subjects absorbed the phosphorus additive as freely as the phosphorus in white bread and more so than the phosphorus in brown bread.[106] In healthy men, a supplement of 1000mg phosphorus did not significantly change fasting plasma phosphate levels.[77]

Karp *et al* carried out two in vitro studies where, the starch and proteins of the food sample were digested enzymatically, in principle, in the same way as in the alimentary canal to differentiate total phosphorus (TP) from digestible phosphorus (DP).[107,108] In cola drinks and beer, the percentage of DP to TP was 87 to 100%.[108] In cereal products, the highest TP content (216 mg/100 g) and DP proportion (100%) were present in industrial muffins, which contain sodium phosphate as a leavening agent.[108] In a large cluster randomized trial in dialysis patients an intervention aimed at reducing phosphate additive intake was successful in modestly reducing serum phosphate.[73] Sigrist compared a high (mainly from non perishable manufactured food products) and low additive diet in CKD and found that diet significantly affected fasting serum phosphate.[68]

Impact of Food Matrix

We examined how the food matrix in high fibre foods and dairy products affects phosphorus absorption. Phytate or phytic acid is found in wholegrains, pulses, nuts and seeds. Phytate reduces the absorption of phosphorus. Schlemmer *et al* reviews phytate, describing food sources, intakes, gastrointestinal degradation and absorption as well as the effects of processing and storage on phytate. Phytate is the salt of phytic acid / myo-inositol-1,2,3,4,5,6-hexakis dihydrogen phosphate.

Phytate bound phosphorus is stable and remains reasonably unavailable for absorption in foods cooked at home. It appears to be stable in the small intestine where phosphorus absorption takes place.[109] Although phytate serves as the major source of energy and phosphorus for seed germination, the bound phosphorus is poorly available to simple-stomached animals.[110] In a small balance study in healthy volunteers during the second World War, absorption of phosphorus from a white bread diet was 59-77% and from brown bread, which is higher in phytate, was 44-55%.[106] In a more recent study in males, absorption on a control 800mg phosphorus diet was 62% and this decreased to 51.3% when 3 bran muffins were added.[101] In diabetic patients with normal kidney function, urinary phosphorus was significantly lower in the high fibre diet suggesting lower gastrointestinal absorption.[111] The New Nordic diet (NND) (higher in nuts, legumes and whole grains and lower in meat) was compared to the average Danish diet and despite a higher phosphorus content in the NND, urinary phosphorus was similar.[112] In an in vitro study by Karp *et al* on plant food and beverages, the highest amount of TP was found in sesame seeds with hull, which also had the lowest percentage of DP (6%) to TP. Legumes contained an average DP content of 38% of TP.[108]

The dairy matrix also appears to affect absorption of phosphorus. Surprisingly, relative to meat, additives and whole grains, dairy products in the form of hard cheese caused the highest serum phosphate, and one of the lowest levels of urinary phosphorus.[76] The Karp *et al* in vitro study on meat and milk products, found the TP and DP contents in dairy products varied from 48% to 100%.[107]

The calcium to phosphorus ratio of diets should also be considered. Studies in young healthy women have shown that a high phosphorus (from supplements/

mainly additives), low calcium diet increases iPTH [113,114] and a high phosphorus (1624mg) high calcium(2044mg) diet suppressed iPTH.[76] Kemi *et al* suggest that a habitual diet with a low calcium to phosphorus ratio of ≤ 0.5 may interfere with homoeostasis of calcium metabolism and increase bone resorption.[115]

Impact of Food Processing and Cooking

Food processes which alter absorption of phosphorus include fermentation, germination, soaking and pressure cooking. These processes reduce the phytic acid content of food which increases the absorption of phosphorus. Various studies have examined each. The phytic acid content of bread containing bran was reduced to about 40% after 2 hours of leavening.[116] Fermentation of bread with yeast reduced phytate phosphorus levels.[117] Sourdough fermentation reduced the phytate content of bread by up to 97%.[118] Germination seems particularly effective at reducing the phytic acid content of legumes.[119,120] Soaking significantly reduced the phytic acid content of the pigeon pea[120] but not the faba bean.[119] While soaking reduced the phytic acid content by 15%, ordinary cooking (boiling) did not reduce it further.[120] Cooking in a pressure cooker, fermentation, germination and dehulling significantly reduced the phytin phosphorus content of mung beans.[121] Domestic cooking processes do not significantly affect the phytate level.[109]

In addition to the effect on phytic acid, some food processes also reduce the phosphorus content. Boiling leaches phosphorus from food.[122-124] Soaking[125] and dehulling of legumes reduces the phosphorus content.[120] Additionally particle size and cooking methods affect phosphorus removal when boiling meat, with slicing meat and pressure cooking achieving the largest reductions.[123]

While many experts consider that additives are very readily absorbed the working group concluded that definitive evidence to support this is lacking. Regardless of the exact level of absorption of additives, the working group still considered them a concern because of their widespread use.[126,127] The consensus was all dietary phosphorus is efficiently absorbed, except when bound by phytate, and that there was sufficient evidence to relax the restriction on phytate bound phosphorus. With regard to dairy products, the working group concluded that different sources of dairy may have different bioavailability but there is at this point, insufficient evidence to recommend one over another. The working group recommended a calcium to phosphorus ratio of ≥ 0.5 whilst acknowledging that the optimum ratio is not defined. It was also agreed that the bioavailability debate is not as relevant, as it is outweighed by the punitively high phosphorus to protein ratio of dairy and therefore dairy products should continue to be limited. It was concluded that fermentation and germination significantly reduced the phytate content of foods and therefore should be avoided.

Topic 2: The Safety and Benefit of Increasing Plant Protein

Pulses including beans and lentils and peas are a cheap and versatile source of quality plant protein, however there are concerns regarding the increased potassium load. Nuts are seen as a convenient food which introduce variety into the diet and are in line with healthy eating and the 2016 European Cardiology Guidelines.[128] There is growing interest in the potential benefits of increased fiber intake through the use of wholegrain cereals and pulses.[129] Sirich describes how

dietary fiber is broken down to provide energy in the form of short chain fatty acids. The gut microbes use this increased energy supply to incorporate dietary protein for growth rather than breaking them down to uremic solutes.[130] It has been shown in hemodialysis patients that an increased fiber intake reduces the plasma levels of selected colon-derived solutes.[130] Increasing fiber has been suggested as a therapeutic intervention which may prove effective in attenuating CKD associated dysbiosis and colonic dysfunction.[131]

The consensus reached by our working group, was that increased whole grains and pulses with consequential increases in fiber should significantly benefit our patients.

We considered the safety of increasing plant protein and whole grains on a potassium restricted diet. While the necessity and benefits of dietary potassium restriction have been inadequately quantified,[132] higher potassium intakes are associated with increased risk of death in long term hemodialysis patients [133] and so are a reasonable cause for concern. Two small dated studies provided us with some limited evidence and reassurance. A detailed balance study showed that while dietary potassium intakes increased by 43% (changing from white to brown bread), gut excretion increased by 127%.[106] Secondly, three high fiber bran muffins per day increased serum phosphate but not potassium.[134]

The consensus was that the increased potassium intake from high fiber foods would be, to some degree, compensated for by increased colonic excretion and it was possible to safely replace some of the animal protein in the diets of patients with CKD and ESKD with more plant protein, such as pulses.

Topic 3: Protein Prescription and the Phosphorus to Protein Ratio

Table 2-2 describes protein requirements which vary between 0.6 to 1.3g/kg depending on stage of CKD and dialysis modality.

All protein intakes necessitates an obligatory phosphorus intake [135-137] but phosphorus intakes may vary considerably for any given protein intake depending on food choices and phosphate additives.[46] Recent opinion suggests that phosphorus restriction can be achieved while maintaining an adequate protein intake.[46,138] In addition, as recently reported by Philips *et al.* protein requirements in the general population are coming under increased scrutiny as concern grows for age related sarcopenia.[139] Phillips also suggests that increased protein intakes, evenly distributed across the day with consideration of dietary sources may be important in terms of maximising muscle protein synthesis.[139]

Table 2-2 Protein Requirements in CKD and ESKD

Protein Requirements /day	CKD	Haemodialysis	Peritoneal Dialysis
Ireland	0.8-1.0g/kg IBW[a,140]	1.0-1.2g/kg IBW[140]	1.2-1.3g/kg IBW[140]
United Kingdom	0.75g/ kg IBW[b,141]	1.1g/kg IBW[142]	1.0-1.2g/kg IBW[142]
United States	0.6g-0.8g /kg BW[c,143]	1.2g/kg IBW[144]	1.2-1.3g/kg BW[144]

[a] CKD stage 3-5 not on dialysis [b] CKD stage 4&5 not on dialysis [c]for eGFR <50ml per minute per /1.73m^2 IBW Ideal Body Weight

Whilst there is a need to maintain an adequate protein intake,[145] high protein foods, differ in the amount of phosphorus per gram of protein, described as the phosphorus to protein ratio. The phosphorus to protein ratio can be described in terms of daily intake, where increased phosphorus to protein ratios have been associated with increased mortality,[86] or at individual food level.[146] At food level,

foods such as oily fish, milk and eggs have the highest phosphorus to protein ratio. However oily fish is an excellent source of vitamin D and omega 3, eggs have an ideal amino acid profile, are a good source of leucine, and are versatile, affordable and easy and quick to cook.[147] More slowly digested proteins found in milk or eggs may allow for the prolongation of muscle protein synthesis.[148] Egg whites have an extremely low phosphate to protein ratio.[149]

The consensus reached was to continue to prescribe the current protein requirements of 1-1.2g/kg ideal body weight per day[140] and that while the phosphorus to protein ratio was a consideration, it needed to be balanced against achieving variety, choice and balance in the diet overall.

Topic 4: Phosphate Additives

The final strategy considered was whether we needed to offer more comprehensive advice regarding food additives. This included looking at whether there was sufficient data to establish the main dietary contributors to phosphorus intake from an additive's perspective. This information was then used in turn to decide on whether there was a need to totally ban all phosphate containing additives from the diet.

Phosphate containing additives have increasingly been used by the food industry.[150] This is a particular challenge in the dialysis population but may also be contributing to a more widespread public health issue.[151] The increased usage of phosphate additives is compounded by efficient gastrointestinal bioavailability and by the fact that their content is not accurately reflected in food composition tables. The EU Commission recommended that phosphate additives which includes phosphoric

acid, phosphates (E 338-341; E 343) and polyphosphates (E 450-452) should be re-evaluated by the European Food Safety Authority (EFSA) with high priority, as set out in Regulation (EC) No 257/2010.

When declared in the ingredients list on food labels, all additives including the main phosphate additives need to be labelled with their functional class or category e.g. emulsifier, acidity regulator, colour etc. followed by their specific name or, if appropriate, E number. Therefore, a food containing any one of the main phosphate additives can be identified from the ingredients list. The Mintel Database is an online database which monitors product introductions in consumer packaged goods markets. Data from the Mintel database indicated that less than 20% of foodstuffs introduced or re launched in Ireland since 2011 contained a phosphate additive.[152] This figure was more modest than Australian data which estimated that 44% of the most commonly consumed food stuffs contained a phosphate additive.[126] This data also revealed which food groups were the most likely to contain phosphate additives, allowing us to highlight to patients what food groups to focus on. Whilst maximum permitted levels of these additives in foods from the EU Regulation on food additives are known (i.e. Regulation (EC) 1333/2008 as amended), this information was not sufficient to tell us what the most significant contributors to phosphorus intake were. We were also aware of some other additives which may contain phosphates such as some modified starches, sodium aluminium phosphate (acidic) (E 541) and riboflavin 5'- phosphate (E101). Modified starches present a particular challenge because if modified starches are chemically treated they are deemed to be food additives but are exempt from having to label their specific name or E number like other food

additives under EU general labelling rules. Therefore if a label contains a modified starch it is impossible to know if it contains phosphate or not.

Primarily taking the results of the Sullivan cluster RCT[73] into consideration, allowed our group to reach a consensus that we should increase our focus on phosphate additives. The consensus reached was to focus on the main phosphate additives as defined by EFSA which included phosphoric acid, phosphates (E 338-341; E 343) and polyphosphates (E 450-452).

DISCUSSION

We report the process by which Irish renal dietitians reviewed the relevant scientific literature for the purpose of updating dietary phosphorus nutrient guidelines in CKD and ESKD. The data provided in this report may facilitate similar revision of renal dietary recommendations in other countries. Our review resulted in three main changes in the way we manage dietary phosphorus (Table 2-3).

Table 2-3 Agreed Changes to Nutrient Based Strategies

1. Introduction of some plant protein in the form of pulses, nuts and whole grains where the phosphorus is largely bound by phytate
2. Careful consideration of protein intake in terms of load and some consideration of the phosphorus to protein ratio of different foods
3. Increased focus on avoiding phosphate additives

1. We introduced some, previously avoided, plant protein in the form of pulses, nuts and whole grains, where the phosphorus is largely phytate-bound and poorly absorbed. Evidence continues to accumulate on the potential benefits of including pulses, nuts and whole grains.[153] The benefits of nuts in reducing the risks of

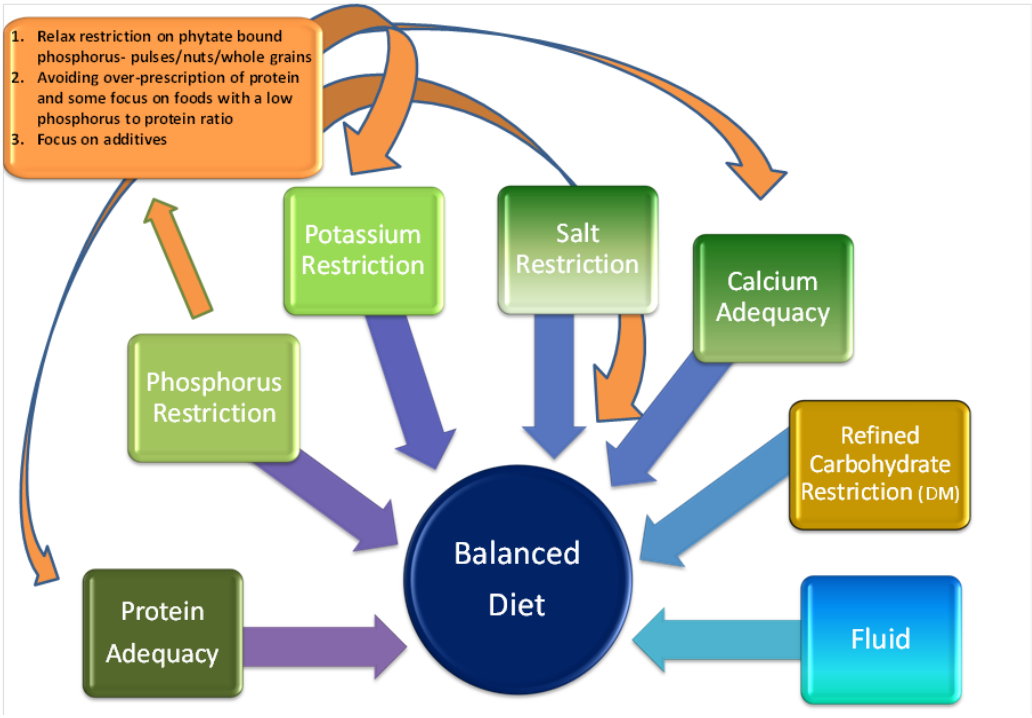
chronic illness[154,155] and mortality [156] have been recently described. There is growing interest in the potential benefits of increased fiber intake through the use of wholegrain cereals and pulses,[129] which may also have a beneficial net effect on calcification.[157] To address concerns regarding the associated dietary potassium load we suggested caution in the magnitude of change recommended in patients particularly in ESKD patients, use of appropriate monitoring of the serum potassium and caution in high risk individuals. 2. We recommended the more accurate prescription of protein to ensure patients consume sufficient protein to meet demands but not any more than that because of the obligatory phosphorus load in protein. Whilst there is much focus on the phosphorus to protein ratio in the literature we concluded that while the phosphorus to protein ratio was a consideration,[86] it needed to be balanced against achieving variety, choice and overall nutritional adequacy. 3. We recommended increasing the focus on avoiding foods containing phosphate additives. Despite limited evidence on the absorption of phosphate additives,[74-76,106] evidence continues to emerge related to the benefits of avoiding these additives.[158] EFSA estimates that phosphate food additives contribute between 6 to 30% of the total average intake of phosphorus,[159] however this is an estimate and does not include all phosphate additives. Renal healthcare experts continue to call for improved food labelling that includes the phosphorus level.[160]

Our review underscores the scarcity of well-designed large controlled trials in the dietary management of CKD and a pressing need for appropriate pragmatic trials in this area. A challenge for this review process is the use of serum phosphorus as a

marker of the effectiveness of interventions in terms of intra-individual variation, fasting versus postprandial levels, diurnal variation and compensatory mechanisms that occur in CKD.[14,161,162]

Management of the renal diet is complex. [163] Dietary restriction of phosphorus is only one of multiple restrictions that make up the renal diet. We rarely manipulate one nutrient in isolation and changes to how we manage one nutrient affects intakes of other nutrients as illustrated in figure 2-4.

Figure 2-4 How Changes to One Nutrient Affect Other Nutrient Intakes.



A renal diet involves manipulation of several nutrients including phosphorus and potassium. Changing dietary phosphorus restrictions by, for example, relaxing the restriction on phytate bound phosphorus through the introduction of pulses, nuts and whole grains, will also increase dietary potassium intake. DM Diabetes Mellitus

In addition, focusing on total nutrient intakes e.g. total phosphorus intake is too simplistic, because the matrix the food is delivered in, affects absorption, as observed with phytate-bound phosphorus. Moreover, the renal diet is a 'complex

intervention' and it must take into account not only nutritional requirements but also trade-off between different strategies (e.g. between protein restriction for the purpose of phosphorus control versus protein requirements for the avoidance of sarcopenia) as well as the individual's specific circumstances. This is particularly relevant as 56% of haemodialysis patients report difficulties tracking nutrient intakes and 59% were too tired following dialysis to cook.[163]

Dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet [164] are gaining increased credence and attention, including in CKD.[165] For renal patients these patterns will need to be individualized, to manage specific nutrient restrictions, and to ensure nutritional adequacy and choice for our patients. This requires the expertise of trained dietitians. The recommendations described in this paper, moves the advice we give to our patients closer to the Mediterranean type dietary pattern.

In order to update our national diet sheet, we developed updated nutrient level recommendations by combining clinical experience and expertise with available research. These nutrient recommendations were then used to develop a national modified diet sheet, which is individualized to the needs of each patient. We propose to evaluate the benefits and safety of this modified dietary advice in a further study. ClinicalTrials.gov Identifier: NCT03146923.

In conclusion our review of both existing interventional and observational data provides the scientific rationale for modified nutrient level phosphorus recommendations in CKD G3 to 5D and highlights the complexity of dietary interventions in renal disease and the need for urgent research in this field.

2.2 Translation of Nutrient Level Recommendations to Control Serum Phosphate into Practical Food Based Advice

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5 Key Words: Hyperphosphataemia, Phosphorus, Potassium, Diet, Phytate

This paper was submitted to the US Journal of Renal Nutrition on 16-12-19.

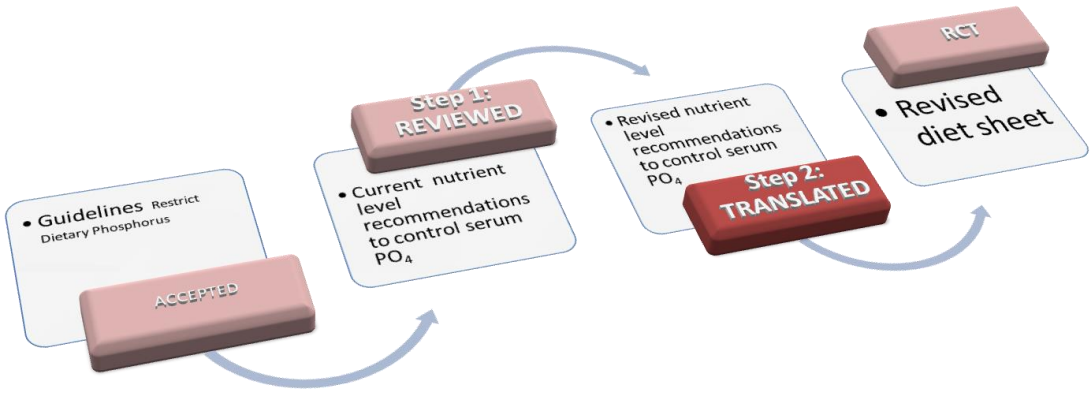
ABSTRACT (150 words)

The control of hyperphosphataemia is key to the management of Chronic Kidney Disease Mineral and Bone Disorder (CKD MBD). Dietary restriction of phosphorus is essential to control hyperphosphataemia. Guidelines for Chronic Kidney Disease (CKD) and End Stage Kidney Disease (ESKD) generally provide high level guidance on whether a nutrient should be restricted, for example restrict dietary phosphorus. Dietitians translate such guidance into nutrient based strategies and finally into food based practical dietary advice for patients to follow. The practical aspects of dietary advice are not well described in the literature. Neither are the challenges of concurrently, altering one nutrient e.g. phosphorus while continuing to restrict others e.g. potassium, whilst maintaining overall nutritional adequacy and maintaining quality of life. In this paper, we describe how we translated updated nutrient level recommendations into practical dietary advice to be delivered at the bedside.

Introduction & Purpose

Dietary phosphorus restriction is recommended to treat hyperphosphataemia in CKD and ESKD.[49,166] In 2015, Irish Nutrition & Dietetic Institute (INDI) renal dietitians undertook to review and update the phosphorus section of the Irish national renal diet sheet. This process required 2 steps (figure 2-5). In the first step described in the previous paper of this chapter, we report on current evidence and how we updated our nutrient based recommendations and strategies. The second step in this process, described here, is to translate the nutrient based recommendations into practical dietary advice for patients in the form of a diet sheet. The aim was to produce a diet sheet that we could use to assess effectiveness, safety and tolerability in a dietary intervention trial in a hemodialysis population (ClinicalTrials.gov Identifier: NCT03146923) to guide national implementation. The trial diet sheet is included as supplementary material.

Figure 2-5 Review Process



This paper describes the three nutrient based strategies identified to improve the control of dietary phosphorus, namely 1) introduction of plant protein in the form

of pulses, nuts and whole grains, 2) consideration of protein intake in terms of load as well as the phosphorus to protein ratio of different foods and 3) focus on additives (ref other paper). It details the process by which we agreed, how to use these strategies to translate high-level nutrient recommendations into specific practical dietary advice. A significant challenge in this process is that individual nutrients such as phosphorus cannot be altered in isolation. The renal diet is a complex intervention which concurrently restricts multiple nutrients and changing advice on one nutrient affects other nutrients as described in the first paper of this chapter. For example, a challenge for us was to continually consider the risks of increasing dietary potassium intake while devising dietary advice for phosphorus.

Introduction of plant protein in the form of pulses, nuts and wholegrains where the phosphorus is largely bound by phytate

As per the Food and Agricultural Organization of the United Nations the term "pulses" is limited to crops from the legume family harvested solely for dry grain, thereby excluding crops harvested green for food (green peas, green beans, etc) which are classified as vegetable crops. Also excluded are those crops used mainly for oil extraction (e.g. soy bean and groundnuts).[167] Table 2-4 summarises the different classification of legumes.

Table 2-4 Classification of Legumes[3]

Dry Seeds	Oil Seeds	Vegetables
Pulses e.g. chickpeas, kidney beans & butter beans	Soybean Groundnuts/ peanuts	Green peas, green beans

Raw pulses when cooked are much higher in potassium than canned pulses and there is a large variability between them. Pulses, canned in water are widely available in Ireland. Based on nutrient analysis chickpeas, kidney beans, and butter beans canned in water were included in the diet sheet.[149] Chickpeas had a particularly good nutrient profile with 7.2g protein, trace sodium, 110mg potassium, 81mg phosphorus and 4.8g fiber per 100g consumed. Tinned pulses on the Irish market are soaked in water for 12-16hrs to rehydrate them and heat treated to 120 degrees for 30mins rendering them commercially sterile (Communication from Bachelors, Valeo Foods 2016). Commercial hummus (made with chickpeas) was noted to be very salty and therefore was not recommended. A recipe for homemade hummus was included in a recipe book compiled to help patients incorporate the changes recommended into their diet. Pulses canned in water, nuts and seeds have an average phosphorus to protein ratio of 14mg/g, 26mg/g and 39mg/g protein respectively.[149] However given their higher phytate content which should reduce absorption of phosphorus, the consensus was to allow some pulses canned in water and nuts. Pulses are explored in more detail and using US data by Byrne & Calvo.[168] As pulses and nuts have a higher potassium content, their intake was controlled as outlined in the increased potassium load section below. Tofu was assessed to be the most suitable soya bean product, however given the significant variety in protein content of products on the supermarket shelf, we opted not to include tofu in the trial diet sheet but to reconsider its inclusion during implementation of the new food changes into the revised national diet sheet.

Nuts have a higher phosphorus to protein ratio and a lower fibre content than pulses. Education regarding portion size of nuts was recommended. We also recommended nuts lower in potassium and phosphorus namely, peanuts and cashew nuts. Even though, it was noted that some lightly salted varieties of nuts only contained 0.2g salt per portion, we chose to recommend unsalted varieties. Peanut butter was also considered a suitable choice, again with a recommendation to educate about portion sizes.

Seeds were considered too high in terms of phosphorus to protein ratio even with phytate to reduce absorption and therefore were not included.

We introduced more whole grains e.g. wholemeal brown sliced pan bread, using the carbohydrate portions from the 2011 Irish food pyramid[169] where breads and cereal portions typically have 2-3.5g protein and 17-20g CHO.

Within the Irish context we established that Irish soda bread, and that the majority of ambient packaged bread (sliced pan) is made on a process where fermentation is minimal (Communication from Odlums, Valeo Foods 2016). Fermentation reduces the phytic acid content of food which increases the absorption of phosphorus, as described in the previous paper in this chapter and therefore we advised the avoidance of fermented breads such as sourdough.

Oats are available in a variety of forms including in porridge, oat based biscuit cereals and oatcakes. Their phosphorus content is lower than wholegrain rice but higher than wholemeal bread. Given their health benefits especially in terms of soluble fibre, consensus was to include these foods. Oat-based biscuits and plain flapjacks were included in the “treat foods” section of the diet sheet.

As the proposed new foods were higher in fiber, it was agreed that the diet sheet should advise on how to introduce these changes to minimise gastrointestinal side effects.

Increased Dietary Potassium Load.

While increasing intake of pulses, nuts and whole grains is more in line with healthy eating, may prevent gut dysbiosis, and is cardio- protective (as described in the previous paper of this chapter), it was agreed that changes needed to be prudent given the risk of hyperkalaemia. It was decided that pulses and nuts should be exchanged for HBV protein. It was estimated that if you swapped one 7g protein exchange of pulses (canned in water) and one 7g protein exchange of nuts, for two 7g protein exchanges of HBV such as 2oz meat, fish or chicken, that would increase your daily dietary intake of potassium by approximately 8 mmoles potassium per day. Each slice of wholemeal bread provided an additional 1mmol potassium per slice over white bread. Wholegrain rice provides an additional 0.5 mmol potassium per 25g uncooked rice while wholemeal pasta provides an additional 1.1mmol potassium per 25g uncooked pasta.

Potential counter measures which served to reduce potassium intake were a more accurate prescription of protein and a dairy restriction of 1 exchange per day. In addition nutrition analysis undertaken for website meal plans at www.irishkidneydiet.ie showed that the current diet sheet provided less than 1mmol/kg. Additional reassurance was provided by evidence that increased fibre intake should increase gut excretion of potassium as described in the previous paper of this chapter.

Careful consideration of protein intake in terms of load as well as the phosphorus to protein ratio of different foods

The group agreed that we should aim for more accurate protein prescription in order to avoid over-prescription of protein which carries an obligatory phosphorus load. High biological protein (HBV) such as meat, poultry, fish and eggs are currently prescribed in protein exchanges. Current practice is that patients are prescribed a daily allowance of protein exchanges based on weight and stage of CKD or dialysis modality, aiming for 70% of protein from HBV sources. One protein exchange provides approximately 7g protein. In our current diet sheet one protein exchange is equal to 25g meat or poultry or 40g fish or 1 egg.

We debated and decided to change from using 40g fish to 25 g as a protein exchange. White fish, oily fish and meat provides approximately 6g, 6-7g and >7g protein respectively per 25g portion. As there is significant variation in protein content of fish, meats and poultry, we looked at a theoretical weekly planner of white fish one day; oily fish one day; red meat two to three days and poultry two to three days a week and averaged protein intakes over the week. Using this planner, 6 protein exchanges, each containing an estimated 7g protein, provided a daily average of 44g HBV protein and 374mg phosphorus. We agreed to recommend fish twice a week, and a mixture of meat or poultry on the other days. It was also agreed that plant based protein exchanges such as pulses and nuts should be counted in the protein exchange list. This meant that on the revised diet sheet HBV protein was providing approximately 50-70% protein in the day.

We considered if it was necessary to count low biological value protein (LBV) such as bread and cereal to allow more accurate protein prescription. Each slice of bread has approximately 3.5 g protein. Current practice is to prescribe 70% HBV protein in terms of animal protein exchanges and dairy exchanges and to allow LBV protein such as bread and cereals freely. It was estimated that this prescription led to an over consumption of protein. While there was consensus that we need to be more prescriptive there was much debate on how we should do this. There were concerns as to whether more accurate prescription would make enough of an impact to be significant in terms of outcome. There were also concerns that prescribing LBV at 30% of protein could lead to over restriction of energy in some patients. However, given the rising levels of overweight and obesity in patients with CKD and ESKD,[170] it was deemed that restriction of energy is indicated in a high proportion of patients. We opted to give specific recommendations for LBV proteins such as bread and cereals adjusting for normal dietary pattern, patient preference and energy requirements.

Increased focus on high protein foods with a low phosphorus to protein ratio

In order to achieve an adequate protein intake with the lowest phosphorus load we considered the phosphorus to protein ratio (mg phosphorus per gram of protein). We reviewed our high protein exchange lists using the phosphorus to protein ratio and found that white fish, meats and poultry contained 7-9mg phosphorus/g protein.[149] Whilst, oily fish such as salmon contained a higher ratio 11mg phosphorus / g protein, it also contains omega 3 and vitamin D. Beef has a lower phosphorus to protein ratio than chicken but this was not considered to be clinically relevant. In terms of phosphorus content, beef is lower than chicken which is lower than fish. In order to maintain variety and choice and to align guidelines with general healthy eating guidelines it was agreed that the phosphorus to protein ratio should not unduly affect the choice of animal protein source and instead to recommend as per healthy eating guidelines. We recommended that patients opted for a variety of choices including fish twice a week. Within each group we did name suggestions in order of phosphorus to protein ratio starting with choice that had the lowest P to protein ratio e.g. Meat: Beef →lamb→ pork; Poultry: Chicken →Turkey; White fish: Sole →Cod →Plaice

Dairy Products have a very high phosphorus to protein ratio at 20-30mg P / g protein. Current practice is to recommend between 1 and 1.5 exchange per day with an exchange containing 7g protein e.g. 200 ml milk. In a survey of units participating in the trial, from 11 responses, 70% recommended 200 ml milk and 30% recommended 300 ml milk per day. Palatability and patient acceptability were considered, as was the risk of calcium deficiency. Data on milk replacers such as rice and oat milk was collected from two local supermarkets including a budget

supermarket and from online sources. It had been hoped that the significant increase in availability of milk replacers on the market would serve to increase choice and palatability for our patients. We had concerns regarding the accuracy of available data, as the phosphorus content of products was surprisingly low given the presence of listed phosphate additives, such as tri calcium phosphate. In addition the market was rapidly changing, the products are expensive and it was difficult to source products that didn't have phosphate added. As a result milk replacers were not included on the trial diet sheet but may be considered again during implementation based on emerging data. Whilst soya milk is not a dairy product it was included as an exchange in the dairy category because it was agreed that it would likely be used as an alternative to milk and it has a comparable protein, potassium and phosphate content. Patients were reminded to check if it had added phosphate. It was agreed to keep milk to 200 ml per day for the trial but to review again prior to national implementation.

Eggs were considered an easy and versatile source of protein. In a survey of units participating in the trial from 11 responses, 46% advised 3-4 eggs per week; 36% allowed 7 eggs per week with 9% (n = 1) allowed an unlimited number of eggs. An egg a day adds approx 40 mg phosphorus and while eggs do contain leucine, so too do most high protein foods. [171] It was agreed to keep eggs to 3-4 per week for the trial but to review again prior to national implementation.

Increased focus on avoiding phosphate additives

Indications from Mintel data[152] are that over 80% of products on Irish supermarket shelves do not have phosphate added. It was felt that this should provide sufficient

choice for patients and for this reason the group opted to advise patients to avoid all foods with phosphate additives. Patients were advised to focus on the main phosphate additives.

We reviewed the data collected from supermarkets on the presence of phosphate additives in chilled and frozen meats and poultry. It was noted that there was quite a variation within categories e.g. breaded fish, breaded chicken with many with and many without phosphate additives. This supported the agreed approach of reading labels. The foods which may contribute more significantly namely bakery products, cakes, biscuits and processed foods were highlighted. At that point in time we did not have sufficient information to warrant advising patients to avoid all modified starch and we choose to focus only on the main phosphate additives.

Boiling

Boiling reduces the phosphorus content of food,[172,173] however the benefit of boiling meat and poultry can only be achieved if you discard the water. Consensus was that patients in general would not support discarding the resultant nutritious stock. We also felt we needed to keep it simple, as many HD patients report difficulties tracking nutrient intakes (56%) and 59% were too tired following dialysis to cook.[163] Table 2-5 summarises the main changes to the diet.

Table 2-5 Summary of Main Changes to the Low Phosphorus Renal Diet

Pulses and nuts were included in the protein exchange list allowing 2 x 7g protein exchanges per day as plant based vegetarian exchanges. Because of concerns re potassium we were cautious in the magnitude of change recommended e.g. we recommended a limited amount of pulses and nuts and choose those with the lowest potassium contents, using pulses canned in water.
Eggs were restricted to 3-4 per week and dairy to 200 ml milk per day or equivalent with agreement to consider again prior to national implementation based on trial results.
Breads cereals and grains were included in daily allowance to avoid over prescription of protein. Wholemeal or wholegrain products were recommended but gradual changes advised. Avoidance of sourdough bread.
There was an increased focus on phosphate additives giving the E numbers and recommending that all labels be checked. Provision of shopping cards to make information more accessible when shopping. Phosphate additive advice was restricted to the main phosphate additives with agreement to consider again based on emerging evidence and the trial results.
A recipe booklet was created to support patients to include new foods such as pulses and nuts into their diet.

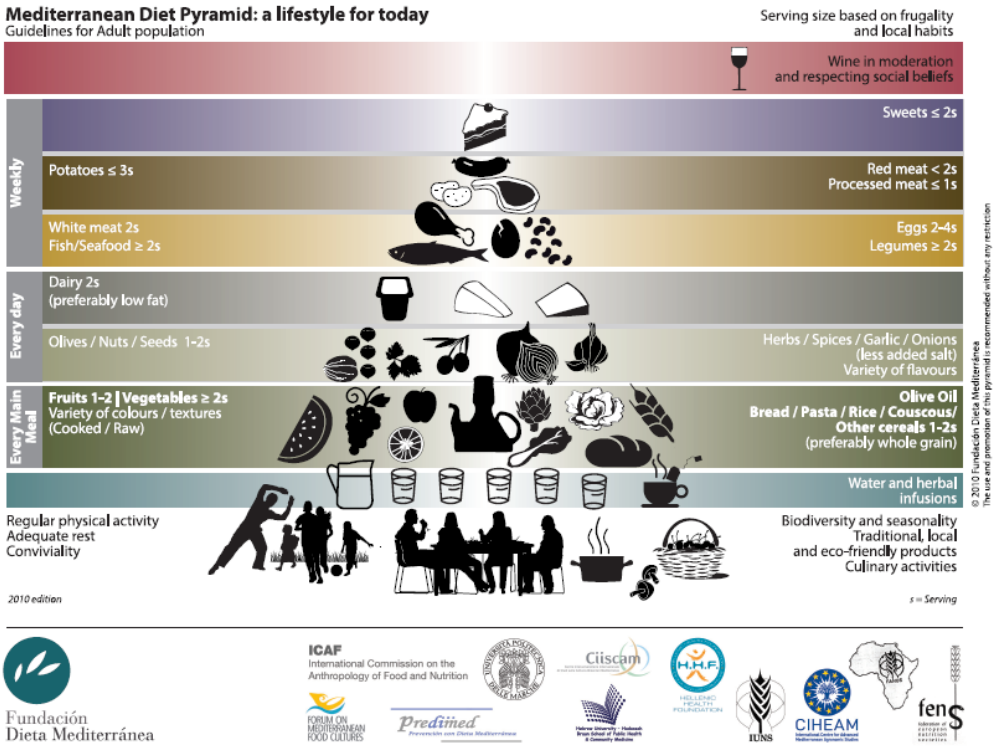
Additional resources

There was agreement on a need to educate re portion sizes for nuts and that showing or giving a sample to patients would be beneficial. Recipes to help patients incorporate the new changes into the diet were compiled. A shopping card with the E numbers of the main phosphate additives was also created. It was agreed that we lacked evidence that healthy eating was beneficial in CKD and ESKD but agreed that we have always tried to incorporate healthy eating as much as possible to ensure an overall balanced intake of all nutrients. It was agreed to produce a separate version of the diet sheet for patients with diabetes which excluded foods with a high refined sugar content. Both versions were reviewed and approved by the National Adult Literacy Agency (NALA) to improve its comprehensibility.[174]

Benchmarking against healthy dietary patterns

There is a growing interest in dietary patterns in CKD particularly in the Mediterranean diet[165] which is described in figure 2-6. We compare our revised national renal diet to the Mediterranean diet in table 2-6. Undoubtedly the recent changes move our diet closer to the Mediterranean dietary pattern however, our diet sheet allows us to individualize based on protein requirement, individual nutrient restrictions and patient circumstances.

Figure 2-6 Mediterranean Diet



Dietary patterns are an attractive option[175] but we also need to continue to individualize nutritional therapy for our patients especially in later stages of CKD and ESKD. The challenge for renal healthcare professionals is how to marry the

complexities of the renal diet such as multiple nutrient restrictions, management of malnutrition and difficulties with adherence ,[46,163,176,177] with a simplified dietary pattern. Challenges include the following: Each food or food group contains multiple nutrients and therefore a change in recommendations to one food group affects multiple nutrients as illustrated in table 2-7. A generic dietary pattern would need to incorporate all possible restrictions which may lead to unnecessary restrictions being imposed. One pattern could not simultaneously meet the protein needs of both CKD and ESKD patients. Whilst beyond the scope of our work, we suggest a need to combine both approaches, to create renal dietary patterns that can be individualized.

Table 2-6 Comparison of the Modified Diet versus the Mediterranean Diet

Food	**Mediterranean Diet**	**Modified Irish Renal Diet** * from individualized protein exchange allowance
Red Meat	<2 servings/week	*2-3 times /week
Processed Meat	≤1 serving / week	Not allowed
White Meat	2 servings/week	*2-3 times/week
Fish	≥2 servings/week	*2 times/week
Legumes	≥2 servings/week	*1-2 servings/day allowed
Eggs	2-4 servings/week	*3-4 per week
Olives/Nuts/ Seeds	1-2 servings/day	*1 serving nuts/day as a protein exchange. Avoid olives & seeds
Dairy	2 servings/day (low fat)	1 servings/day
Wholegrain Bread/Cereals	1-2 servings/ main meal	__ servings /day individualized
Potatoes	≤ 3 servings weekly	2 /day - double boiled if hyperkalaemic
Fruit	1-2 servings/ main meal	2 servings/day
Vegetables	≥2 servings/main meal	2 servings/day
Olive Oil	With meals	Allowed
Treats	≤2 servings/week	Occasionally
Wine	In moderation	Restrict if hyperkalaemic
Herbs/Spices/Garlic/Onion	Daily	Allowed (Onions counted as vegetable)

Table 2-7 How Changes to Recommendations Affects Nutrient Intakes

Food Groups	Individualized Nutrients	Restricted Nutrients	Encouraged Nutrients
Protein			
Animal protein	↑ Protein highest quality	↑P, ↑ K^+	
Vegetable protein	↑ Protein	↑P, ↑ K^+	↑ Fibre
Dairy	↑ Protein	↑↑P	
Fruit & Vegetables		↑ K^+	↑ Fibre
Cereals			
Whole grains	↑Energy	↑P, ↑ K^+	↑ Fibre
Refined	↑ Energy		

P Phosphorus K+ Potassium

In summary, we produced a revised low phosphorus diet sheet by combining available evidence with firsthand knowledge of the complexities of the renal diet to produce practical food based advise for our patients to be assessed at multicentre trial (ClinicalTrials.gov Identifier: NCT03146923) prior to national implementation.

My Contribution to Chapter 2

2.1 Revising Dietary Recommendations for Phosphorus in Chronic Kidney Disease G3- 5D

2.2 Translation of Nutrient Level Recommendations to Control Serum Phosphate into Practical Food Based Advice:

I conducted the literature review, with some assistance from the Librarian in the Mercy Hospital. Abstracts were independently reviewed and selected by 2 dietitians. I reviewed and incorporated selected papers into a narrative review, seeking further review and group discussion as required. I coordinated the working group of 7 dietitians and documented the proceedings of 2 meetings and 36 conference calls, over which I led the assessment of the literature, agreed the main changes to the nutrient based recommendations and translated these revised nutrient based recommendations into practical dietary advice for patients. I wrote the scientific paper with each author contributing to the review process. Both papers were submitted to the Journal of Renal Nutrition on 16-12-19.

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

CORA
Cork Open Research Archive
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Byrne, F. N. 2020. Dietary phosphorus in chronic kidney disease. PhD Thesis, University College Cork.

Please note that Chapter 3 (pp. 53-72) is unavailable due to a restriction requested by the author.

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Chapter 4: Feeding Trial

The Effect of Dietary Phosphorus Load and Food Matrix on Postprandial Serum Phosphate in Haemodialysis Patients

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5 key words: Hyperphosphataemia, Phosphorus, Potassium, Diet, Haemodialysis

This paper was submitted to Nephrology Dialysis Transplantation on 17-12-19.

Abstract

Introduction: Potential dietary strategies for controlling hyperphosphataemia include the use of protein sources with lower phosphorus bioavailability such as pulses and nuts, focus on phosphorus to protein ratios and the avoidance of all phosphate additives.

Aims: The aim of this study was to investigate the acute postprandial effect of a modified low phosphorus diet versus standard low phosphorus diet on serum phosphate, potassium and intact parathyroid levels in prevalent haemodialysis (HD) patients.

Method: We conducted a controlled crossover feeding study in 8 HD patients. The main meal of the modified diet included beef, which has a relatively low phosphorus to protein ratio and some pulses and nuts which have a higher phytate content, conferring reduced phosphorus bioavailability. Serum samples for phosphate, potassium and intact parathyroid hormone (iPTH) were taken before the main meal and at one hour intervals for the four hours after completion of the meal.

Results: In this study we report an average decrease in both serum phosphate and serum potassium readings when patients consumed the modified diet. At 4 hours post-meal, individuals on the modified diet had serum phosphate readings 0.30 mmol/l lower than when on the standard diet (p-value = 0.015, CI -0.57, -0.04). The

corresponding change in serum potassium at 4 hours was a decrease of 0.675 mmol/l (p-value = 0.011, CI -1.25, -0.10).

Conclusion: A modified low phosphorus diet allowed for greater food choice and resulted in significant reductions in postprandial serum phosphate and potassium levels compared with the standard diet.

4.1 Introduction

Hyperphosphataemia is associated with increased mortality, in end stage kidney disease.[15,16] Higher phosphate levels, even within normal range are associated with increased mortality in those in the earlier stages of chronic kidney disease (CKD), and in patients with normal renal function.[17-22]

Hyperphosphataemia is a major therapeutic target in the management of Chronic Kidney Disease Mineral and Bone Disorder (CKD MBD) and the use of phosphorus restricted diets is well established in the treatment of hyperphosphataemia in patients with CKD MBD.[10]

There are challenges with dietary phosphorus restriction in the management of hyperphosphataemia. Few high quality trials have examined the impact of the dietary restriction of phosphorus and the evidence base is therefore weak.[45] Efforts to control total phosphorus intake may lead to the unnecessary restriction of healthy higher fibre foods such as pulses and whole grains where the phosphorus is largely bound to phytate and thus unavailable for absorption.[109] Serum phosphate is not an ideal biomarker to use as an outcome measure in healthy or CKD

populations. Circadian rhythm[233-237] and fasting versus non fasting measurements[77,235,236,238,239] can effect serum phosphate, challenging the interpretation of concentrations.

The mechanism of dietary phosphorus absorption remains poorly understood[26,36] and we have limited data on postprandial changes in serum phosphate level.[235,240,241]

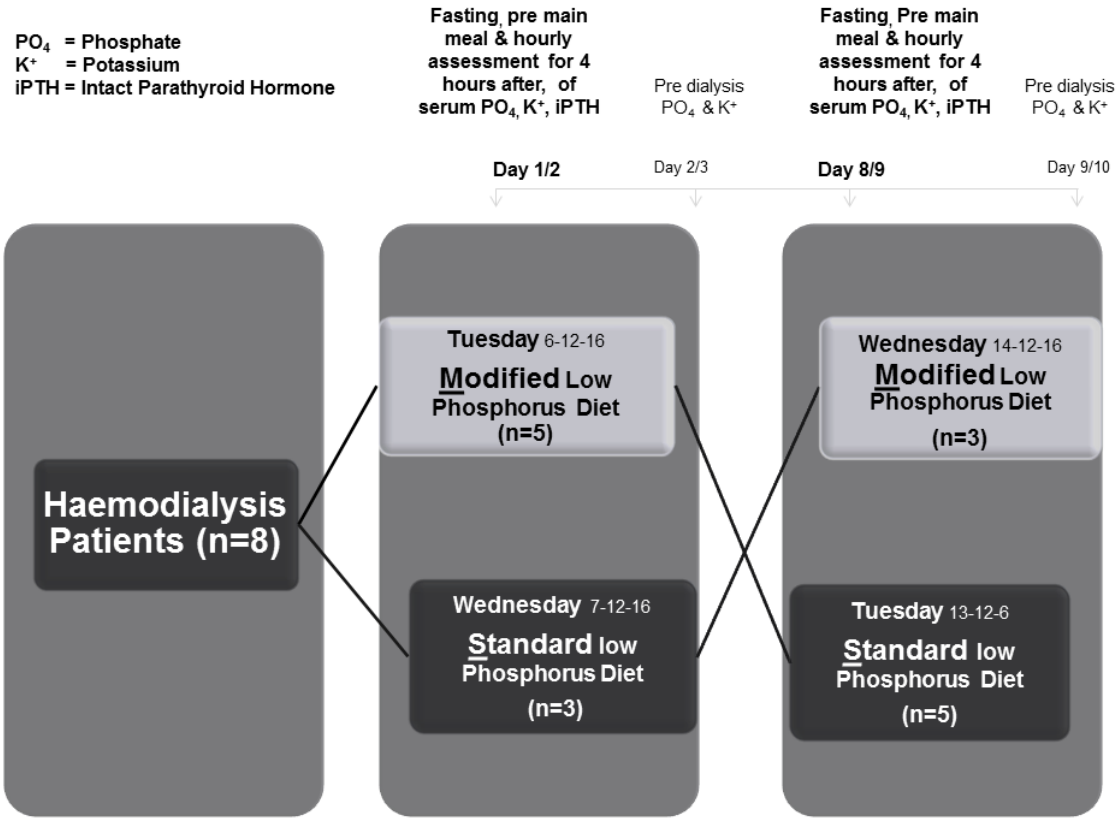
Following a review of emerging evidence, a national working group of Irish dietitians identified three strategies to improve the management of dietary phosphorus restriction; (1) the introduction of plant protein in the form of pulses, nuts and whole grains, (2) consideration of protein intake in terms of load as well as the phosphorus to protein ratio of different foods and (3) reduction of phosphate additive-containing foods. The rationale for this study was to examine the potential benefit of modifying the standard diet as used in clinical practice. We wanted to improve the quality and choice of foods allowed on the renal diet. This echoed a growing wish internationally to liberalise the renal diet and to include vegetarian options.[183,242,243]

The feeding study described here was conducted to assess the effect of these proposed changes in a controlled environment over a short time period, providing insight into acute biochemical changes that occur in the postprandial phase. We investigated the effect of a modified diet which included more wholegrains, pulses and nuts on postprandial serum phosphate, potassium and iPTH levels.

4.2 Methods

Study design. We conducted a crossover study comparing the effect of two diets, a standard low phosphorus diet and a modified low phosphorus diet as described in Figure 4-1.

Figure 4-1 Study Design and Outcome Assessments



5 participants attending the first day were randomised to modified diet. 3 participants attended the following day and received the standard diet. All participants returned the following week and received the opposite diet. On each day participants had fasting bloods on arrival, before the main midday meal and hourly following completion of the meal for 4 hours. Pre dialysis bloods were taken the following day before dialysis.

Participants were recruited from the Haemodialysis Unit at Cork University Hospital. All participants provided informed written consent and the protocol was approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals and conformed with the 1975 Declaration of Helsinki, as revised in 2013. Patients

on trice weekly dialysis, who attended Monday and Wednesday or Tuesday and Thursday, were screened. The entry criteria were as follows: > 18 years of age; on dialysis for > 3 months; pre-dialysis serum phosphate < 2.5 mmol/L and serum potassium < 6.3 mmol/L on most recent routine monthly blood test; urinary outputs of < 200 ml/day by self report; no history of diabetes mellitus, parathyroidectomy or calciphylaxis; and being in their usual state of health.
The study took place at the Health Research Board (HRB) Clinical Research Facility - Cork in the Mercy University Hospital on the day between two dialysis sessions. Each participant attended the research centre on two separate days, one week apart, in December 2016.

On one of the days, participants were directly observed eating a diet based on current dietary advice and on the other day food based on the modified low phosphorus diet. Catering staff, who were blinded to the identity of the participants, provided meals in random order. Participants were blinded to the initial meal selection until the day of the study. Participants were asked to attend the research centre between 8 and 9 am having completed an overnight fast and were requested not to take their phosphate binders on the day of the study.

Upon arrival at the unit participants had an initial blood draw and breakfast was served. Two participants had a planned late arrival on both weeks and so were absent at the initial fasting blood draw. They were provided with a packed breakfast to have on the morning of the study prior to attending the research unit. All participants had a pre-prandial blood draw immediately before lunch, which was

served between 12 noon and 12.30pm. Bloods were collected at hourly intervals following completion of the lunch for 4 hours (1, 2, 3, 4 hours), and a light evening meal was provided prior to departure from the unit. This procedure was repeated the following week, where participants received the alternate diet plan. All serum samples were spun and frozen at -80^{o}C and subsequently analysed by the Biochemistry Department at Cork University Hospital. A pre dialysis sample was taken the day after the study. Potassium was measured by ion selective electrode and phosphate using the ammonium molybdate method, both on an AU analyser. iPTH was measured on the Abbott architect analyser by chemiluminescent immunoassay. As part of standard care monthly pre-dialysis blood samples were routinely taken and analysed in the same laboratory. Pre-dialysis phosphates from three months before and three months after the study were collected following the study to further contextualise the variability in baseline phosphate levels seen in the study.

Interventions: Table 4-1 describes the two diets. The standard diet was based on the current dialysis diet sheet.[244] The modified diet included some plant based protein and more whole-grains. Nutrient analysis was carried out using nutritics software[245] using the McCance and Widdowson's composition of foods integrated dataset.[149] The potassium data was adjusted to account for leaching of potassium by double boiling the potatoes.[246,247]

Table 4-1 Description of the Diets

	Standard Diet (S) (based on current management)	Modified Diet (M) (based on proposed new diet sheet)
Light Breakfast	Tea & 15ml milk 100 ml orange juice 2 slices white bread toasted with spread & marmalade	Tea + 35ml milk 100 ml orange juice 1 slice white bread & 1 slice wholemeal toasted with spread & marmalade
Main meal	250 ml milk *Salmon &white sauce 200g potatoes (double boiled) 100g carrots 75g broccoli 1 slice Madeira cake	130 ml milk Chickpea soup (100g pulses) *Beef & gravy 200g potatoes (double boiled) 120g carrots Meringue with strawberries & cream 25g nuts
Evening meal	Tea & 15ml milk 2 slices white bread toasted with spread & jam Apple	Tea & 35 ml milk 1 slice white bread 1 slice wholemeal bread with spread & jam

Table 4-1 describes the dietary intake on both the standard and modified diets. *The salmon and beef portions were individualised to achieve a prescribed intake of 1.1g protein/kg ideal body weight per day.

Both diets were tailored for each participant to provide 1.1g protein/kg ideal body weight. The major differences between the diets, were at the main meal. The standard diet main meal contained a higher proportion of foods with a higher phosphorus to protein ratio (salmon and dairy), and foods with higher phosphorus bioavailability (cake). The modified diet, representative of the proposed modified phosphorus diet used food of lower phosphorus to protein ratio such as beef and less dairy. Approximately 30% dietary phosphorus in the modified diet came from foods with significant phytate content such as pulses, nuts and whole grains. When consuming the main meals, participants were advised to focus on the main protein

and phosphorus sources namely soup, beef, milk and nuts for the modified diet and salmon, milk and cake for the standard diet. Whilst in usual clinical practice, participants are advised to spread their dietary allowances over the day, on special occasions such as a wedding, for example, they are permitted to keep their allowances for a single meal. On this basis, 80% of the protein allowance in our study was prescribed at the main meal. Food that was not consumed was weighed to ensure accurate assessment of food intake. Food samples were sent to the Public Analyst Laboratory in Cork for analysis of total phosphorus using the molybdenum blue method (a colorimetric method). Participants were advised to revert to their regular dietary routine between the interventions.

Outcomes: Outcome measures included serum phosphate, potassium and iPTH, obtained in early morning (fasting), pre-prandial, at 1,2,3 and 4 hours post main meal consumption and pre-dialysis the following day.

Statistical Analysis

The effect of diet on serum phosphate and serum potassium levels was examined using a mixed effects model with diet and time as fixed effects and patient as a random effect on the intercept using the lmer function from the lme4 package (1.1-21). An interaction term between time and diet was included in both models. The difference between mean serum levels following the standard and modified diets at each time point was tested using the General Linear Hypotheses function (ghlt) from the multcomp package (1.4-10). Differences in phosphorus content of foods between estimation methods were assessed using paired t-tests. All statistical analyses were performed using R version 3.6.

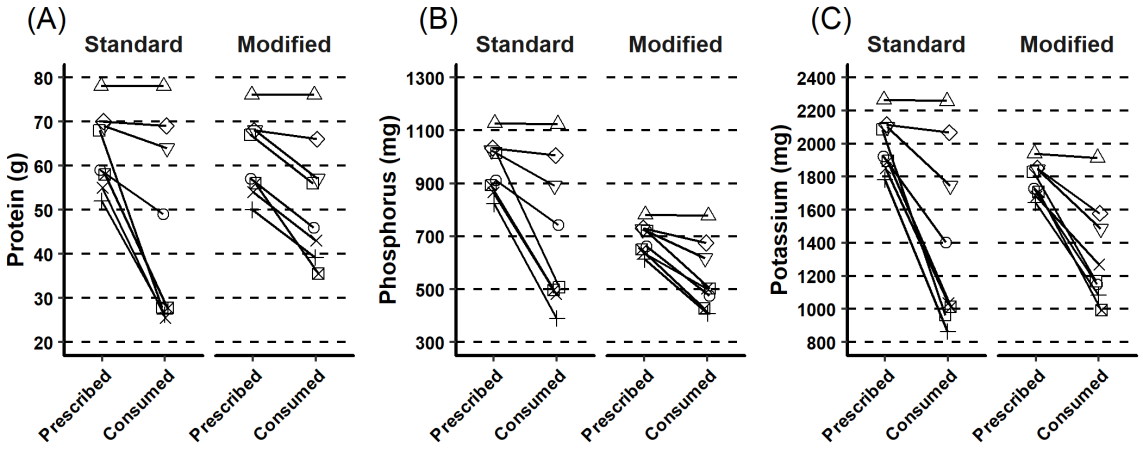
4.3 Results

We approached 16 potentially eligible patients, who attended HD on Monday and Wednesday or Tuesday and Thursday; of these 5 had scheduling conflicts and 3 declined to participate. The baseline characteristics of the 8 enrolled participants are as follows: mean (SD) age was 66.6 (7.8) ranging from 55.9 to 77.1years. The mean (SD) body mass index (BMI) was 25.2 (4.0) kg/m^2 ranging from 17.9 to 31.3. Their dialysis vintage was 52 months ± 46.4, ranging from 19 to 164 months. There were seven males and one female. Four had a fistula and four had a line for dialysis access.

Five participants commenced on the modified diet and three began on the standard diet. One male assigned to the modified diet, arrived without fasting, and his early morning blood test was therefore omitted from the analysis. Participants took an average 41 minutes to consume the standard diet main meal and 37 minutes to consume the modified diet main meal. Additionally, a study deviation from the protocol was noted for participant 8, who ate in a fast food restaurant after leaving the unit; therefore his pre-dialysis sample for the following day was excluded from the analysis.

Compared to the standard diet, participants consumed a mean of 6.4g more protein per day ($p = 0.185$, CI; -3.9, 16.8); 156 mg less phosphorus ($p = 0.029$, CI; -292.4, -20.9) and 88.6mg (2.3mmoles) less potassium ($p = 0.41$. CI; -327.6, 150.3) on the modified diet (Figure 4-2). On the modified diet participants consumed 7.0 g more fibre ($p < 0.001$, CI; 5.8, 8.2).

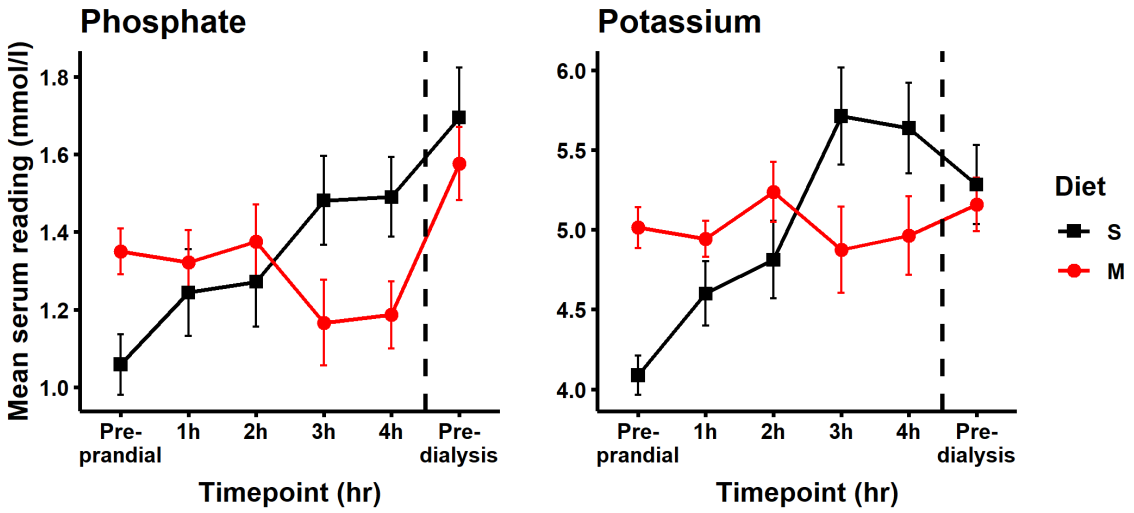
Figure 4-2 Protein, Phosphorus and Potassium Intake



Main meal dietary intake of both prescribed and consumed diet components. (A) protein, (B) phosphorus and (C) potassium of each individual is given. Participants are identified by symbols on both the standard and modified diet. Overall, participants consumed less than prescribed

Serum phosphate was reduced in participants while following a low phosphorus modified diet. The four hourly measurements of serum phosphate post-meal describe an elevation in serum phosphate following consumption of the standard diet and an overall decrease in serum phosphate following consumption of modified diet (Figure 4-3).

Figure 4-3 Serum Phosphate and Potassium Levels.



Participants on modified diet M (red line with circle) exhibited elevated levels of pre-prandial serum phosphate initially. Thereafter, serum readings for participants on standard diet S (black line with square) increased steadily over time and remained elevated the following day. This contrasted with an overall decrease in serum phosphate following consumption of the main meal. Points represent the mean ± SD.

The pre-prandial time point data indicated that those participants assigned to the modified diet had a mean starting phosphate serum reading of 0.291 mmol/L higher than those on standard diet (Table 4-2 and Figure 4-3), 95% CI: 0.026, 0.556).

Table 4-2 Mixed Effects Model Output of Serum Phosphate

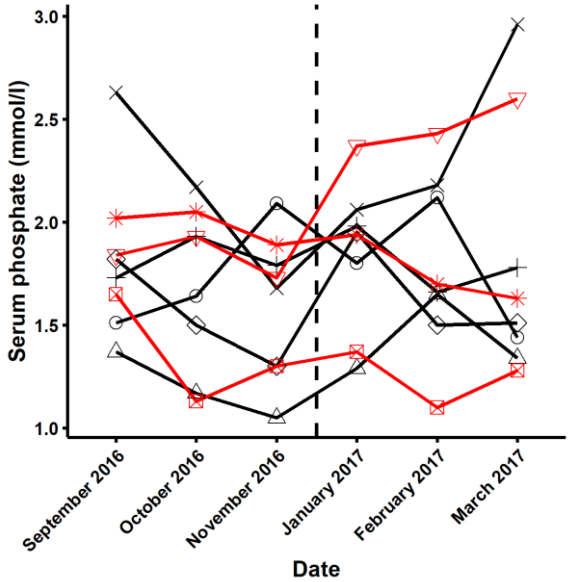
Time point	Mean mmol/L	Std	p-value	95% Confidence Interval	
				Lower	Upper
Pre-prandial	0.291	0.101	**0.023**	0.026	0.556
1 h	0.078	0.101	0.970	-0.187	0.342
2 h	0.104	0.101	0.885	-0.161	0.369
3 h	-0.315	0.101	**0.010**	-0.580	-0.050
4 h	-0.304	0.101	**0.015**	-0.569	-0.039
Pre-dialysis	-0.104	0.104	0.901	-0.379	0.171

The mixed effect model describes the change in serum phosphate when switching from the standard to the modified diet. Fixed effects were diet and time point which included an interaction term, with patient included as a random effect.

Similar between group differences, were seen in the fasting samples taken on arrival. The mean change in serum phosphate from pre prandial levels was smaller at all 4 time points on the modified diet relative to the standard diet. Using a mixed effect model to describe the change in serum phosphate when switching from the standard to the modified diet, we observed significant mean reductions in serum phosphate at 3 hours, -0.32 mmol/L (95% CI: -0.58, -0.05), and at 4 hours, -0.30 mmol/L (95% CI -0.57, -0.04), Table 4-2.

To further evaluate the differences seen in pre-prandial baseline phosphate levels between the modified vs. the standard diet, we examined the pre-dialysis phosphate levels measured in routine testing in the 3 months prior to and following the study in a *post hoc* analysis. These measurements showed substantial within subject variability (Figure 4-4) and were compatible with the differences in baseline values seen within participants in the study.

Figure 4-4 Within Person Variability in Pre-Dialysis Serum Phosphate



This figure describes the variability, in the 3 months before and after the study in the 3 participants who started with the standard diet (black line) and the 5 participants starting with the modified diet (red line).

The mean (SD) pre and post study, routinely measured serum phosphate levels were similar in those assigned initially to standard diet (1.75 ± 0.42 mmol/L, range 1.05 – 2.96) versus modified diet (1.78 ± 0.44 mmol/L, range 1.10 – 2.60) respectively, in keeping with our interpretation that the differences in the point estimates of baseline serum phosphate were consistent with the inherent variability in serum phosphate.

When switching from the standard to the modified diet, serum potassium decreased by -0.84 mmol/L (95% CI: -1.41, -0.27) and -0.68 mmol/L (95% CI -1.25, -0.103), at the three and four hour post-meal time points, respectively (Table 4-3 and Fig. 4-3).

Table 4-3 Mixed Effects Model Output of Serum Potassium

Time point	Mean mmol/L	Std	p-value	95% Confidence Interval	
				Lower	Upper
Pre-prandial	0.975	0.226	**0.001**	0.381	1.569
1 h	0.363	0.226	0.494	-0.230	0.957
2 h	0.425	0.217	0.268	-0.147	0.997
3 h	-0.838	0.217	**0.001**	-1.410	-0.265
4 h	-0.675	0.217	**0.011**	-1.247	-0.103
Pre-dialysis	-0.098	0.243	0.999	-0.737	0.540

The mixed effect model describes the change in serum potassium when switching from the standard to the modified diet. Fixed effects were diet and time point which included an interaction term, with patient included as a random effect.

While dietary potassium intakes were similar, serum potassium was stable or reduced following consumption of the modified meal and steadily increased for 3 hours after consumption of the standard meal (Figure 4-3). Nine samples were recorded with serum potassium > 6.0 mmol/L and were classified as hyperkalaemic. Of these, eight were from participants while on the standard diet (Figure 4-5).

Figure 4-5 Serum Potassium

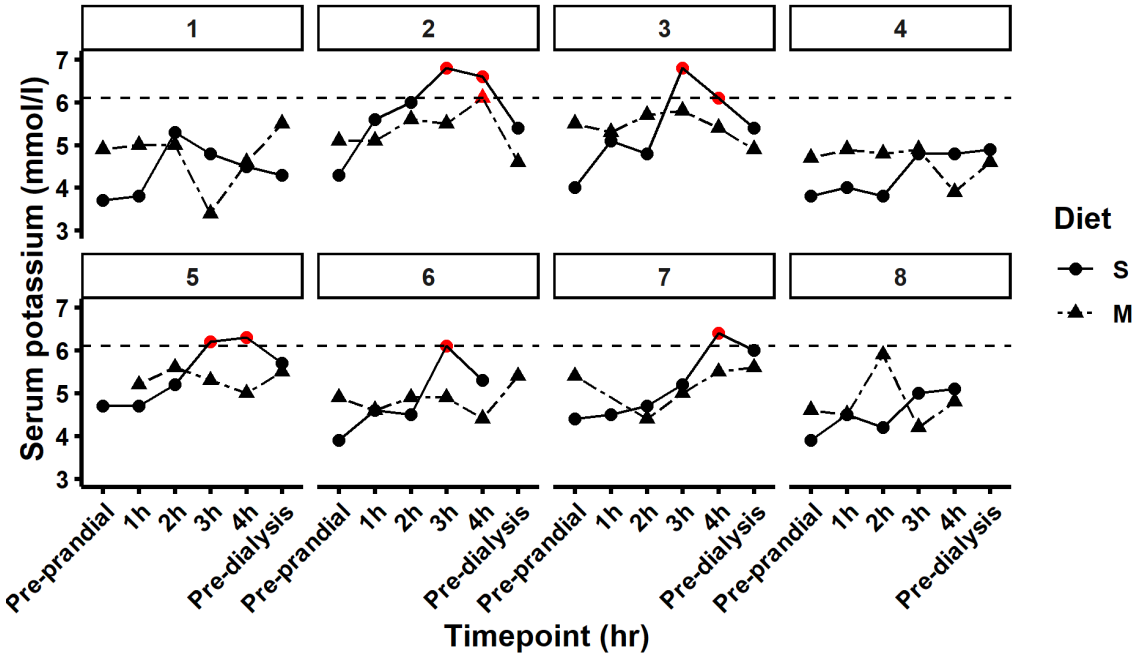
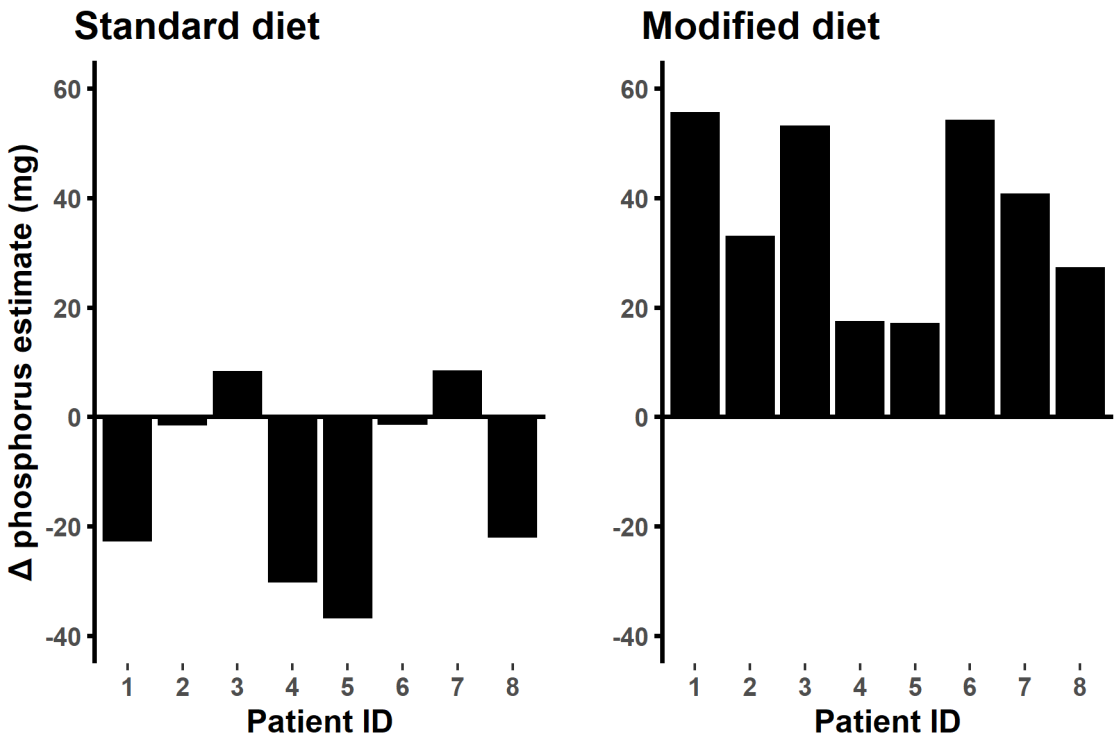


Figure 4-5 maps serum potassium on each diet standard (s) and modified (M) at 6 time points pre-prandial, 1, 2, 3 and 4 hours after the meal and pre dialysis the following day. Five participants had a potassium reading of > 6.0 mmol/L (dashed line) during the study timeframe. Eight of the nine elevated readings were recorded in the standard diet cycle of the study.

This hyperkalaemia was transient with no participant remaining hyperkalaemic the following day pre dialysis. The small sample size and high variability in iPTH analysis, made it impossible to interpret the data.

The food composition tables provided a similar estimate of phosphorus content from standard diet food samples whereas the food composition tables overestimated phosphorus by 37 mg/ day for modified diet food samples ($p < 0.001$, 95% CI 24,51) (Figure 4-6).

Figure 4-6 Laboratory Analysis versus Food Composition Table Estimates



This figure shows the difference in food composition table reading minus public lab reading. On the standard diet the food tables estimate of daily intake were similar to the laboratory analysis (p= 0.148) while on the modified diet the food table overestimated the phosphorus content by 37.4mg/day (p= 0.008)

4.4 Discussion

Dietary intake of phosphorus was lower on the modified diet, while dietary potassium and protein intakes were similar on both diets. Both serum phosphate and serum potassium were reduced at 3 and 4 hours on the modified as compared to the standard low phosphorus diet. A possible explanation might be that the food matrix reduced absorption.[109,248]

The observed lower serum phosphate is consistent with the decreased dietary phosphorus intake consumed with the modified diet, due to food choices with

lower phosphorus to protein ratios and the likely lower bioavailability of phosphorus from the phytate sources of pulses and nuts. Physiologically serum phosphate has a circadian pattern[233-237] although the responsible mechanisms are poorly understood.[249] However circadian patterns were controlled for during our study, as food was served at the same time on each trial day.

Although debated there is evidence that phosphorus load influences serum phosphate levels. We demonstrated that natural, solid food can affect phosphate in the postprandial phase. Preliminary experiments by Brown *et al* with solid meals failed to result in significant increases in serum phosphate, however when a drink with a phosphorus supplement was used , serum phosphate was significantly increased at 2 and 4 hours (n=8).[241] However, in a feeding study on 30 HD patients, a meal containing 1g calcium and 2g phosphorus as a phosphorus supplement, did not increase postprandial serum phosphate.[240] Our results support the finding by Ix et al[235] in 11 CKD patients that solid food can affect serum phosphate. While Ix *et al* varied protein to achieve a difference in dietary phosphorus intake we maintained similar protein intakes in both groups and still demonstrated a difference in serum phosphate.

Our study focused on the effect of diet on postprandial serum phosphate. The relationship between diet and phosphorus intake and serum phosphate levels is complex and the relative clinical or prognostic importance of fasting versus postprandial serum phosphate is not clear. In healthy populations dietary phosphorus load causes serum phosphate to rise [74,236,238,239,250] but does not affect subsequent fasting levels.[77,236] While fasting serum phosphate levels are a poor indicator of phosphorus load in CKD[235] fasting levels may be a more reliable

predictor of mortality.[251,252] Potential mechanisms of harm have been identified for both non-fasting and fasting serum phosphates. A phosphorus load that induces postprandial hyperphosphataemia impairs endothelial function,[238,239] while a phosphorus load sufficient to rise subsequent fasting phosphate, significantly increases blood pressure and pulse.[253] While experts suggest research efforts should be focused on altering fasting levels which may be most harmful[162], there is still merit in focusing on postprandial measures where effects of diet are more evident.[235]

Despite similar dietary potassium intakes on the standard and modified diet, serum potassium were reduced at 3 and 4 hours post-meal consumption in participants who consumed our modified low phosphorus diet compared with the standard diet. This suggests that the food matrix of the modified diet foods may also reduce the absorption of potassium. We also observed a transient hyperkalaemia in five participants on the standard diet during the postprandial period that had resolved by the time a pre dialysis sample was taken the following day (Figure 4-5). This is of significance as we rarely check postprandial potassium levels and might underestimate the magnitude of the postprandial spike. This result also indicates that caution may be required in permitting patients to save their dietary allowances for one meal, as with special occasions, and it may be more prudent to spread allowances over the day, from both a protein utilisation and potassium load safety viewpoint.[176]

In our study, the food composition tables overestimated the phosphorus content of the modified diet in comparison to direct analysis and similarly estimated the phosphorus content of the standard diet (Figure 4-6). This conflicts with widespread

concerns among renal health care professionals that food composition tables underestimate the phosphorus content of foods. This may be partially explained by the fact that most of the food consumed in our study was fresh and unprocessed and the concern from renal healthcare professionals is largely focused on processed foods. Whilst the food composition tables are regularly updated, we should be mindful of their limitations as eloquently described by the creators of the UK Food Composition Tables "There are two schools of thought about food tables. One tends to regard the figures in them as having the accuracy of atomic weight determinations; the other dismisses them as valueless on the ground that a foodstuff may be so modified by the soil, the season or its rate of growth that no figure can be a reliable guide to its composition. The truth, of course, lies somewhere between these two points of view".[254] The limitations of the current UK dataset as it relates to phosphorus, such as the use of composite samples, are described by Hannah *et al.*[255] In keeping with a study by Tsai *et al* [173] our results, provide reassurance regarding the reasonable reliability and accuracy of food composition tables, especially with regard to unprocessed foods.

There were some limitations to our study including a small sample size. There was unexpected pronounced difference between the baseline pre-prandial phosphate levels between the modified and the standard diet, a substantial concern in any crossover design. Serum phosphate levels are challenging to interpret.[14] Levels are affected by many factors including circadian rhythm[233-237] and food intake,[235] however these were controlled for in the study. The differences may have occurred simply due to sampling variability given the small sample size and substantial variability in the within subject serum phosphate level, which we demonstrate in a

post hoc review of the routine dialysis bloods of the study participants before and after the study (Figure 4) and as reported by other studies.[256,257] However this variability should not substantially impact on the additional effect of diet relative to the measured baseline, especially in the setting of a short term follow-up of serum phosphate levels in the immediate postprandial hours, conducted in a controlled environment, where the food, timing of food, biochemical assays and medications were all strictly controlled.

Conclusion Our understanding of gastrointestinal absorption of phosphorus is surprisingly limited and requires further investigation. On the modified diet, the serum potassium and phosphate levels were significantly lower at 3 and 4 hours postprandial. This feeding study supports the postprandial safety and tolerability of the modified versus the standard diet, allowing for further evaluation of the modified diet in an appropriately monitored, longer duration, randomised controlled trial (Clinicaltrial.gov : NCT03146923).

My Contribution: I developed the research idea, proposal, study design and protocol, under the supervision of my PhD Supervisors and with clinical opinion from Barbara Gillman. I recruited and consented all participants, and was responsible for the acquisition of all data. I developed the research questions. I completed and quality controlled the database and worked closely with Brendan Palmer Statistician in the analysis and interpretation of data. I wrote the scientific papers with each author contributing to the review process.

Chapter 5: Multicentre Randomized Controlled Trial

A Randomized Controlled Trial of a Standard versus a Modified Low Phosphorus Diet in Irish Hemodialysis Patients

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This paper was submitted to Clinical Journal of the American Society of Nephrology, a US journal on 17-12-19. Therefore US spelling was used, and the units for phosphate used were mg/dl. To convert mg/dl phosphate to mmol/L multiply by 3.097.

Abstract

Background and objectives: The standard low phosphorus diet restricts foods such as pulses, nuts and whole grains to control hyperphosphataemia. These foods are also rich in phytate, which binds dietary phosphorus, reducing its absorption. Based on clinical experience and evidence, we developed a modified low phosphorus diet. The modified diet introduced some pulses and nuts, increased the use of whole grains, increased focus on the avoidance of phosphate additives and introduced the prescription of low biological value protein such as bread. We conducted a randomized controlled trial to evaluate the effectiveness, safety and tolerability of the modified diet.

Design, setting, participants and measurements: Multicentre, pragmatic, parallel arm, open label, randomized controlled trial of modified vs. standard diet in 74 adults on hemodialysis with hyperphosphataemia over 1 month. Participants were re-educated on the standard diet or educated on the modified diet by a renal dietitian. Biochemistry was assessed using routine monthly labs. Dietary intake was assessed using a 2 day weighed intake of food and tolerability was assessed using a patient questionnaire.

Results: There was no significant difference in the change in serum phosphate between the standard and modified diets. While total dietary phosphorus intake was similar, phytate bound phosphorus, found in pulses, nuts and whole grains, was significantly higher in the modified diet ($p<0.001$). Dietary fiber intake was also significantly higher ($p<0.003$), as was the percentage of patients reporting an increase in bowel movements while following the modified diet ($p=0.008$). There

was no significant difference in the change in serum potassium or in reported protein intake between the two diets. Both diets were similarly well tolerated.

Conclusions: The modified low phosphorus diet was well tolerated and was associated with similar phosphate and potassium control but with a wider food choice and greater fiber intake than the standard diet.

5.1 Introduction

Hyperphosphataemia is common in end stage kidney disease (ESKD) and is associated with excess morbidity and mortality. Dietary phosphorus restriction is recommended to control hyperphosphataemia.[49,161] Traditionally total phosphorus intake is reduced by moderating protein intake, by restricting food with a high phosphorus content (e.g. dairy, whole grains, pulses and nuts) and by avoiding phosphate additives.

Emerging opinion supports the introduction of more plant protein in the form of whole grains, pulses and nuts where the phosphorus is largely bound by phytate and therefore not as available for absorption.[47,48,177,180,192,258] Avoidance of additives has been shown to improve phosphate control.[73] As there is a strong linear relationship between dietary protein and phosphorus intakes,[137] prescription of protein is essential. This is both to ensure increased protein needs are met, but also to avoid over-consumption of protein which carries an obligatory phosphorus load. It should be possible to ensure adequate protein intake whilst restricting phosphorus.[46]

Based on this emerging evidence, we revised the Irish national low phosphorus diet sheet. We conducted a multicentre, pragmatic, parallel arm, open label, randomized controlled trial (RCT) of the efficacy, safety and tolerability of the modified diet in order to guide implementation.

The primary study objective was to determine if the modified low phosphorus diet was comparable to current management in reducing serum phosphate levels in hemodialysis (HD) patients. The secondary objectives were to determine self-reported tolerability, safety in respect of hyperkalaemia and the nutritional

composition, specifically the phosphorus, the phytate bound phosphorus and fiber content of the modified diet.

5.2 Methods.

The protocol for this national, multicentre, pragmatic, parallel arm, open label RCT was developed according to the SPIRIT statement[259] and in accordance with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov: NCT03146923. Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals ECM 4(I) 10/01/17 and at each center where the trial took place. All participants provided written informed consent.

Practising clinical dietitians from all dialysis units in Ireland, were invited to participate in the trial. 15 dietitians from nine university hospital dialysis units and four satellite dialysis units agreed to participate. Training, including Good Clinical Practice, general research training and methodology specific to the trial, was provided at a two day training programme held by the Health Research Board Clinical Research Facility Cork (HRB CRF-C) at University College Cork in January 2017.

Inclusion criteria were: ≥18 years; a self-reported urine output less than 400 ml per day; treatment with hemodialysis for greater than 3 months and an average serum phosphate >5mg/dl over the last 3 months. Exclusion criteria were hyperkalemia (pre dialysis serum potassium of >6 mEq/l in the month preceding the trial); parathyroidectomy, an abnormal corrected serum calcium in the preceding month and acute concurrent illness, requiring hospitalisation in the two weeks prior to

recruitment. Patients with abnormal serum corrected calcium were also excluded as this may have warranted intervention during the trial.

All participants were receiving standard care which involved one-to-one counselling with the patient and his/her relevant family members or carers regarding a diet which provides approximately 1000 mg phosphorus per day and is based on the national diet sheet 'Eating Well with Kidney Disease'.[244] It includes the following main components: Restricting protein intake to requirements of 1-1.2g/kg Ideal Body Weight (IBW); aiming for 70% high biological value (HBV); restricting dairy intake (1-1.5 portions per day equivalent to 200-300 ml milk); avoiding foods high in phosphate and avoiding foods with phosphate additives.

Table 5-1 summarises the main changes made to the modified diet. We attempted to blind patients, by avoiding the use of terminology such as old and new and by retyping the standard diet sheet to match the font, layout and introduction of the modified diet sheet. Both diet sheets were approved by the National Adult Literacy Agency (NALA).

From one week before the trial began, relevant medications, dialysis times or dialysate were not changed unless approved by the nephrologists. Following randomization and baseline bloods, patients randomized to standard care were re-educated regarding their diet and provided with the standard diet sheet. Patients following the modified diet were educated and provided with their diet sheet, product samples of pulses and nuts, a recipe booklet, and a shopping card of phosphate additives to look out for.

Table 5-1 Summary of Changes in Modified Diet Sheet

Nutrient based Recommendations	Food based Recommendations
Inclusion of foods with reduced phosphorus bioavailability due to phytate content.	Two of the daily allowances of high biologic al value (HBV) protein exchanges (7g protein/ exchange) are replaced with plant based vegetarian protein exchanges e.g. replace 2 oz meat with 4 oz pulses and 1oz unsalted peanuts. Whole grain breads & cereals are encouraged
Focus on more accurate protein prescription of 1.1g protein/ kg IBW thus avoiding over prescription of protein which carries an obligatory protein load and include some focus on phosphorus to protein ratio.	Bread cereals and potatoes have been included in prescribed daily protein allowances Target % protein from high biologic al value (HBV), changed from 70% to 50-70% Fish has been reduced to 1oz (25g) fish per 7g protein exchange Two portions fruit & two portions of vegetable were counted as 4g protein Phosphorus to Protein ratio Beef has lowest P: Protein ratio 7mg/g with oily fish having the highest ratio 11mg/g however consensus reached was not to focus on the ratio in this food group and to broadly follow healthy eating guidelines and to encourage variety including fish twice a week. Dairy products are restricted to 1 portion per day P: Protein ratio 20-30mg/g Egg white which have an extremely low ratio 1.1mg P/g protein are included
Full avoidance of phosphate additives from the European Union list of authorised phosphate additives in foods.	Check for Phosphate E numbers E338, E339,E340, E341, E343, E450, E451, E452 and E541. We also advised to check for “phos” on ingredient lists giving examples we commonly encountered on labels such as diphosphate, sodium polyphosphate, calcium triphosphate.

Both groups were given weighing scales to help with portion control, especially for high protein foods such as meat and fish.

The trial started with the education of the participants on their assigned diet, following their routine monthly dialysis laboratory tests, which served as baseline bloods, and ended at the following month's routine set of laboratory tests which served as the end of intervention bloods. In units that had access to a suitable freezer, an additional sample was taken to assess C-terminal FGF23.

In the days leading up to the end of intervention bloods, patients kept a two day weighed intake, including one dialysis and one non dialysis day to assess dietary changes. The days were non-consecutive days. Participants were educated on how to do the weighed intake and were asked to collect labels so that the researcher could more accurately capture foods that had phosphate additives. If the weight of the food was not available, we used the hierarchical approach to quantification, previously described.[260] Nutrient analysis was carried out using Nutritics Software.[245] A bespoke additional data field was added to the software to allow the dietitian to tag foods with a significant phytate content including pulses, nuts and wholemeal / wholegrain breads, cereals, pasta and rice. Foods identified as having a phosphate additive were also marked on data entry using a second added field. Nutritics contains multiple nutrient databases, however we restricted the databases used to McCance and Widdowson's composition of foods integrated dataset,[149] the USDA Food Composition Databases[261] and the Irish food composition databases.[262]

To standardise food coding practise and data entry, the coordinating centre provided units with a list of standard food codes for foods generated from the diet sheets, and for any new recipes or new food codes required. Food code queries

were answered by the co-ordinating center, collated and shared with all centers. Participants were also asked to complete a tolerance questionnaire. When the trial concluded, each patient was advised to go back to following the standard diet. There are no core outcome sets for ESKD. Based on prior trials,[73] and audit of phosphate data, it was calculated that we would require a total of 56 participants in each arm, using an independent sample t-test with a 1:1 allocation ratio and a 2-sided type I error of 0.05 and a power of 90% and an effect size of 0.73. Power remained at 80% even with 64 analysable participants (32 in each arm), all else being equal.

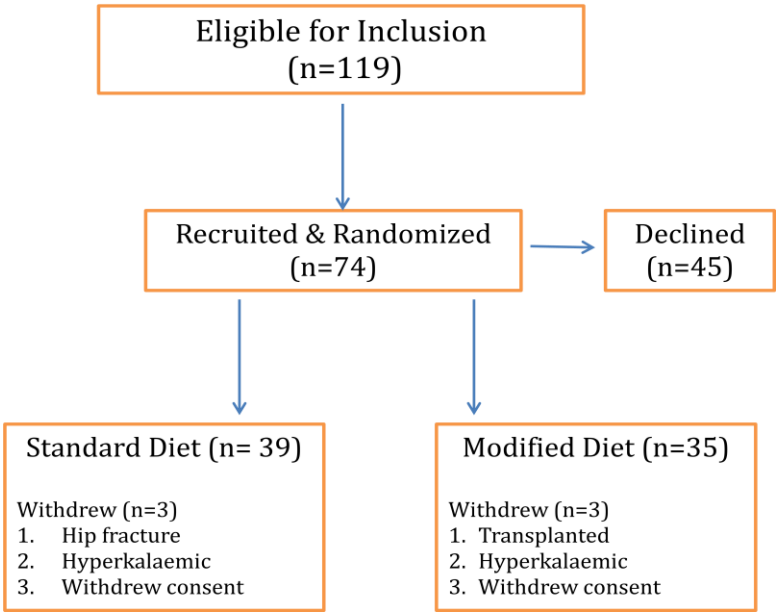
The specific randomization list was designed by an independent trial statistician and participants were randomly assigned to either the control or intervention group with a 1:1 allocation as per a computer generated randomization schedule, stratified by site and by baseline phosphate using permuted blocks of random sizes and allocated using a sequentially numbered, opaque, sealed envelope approach. The block sizes were not disclosed, to ensure concealment. The allocation of patients to treatment arms was revealed after the patient was consented. Patients were withdrawn from the study if they had a confirmed serum potassium of ≥6.3 mEq/L. Statistical analysis was performed by staff at the HRB CRF-C. When describing the demographics, categorical data were described as counts and percentages, and continuous variables were summarized using medians and min/max values. The study outcomes were explored using simple or multiple linear regression. We report estimates, 95% CI, and the corresponding p-values. Analysis of categorical patient survey data was performed using a Fisher Exact test. Analyses were done on an intention-to-treat (ITT) basis. All analyses were conducted using

the R Project for Statistical Computing version 3.6. The analysis code and standard operating procedure for the trial will be made available online at https://zenodo.org/.

5.3 Results

Figure 5-1 describes the study flow. Of the 74 participants recruited, 52 participants were recruited in March 2017 and 22 were recruited in May 2017. 39 were randomized to the standard arm and 35 to the modified diet arm. The data presented is the ITT analysis of all patients excluding instances where an endpoint sample where not recorded.

Figure 5-1 Flow Diagram



This flow diagram shows recruitment process (Inclusion, recruitment and randomization of study participants)

Table 5-2 summarises the baseline charateristic of the trial population. The study population was 69% male and predominanately caucasian. There were more patients with diabetes randomized to the modified arm (n=17) than to the standard arm (n=10).

Table 5-2 Demographics and Medications

Variable	Standard diet (n = 39)			Modified diet (n = 35)		
	n (%)	median	min - max	n (%)	median	min - max
Male	26 (66.7%)			25 (71.4%)		
Caucasian	38 (97.4%)			33 (94.3%)		
Diabetes as a comorbidity	10 (25.6%)			17 (48.6%)		
Diabetes as a cause of ESKD	8 (20.5%)			14 (40%)		
Age (y)		59.9	(28.7, 88.3)		61.0	(29.3, 84.9)
Baseline dry weight (kg)		81.5	(57.5, 149.1)		80.0	(49, 132)
End of intervention dry weight (kg)		80.9	(58, 150)		79.8	(49, 134)
Height (m)		1.70	(1.51, 1.86)		1.67	(1.47, 1.87)
BMI (kg/m2)		28.4	(21.8, 48.9)		27.7	(17.9, 48.4)
IBW (kg)		71.2	(57.3, 86.2)		67.7	(49, 83.7)
Recommended protein intake 1.1 g/kg IBW		78.3	(63, 94.8)		74.5	(53.9, 92.1)
Baseline serum phosphate (mg/dL)		5.92	(3.53, 12.1)		6.13	(3.90, 10.2)
Medications[a, b]						
Vitamin D native IU	11 (28%)	800	(343, 7142.9)	10 (29%)	800	(200, 5714)
Alfacalcidol (mg)	23 (59%)	0.5	(0.11, 1.0)	20 (57%)	0.37	(0.25, 1.0)
Paricalcitol oral (mg)	4 (10%)	2	(1.43, 4)	7 (20%)	1.71	(1, 2)
Paricalcitol IV (mg)	3 (8%)	1.07	(0.86, 2.14)	1 (3%)	2.14	NA[c]
Calcitriol (mg)	0 (0%)	NA	NA	1 (3%)	12.5	NA
Cinacalcet (mg)	5 (13%)	60	(30, 120)	6 (17%)	60	(30, 120)

Table 5-2. Demographics and Medications continued

Variable	Standard diet (n = 39)			Modified diet (n = 35)		
	n (%)	**median**	**min - max**	**n (%)**	**median**	**min - max**
Cinacalcet (mg)	5 (13%)	60	(30, 120)	6 (17%)	60	(30, 120)
Binders[a, b]						
Sevelamer carbonate (mg)	14 (36%)	7200	(800, 9600)	12 (35%)	4800	(1600, 14400)
Sevelamer hydrochloride (mg)	9 (23%)	4800	(1600, 7200)	8 (24%)	4800	(2400, 7200)
Calcium carbonate (mg)	4 (10%)	1500	(1250, 3000)	1 (3%)	1500	(1500, 1500)
Calcium acetate (mg)	12 (31%)	2500	(1000, 4000)	13 (38%)	3000	(1000, 3000)
Calcium acetate Magnesium carbonate (mg)	1 (3%)	870	NA	0 (0%)	NA	
Lanthanum carbonate (mg)	4 (10%)	2625	(1500, 4000)	2 (6%)	3500	(3000, 4000)
Sucroferric oxyhydroxide	3 (8%)	1500	(3, 1500)	5 (15%)	1500	(1500, 1500)
Alucaps (mg)	1 (3%)	1425	NA	0 (0%)	NA	

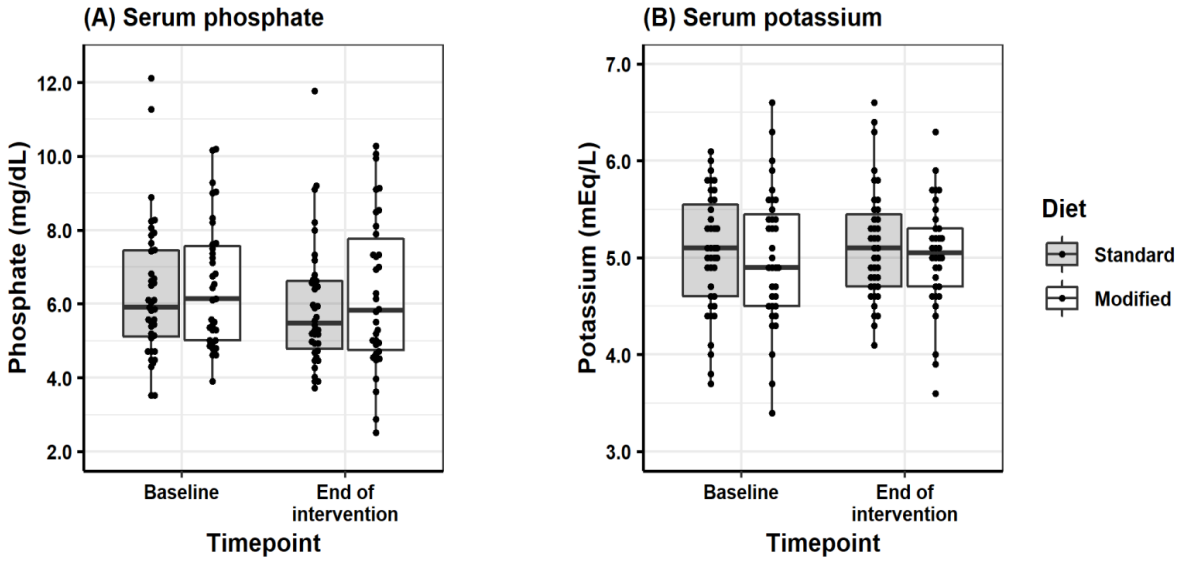
[a] Number of patients on the medication/binder by trial arm

[b] Median intake of those patients on the medication/binder by trial arm with associated minimum and maximum amounts

IBW Ideal Body Weight NA - Not Applicable

Table 5-3 describes the pre specified trial outcome measures. There was no significant difference in serum phosphate or serum potassium after 1 month between the standard and modified diets (table 5-3 and figure 5-2).

Figure 5-2 Serum Phosphate and Potassium

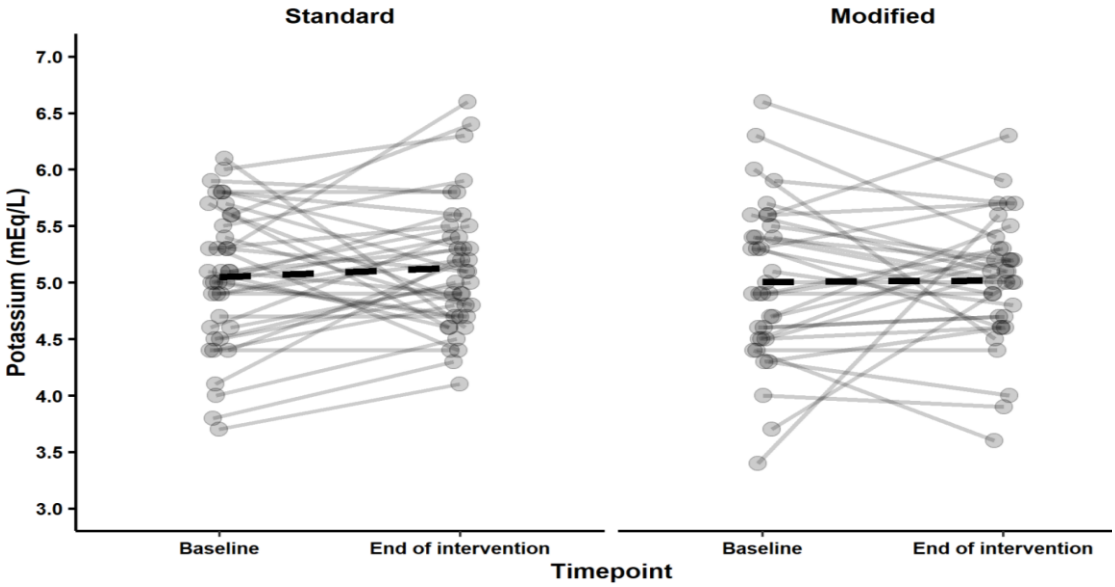


Box plot A shows serum phosphate at 2 time points baseline and end of intervention with the standard diet shaded and the modified diet in white. The box represents the interquartile range with the thick line in the box representing median values. In both arms of the trial (standard and modified) there was a small decrease in serum phosphate likely reflecting education, however no statistically significant differences were observed for the primary outcome of serum phosphate and potassium between standard and modified diet. A similar pattern was seen for potassium.

Significant variability in serum potassium was observed in both groups as demonstrated in figure 5-3. One patient from either arm was withdrawn due to hyperkalaemia; withdrawal of the participant assigned to the modified diet, occurred at the baseline tests stage, prior to the education step and initiation of the modified diet. On the standard diet arm there were 3 deviations, one change to

medication, one change to dialysis times and a new catheter. On the modified arm, there were also 3 deviations, one change to medication, one change to dialysis times and one change of dialysate.

Figure 5-3 Serum Potassium



Each figure draws a line for each subject from baseline potassium to end of intervention potassium, firstly for the standard diet and then for the modified diet. At an individual level there was significant variability in serum potassium in both arms of the trial

Table 5-4 describes mean dietary intake on the dialysis day and the non dialysis day as assessed by the two day weighed intake record at the end of the intervention period.

Table 5-3 Main Study Outcomes

Variable	n[a]		Change from baseline		Analyses to determine the impact of diet[b]			
	Standard	Modified	Standard	Modified	Estimate[c]	p-value	95% CI	
Primary outcome								
Serum phosphate (mg/dl), mean (SD)	38	34	-0.336 (1.536)	-0.295 (1.456)	0.133	0.69	-0.537	0.803
Secondary outcomes								
Total phosphorus intake (mg), mean (SD)	30	30	NA[d]	NA	77.5	0.343	-84.7	239.7
Phytate-bound phosphorus intake (mg), mean (SD)	30	30	NA	NA	207.8	< 0.001	130.4	285.2
Fibre intake (g), mean (SD)	30	30	NA	NA	4.65	< 0.003	1.68	7.61
Intact PTH (pg/ml), median (IQR)[e]	35	31	-3.9 (20.7)	-0.7 (25.0)	0.995[f]	0.968	0.780	1.270
Exploratory Endpoint								
C-terminal FGF23 RU/ml, median (IQR)[e]	15	12	-50 (4065)	-105 (2570)	0.98[f]	0.912	0.681	1.141
Safety Endpoints								
Serum Potassium (mEq/L), mean (SD)	39	34	0.08 (0.60)	0.01 (0.69)	-0.097	0.422	-0.335	0.142

[a]Number of complete data points available for analysis

[b]Serum phosphate and serum potassium were described by multiple linear regression of endpoint explained by covariates of baseline and diet. Intact PTH and FGF23 were described by multiple linear regression of log(endpoint) explained by covariates of log(baseline) and diet. Total phosphorus intake, phytate-bound intake and fibre intake were described by simple linear regression of intake explained by diet.

[c]The standard diet was set as the reference level for all linear models

[d]Not applicable

[e]Variables intact PTH and FGF23 displayed non-parametric distributions

[f]For log-log transformations, the estimated effect of a change in diet, from standard to modified, is to change intact PTH by a factor of 0.995 and FGF23 by a factor of 0.98, respectively

SD standard deviation; CI Confidence Interval; PTH parathyroid hormone; FGF fibroblast growth factor

Table 5-4 Dietary Outcome Data from End of Trial Food Diaries

Variable	Standard diet (n= 30) Mean ± SD (min, max)		Modified diet (n= 30) Mean ± SD (min, max)		p-value
Dialysis Day					
Energy (kcal)	1620.6 ± 561.4	(647.4, 3056.2)	1451.8 ± 379	(720.3, 2297.6)	0.18
Fiber (g)	14.6 ± 5.9	(3.9, 25.5)	19.2 ± 6.6	(7.1, 34.7)	< 0.01
Sodium (mg)	1759.5 ± 747.1	(647.4, 3399.1)	1461 ± 661	(404.5, 3433.7)	0.11
Potassium (mg)	1834.9 ± 665.6	(426, 3129.6)	1934.7 ± 700	(797, 3637.8)	0.57
Phosphorus (mg)	1012.1 ± 330.6	(207.9, 1584.9)	1038.3 ± 337.9	(391.2, 1887)	0.76
Recommended protein intake (1.1g/kg IBW) [a]	78.7 ± 7.57	(63, 94.8)	74.26 ± 10.72	(53.9, 92.1)	0.07
Recorded protein intake (g) [b]	71.38 ± 26.44	(14.5, 120.4)	65.79 ± 22.72	(19.3, 118.1)	0.38
ΔProtein (g)	-7.31 ± 22.9	(-63.0 - 33.7)	-8.48 ± 19.2	(-49.0 - 49.3)	0.83
Potential Renal Acid Load (mEq)	20.4 ± 13.7	(-18.7, 43.8)	16.7 ± 12.6	(-9.09, 53.2)	0.27
Non Dialysis Day					
Energy (kcal)	1432.4 ± 534.8	(526.5, 2615.3)	1388.7 ± 443.2	(744.9, 2300.6)	0.73
Fibre (g)	13.5 ± 6.1	(4.3, 32.4)	18.3 ± 6.1	(5.7, 31.1)	< 0.01
Sodium (mg)	1454.8 ± 731.6	(260.3, 4107.2)	1285.5 ± 681.1	(524, 3526)	0.36
Potassium (mg)	1813.5 ± 606.3	(686.2, 2800.5)	1923.8 ± 621.4	(1166.4, 3479.8)	0.49
Phosphorus (mg)	862.3 ± 328.2	(159.6, 1484.5)	981.8 ± 387.6	(495.4, 2157.6)	0.2
Recommended protein intake (g/ kg IBW)	78.7 ± 7.57	(63, 94.8)	74.26 ± 10.72	(53.9, 92.1)	0.07
Recorded protein intake (g)	62.43 ± 24.27	(16.5, 120)	64.62 ± 21.16	(26.3, 110.8)	0.71
ΔProtein (g)[a]	-16.3 ± 22.3	(-61.0 - 35.8)	-9.64 ± 21.2	(-61.1 - 33.2)	0.24
Potential Renal Acid Load (mEq)	13.3 ± 15.1	(-17.4, 44.8)	15.3 ± 11.9	(-9.0, 54.5)	0.57

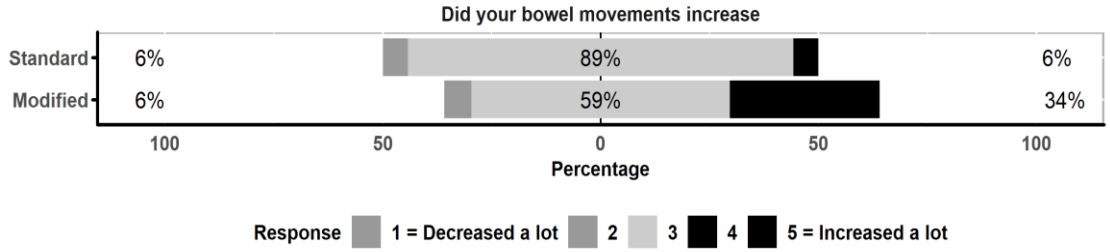
[a] IBW Ideal Body Weight: IBW = weight equivalent to BMI of 20 where BMI <20; IBW = actual body weight when BMI 20-25; IBW = weight equivalent to BMI of 25 where BMI >20. [b] Estimates are given in grams difference between recorded protein intake minus the recommended protein intake

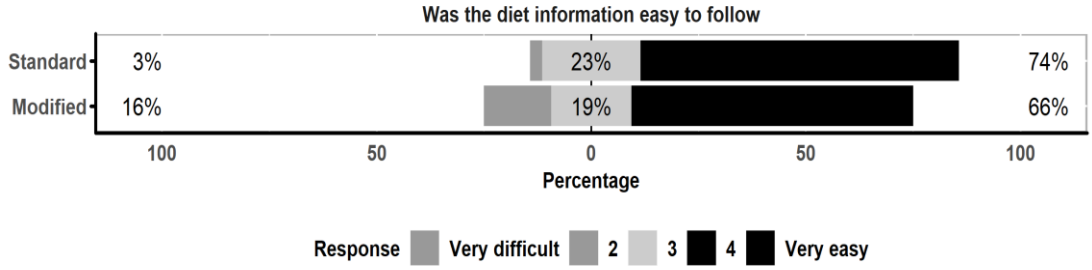
Nutrient intakes were not significantly different between the two groups with the exception of dietary fiber. While total dietary phosphorus was similar, there were significant differences between the standard and modified diets when we divided the food sources of dietary phosphorus into foods where phosphorus is or is not bound by phytate (Figure 5-4). Combining dialysis and non dialysis days, those following the modified diet consumed more fiber and phytate bound phosphorus than those assigned the standard diet: Mean = 4.65g (95%CI 1.68,7.61) $p<0.003$ and 208 mg (95% CI 130, 285), $p<0.001$, respectively.

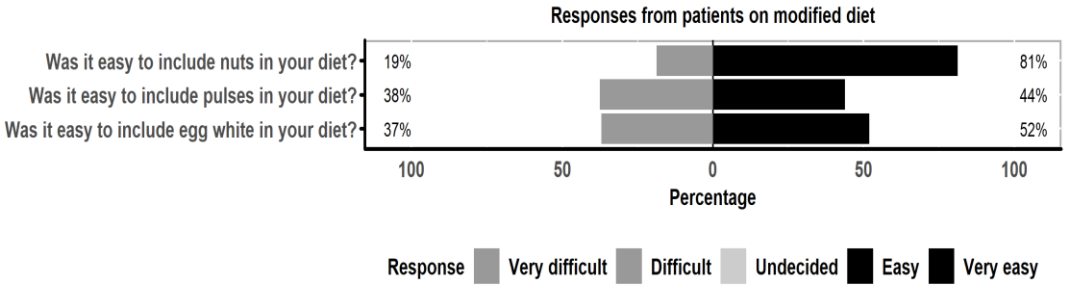
Reported protein intake was less than the target prescribed in both arms but was not significantly different between arms (Table 5-4). Mean (SD) reported energy intake (kcals) divided by the basal metabolic rate (BMR) calculated using the Schofield equation was 0.97 (0.32) and 0.86 (0.35) on the dialysis day and non dialysis day respectively in those following the standard diet. It was 0.88 (0.21) and 0.84 (0.25) on the dialysis day and non dialysis day respectively in those following the modified diet. There were no significant differences in weight or pre dialysis urea between the two groups. Overall 26 foods were consumed that contained phosphate additives in those following the standard diet (14 patients) compared with 22 entries for the modified diet (12 patients).

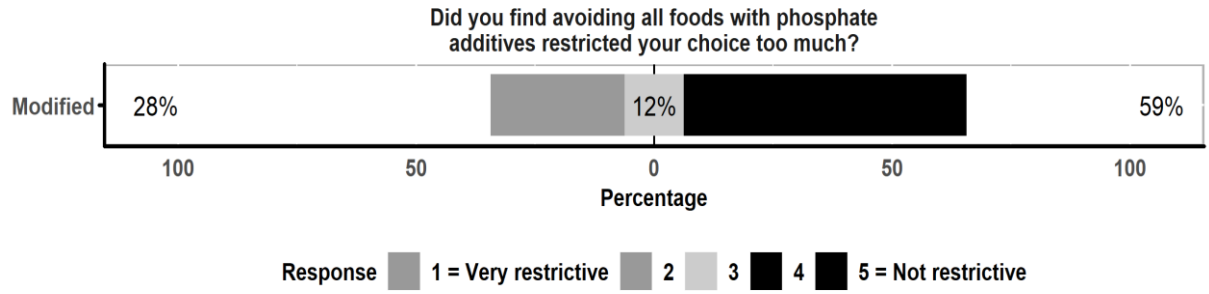
Seventy four percent of those following the standard diet and 66% following the new modified diet found the diet easy to follow ($p=0.5$). 6% of those following the standard diet and 34% following the modified diet reported an increase in bowel movements ($p=0.008$). On the modified diet, 81% of participants found it easy to include nuts, 44% found it easy to include pulses and 52% found it easy to include egg whites in their diets (Figure 5-4).

Figure 5-4 Tolerance









Participants following the modified diet were ask about the ease of including new foods such as nuts , pulses and egg white and about how restrictive avoiding all foods with additives and were asked to give a rating between 1-5.

5.4 Discussion

Controlling phosphate load remains the primary goal in the treatment of hyperphosphataemia.[31] In this study we tested a modified phosphorus diet. The recommended changes to the national diet sheet summarised in Table 5-1 were based on a review of the literature and expert consensus. Because of concerns re hyperkalaemia and dietary potassium intakes there was caution in the magnitude of change recommended e.g. we recommended a limited amount of pulses and nuts and chose those with the lowest potassium contents, using pulses canned in water.

Neither dietary phosphorus intake nor serum phosphate were significantly different between the modified and standard diets. A possible explanation for the unchanged serum phosphate is that the dietary change achieved, was not of sufficient magnitude to reduce serum phosphate in our study population. We had anticipated that total phosphorus intake would not change because, while avoiding excessive protein intake, avoiding additives and reducing phosphorus to protein ratios would reduce total phosphorus intake, changing to plant based proteins and choosing whole grains would increase total phosphorus intake. We were therefore dependent on reduced absorption from phytate bound phosphorus to effect a change on serum levels. On the dialysis day patients consumed on average 208mg more phytate bound phosphorus while following the modified diet. If we estimate a 30% lower absorption with phytate bound phosphorus[263] then those following the modified diet may have absorbed only 62mg less phosphorus. Secondly, the precision of these estimates are limited by the modest sample sizes especially given the marked variability in serum phosphate levels. Finally the blood samples were

taken at various time points during the day and included both fasting and non fasting samples, which may influence the serum phosphate level.[236,264] Future trials should consider a larger sample size with longer follow up and more uniform timing of samples.

While the mean dietary potassium intake was higher in those following the modified diet, the difference was not significant and comparable serum potassium control was maintained across the two groups. The risk of hyperkalaemia from increasing dietary potassium intake from whole grains and plant based protein in ESKD needs further investigation.

Protein intakes were lower than recommended, but may be in part explained by under-reporting. Such under-reporting, is common in dietary surveys[265-267] but is unlikely to be of a differential magnitude between our study arms. There are also concerns in the literature regarding the accuracy of phosphorus content in standard food tables, particularly in foods containing phosphate additives.[160,255] As the level of consumption of foods containing phosphate additives in this study was low overall, this may not be a significant limitation.

Fiber intakes were significantly increased in the modified diet, though still not sufficient to meet general population recommendations. The increase in fiber intake is supported by the observation that patient's bowel motions increased in those following the modified diet. This is clinically significant because constipation has been reported in up to 72% of dialysis patients.[268] An increase in fiber intake has also been shown to reduce levels of uremic toxins in CKD and ESKD.[214,216] Uremic toxins may contribute to poorer outcomes.[219-221,269] Although various interventions such as increasing fiber may alter the composition of intestinal

microbiota in CKD and ESKD and reduce uremic toxins, clinical benefit is not yet confirmed.[269]

In this study, patients were encouraged to swap two animal based protein exchanges such as a 2oz meat portion for two plant based protein exchanges such as 8oz of pulses. 2016 was declared the International Year of the Pulse to heighten public awareness of the nutritional benefits of pulses[270] and these benefits may extend to the CKD population.[153] Results from different studies seem to confirm a kidney-protective effect of plant-based diets[217,243,271] and recent reviews suggest that liberalizing the diet to allow plant foods may significantly improve the health and wellbeing of our CKD and ESKD patients.[177,272]

Fifty five percent of dialysis patients recall "feeling deprived with dietary restrictions".[163] This modified diet introduced pulses, peas and nuts and relaxed restrictions on whole grains. Increasing choice was a strong reason to guide adoption.

As renal health care professionals, our discussions have focused on nutrient based recommendations e.g. high protein, low phosphorus, low potassium, and low salt. The role of the renal dietitian has always been to translate multiple nutrient restrictions into individualized practical food based recommendations. The dietitian aims to achieve this within a balanced healthy diet, whilst maintaining quality of life. This is a complicated and evolving science and one that requires significant research.[175,176] In this trial, we tested food based recommendations, individualised to meet each patient's requirements. While the focus was only on phosphorus, all other nutrient restrictions were considered and incorporated into the prescribed diet.

Recently nutrition science, is moving towards dietary patterns or food based recommendations, with dietary patterns such as the Mediterranean diet and the New Nordic Diet gaining credence in people with kidney disease.[165,273] Instead of looking at individual nutrients or foods, dietary patterns describe the overall diet; the foods, food groups, and nutrients included; their combination and variety; and the frequency and quantity with which they are habitually consumed.[274] Dietary patterns examine the effects of overall diet and represent a broader picture of food and nutrient consumption, and may thus be more predictive of disease risk than individual foods or nutrients.[275] We eat food not nutrients and as demonstrated by dietary phosphorus that is phytate bound, the matrix that food is digested in has a huge bearing on absorption. Educating patients using dietary patterns such as the Mediterranean diet pyramid[165,276] may be an adequate dietary management strategy in the earlier stages of CKD, but in the later stages of CKD and ESKD, the prescribed dietary pattern will need to be more carefully individualised, due to concerns regarding intakes of specific nutrients, in particular, potassium and because of the need to individualise protein requirement based on the patient's stage of disease and treatment prescribed. The suggested changes, tested at trial, move our recommended renal diet closer to the Mediterranean dietary pattern while retaining the ability to individualise nutrient restrictions.

Clinical Practice Guidelines for Nutrition in CKD which is being jointly undertaken by KDOQI, in collaboration with the US Academy of Nutrition and Dietetics are due for publication in 2020. These nutrient based guidelines should be translated into food based recommendations like our individualised diet plan and tested in an RCT trial. Undertaking these trials is undoubtedly challenging[277] but absolutely essential and

necessary to demonstrate the effectiveness of dietary interventions and to improve dietary strategies in CKD and ESKD.[183] Research in dialysis patients is particularly important due to concerns re hyperkalaemia. While this advice may need to be used more cautiously in hyperkalemic patients, our study in a dialysis population, provides an important first step towards safely reducing restrictions and exploring the effect of a specific dietary pattern on biochemical parameters and tolerance.

My Contribution: I developed the research idea, proposal, study design and protocol and standard operating procedures, under the supervision of my PhD Supervisors and with clinical opinion from Barbara Gillman. I coordinated ethical approval application, training, data acquisition and quality control across all canters. I recruited and consented 9 participants. I completed and quality controlled the trial database, developed the research questions and worked closely with Brendan Palmer Statistician in the analysis and interpretation of data. I wrote the scientific papers with each author contributing to the review process. This paper was submitted to the Clinical Journal of the American Society of Nephrology on 17-12-19.

Chapter 6: Discussion & Conclusions

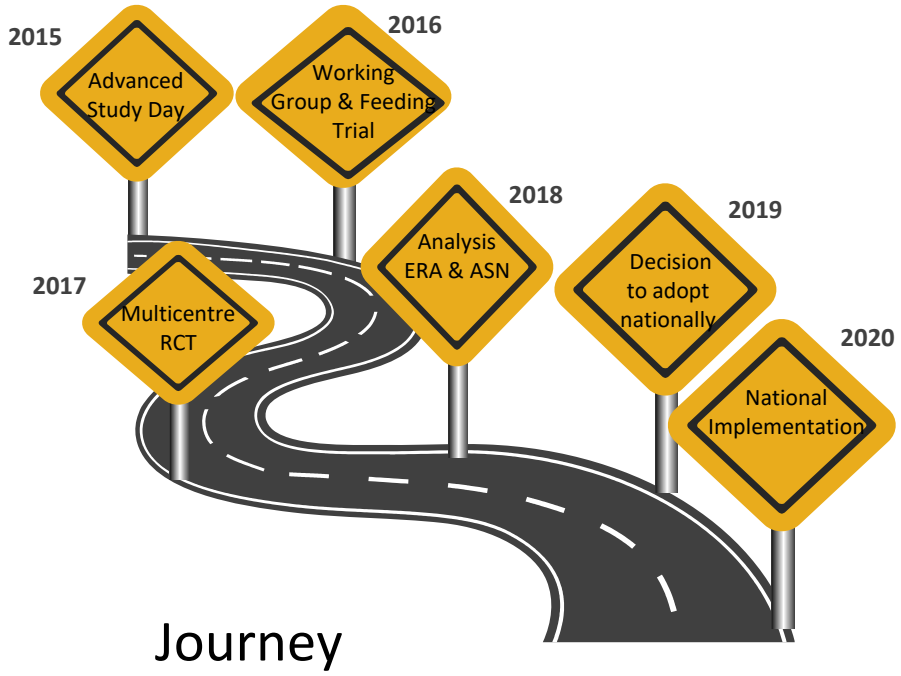
6.1 Process Summary

In 2015 an advanced study day on dietary phosphorus, bringing together experts from various fields, established the need for revision of the advice we give to Irish CKD and ESKD patients. In 2016, the existing evidence was reviewed (chapter 1) and translated into a revised or modified low phosphorus diet sheet (chapter 2), in collaboration with practicing renal dietitians. The proposed modified diet was then tested in a proof of concept feeding study (chapter 4) and multicentre RCT (chapter 5).

Figure 6.1 describes the process of revising, testing and implementing the new dietary guidelines to manage hyperphosphataemia. The diet sheet was adopted nationally in January 2019. Implementation is underway and there is a plan for a national roll out of the modified diet in January 2020. The involvement of frontline dietitians at every step has been critical both to the success of this research project and to the implementation of the findings. Irish renal dietitians had successfully undertaken a number of previous collaborative projects including the development of a cookery book for dialysis patients www.trulytasty.ie and a website www.irishkidneydiet.ie. The experience in functioning as a cohesive working group where inputs from all members were considered and valued and where a consensus could be fairly agreed was essential especially during the work to revise the dietary advice (chapter 2). Where time and resources allow or where a new

working group is convened in the future, a more formal consensus-based decision-making processes should be considered.[51]

Figure 6-1 The Research Journey 2015-2020



Submitted for publication individually, each chapter (2-5) includes a discussion and conclusion section. In this, the final chapter, we briefly summarise the findings, how this work contributes to the field in the context of recent developments, implementation, the direction that dietitian led clinical research needs to take and the overall implications of our research.

6.2 Summary of Findings

We suggested three changes to the way in which we manage hyperphosphataemia through diet; to relax dietary restrictions of phytate phosphorus; to ensure

adequate but not excessive protein intake, with some focus on the differing phosphorus to protein ratios of food; and to avoid all phosphate additives. These changes were incorporated into the modified renal diet. The feeding trial established that the modified diet blunted postprandial hyperphosphataemia and hyperkalaemia. It also established the presence of transient increased levels of potassium in the postprandial phase which had declined by the next dialysis. The RCT established that the modified renal diet with its wider food choice, had significantly higher fibre intake, was well tolerated, provides comparable serum phosphate and potassium control to the standard renal diet but may need to be used more cautiously in hyperkalaemic patients. The contribution from phosphorus food additives was lower than we had expected.

6.3 Recent Developments and Contribution of this Research

6.3.1 Global Context

In a global context the EAT–Lancet Commission have described a universal healthy reference diet for the world population that has benefits for the health and sustainability of the global population.[278] The introduction of more plant based foods into our renal diet moves the modified renal diet closer to that universal healthy reference diet.

6.3.2 Dietary Patterns

Evidence[279,280] and opinions[165,273] continue to emerge, to support the use of specific dietary patterns such as the Mediterranean Diet in CKD. Instead of looking at individual nutrients or foods, dietary patterns describe the overall diet; the foods,

food groups, and nutrients included; their combination and variety; and the frequency and quantity with which they are habitually consumed.[274] Dietary patterns examine the effects of overall diet and represent a broader picture of food and nutrient consumption, and may thus be more predictive of disease risk than individual foods or nutrients.[275] Educating patients using dietary patterns may be an adequate dietary management strategy in the earlier stages of CKD, but in the later stages of CKD and ESKD, the prescribed dietary pattern needs to be carefully individualised to ensure adequate protein intakes while achieving individual nutrient restrictions. The suggested changes, tested at trial, move our recommended renal diet closer to the Mediterranean dietary pattern while retaining the ability to individualise nutrient restrictions.

6.3.3 Benefits of Increased Fibre Intakes

Mounting evidence suggests that CKD is accompanied by changes of gut bacterial populations and defects in the intestinal barrier leading to systemic inflammation.[269] Increasing fibre, has been suggested as a therapeutic intervention which may prove effective in attenuating CKD associated dysbiosis and colonic dysfunction.[131] Targeting the intestinal microbiome is a cheap and non-invasive therapeutic option, with a potential to beneficially impact a large number of patients.[281] Both our trials showed a significant increase in fibre intake, which is further evidence of support for the modified diet sheet.

6.3.4 Risk of Hyperkalaemia

Experts continue to call for liberalization of the renal diet and the inclusion of more plant-derived foods, whilst acknowledging the need for careful monitoring of

potential risks such as hyperkalemia.[282] In the feeding study despite similar dietary potassium intakes, postprandial potassium levels were much more stable and lower on the modified diet. In the RCT we included more whole grains, pulses and nuts but judicious choices meant that dietary potassium intakes were not significantly higher on the modified diet. While this research was an important first step, given the risk of hyperkalaemia, this needs rigorous investigation especially in the dialysis population.

6.3.5 Phosphate Additives

The long awaited European Food Safety Authority (EFSA) review on phosphate additives was published in 2019.[159] Therefore following our multicentre trial, we reviewed our modified diet against these recommendations.

This EFSA report, only deals with the main phosphates E 338-341, E343, E 450-452 and sets a group acceptable daily intake (ADI) for phosphates of 40mg/kg expressed as phosphorus (P). This ADI is equivalent to 2800mg phosphorus in a 70kg adult. The ADI is defined as the amount of a food additive, expressed as mg/kg body weight that can be ingested daily over a lifetime without incurring any appreciable health risk. While the ADI does not apply to people with moderate to severe reduction in kidney function, which is considered a vulnerable population group, it impacts the level of phosphates being added by the food industry.[283] This ADI of 2800mg is not significantly different from the previous recommendation.[284]

In adults, exposure estimates to the phosphate additives E 338-341, E343, E 450-452 alone, using the worst case scenario which is based on the maximum permitted levels of these additives, contributed 1530-3438mg phosphorus per day.[159] This

may be concerning for CKD patients who are aiming to restrict phosphorus to approximately 1000mg per day from both food and additive sources. It can be argued that in a more realistic and refined exposure assessment using data supplied by industry on actual usage levels, at mean levels of intake, phosphate additives (E 338-341, E343, E 450-452) contributed between 319-722mg phosphorus per day to the diet in brand loyal adult consumers and 126-278mg phosphorus per person in non brand loyal consumers.[159] Exposure to total phosphorus via the diet which includes naturally occurring dietary phosphorus, phosphate additives (E 338-341, E343, E 450-452) and all other phosphate containing additives estimates mean dietary exposure to phosphorus (minimum to maximum across the surveys in mg P/person/day) as 1204-1625mg for adults. At the 95th percentile this increased to 1829-2728mg /day.[159] According to the EFSA opinion on phosphates, food additives indicatively contribute between 6 to 30% of the total average intake of phosphorus. The main food categories contributing to the exposure of phosphate additives (E 338-341, E 343, E 450-452) using the regulatory maximum level exposure assessment scenario were bread and rolls and fine bakery wares.[159] In the second scenario assessed which was the brand-loyal refined estimated exposure scenario, the main food categories contributing to the total mean exposure estimates were bread and rolls and fine bakery followed by meat products for adults and the elderly.[159] In the third scenario assessed which was the non-brand-loyal refined estimated exposure scenario, the main food categories contributing to the total mean exposure for adults and the elderly were again bread and rolls, fine bakery wares and meat products for adults and the elderly.[159]

The EFSA report indicated that the percentage of foods per MINTEL subcategory labelled to contain phosphates (E 338-341, E343, E 450-452) was on average 9.6% and that approximately one-third of the products are labelled as containing diphosphate (E450). For the following subcategories, the percentage of foods labelled with the phosphates (E 338-341, E343, E 450-452) mentioned above was above 25% (Evaporated milk; Processed Cheese; Cakes, Pastries & Sweet Goods; Sandwiches/Wraps; Instant Noodles; Creamers; Poultry Products; Plant Based Spoonable Yogurts (Dairy Alternatives); Frozen Desserts; Meal Replacements & Other Drinks; Meat Products; Sports Drinks; Sweet Biscuits/Cookies).[159]

The EFSA report, only deals with the main phosphates E 338-341, E343, E 450-452. does not deal with the "other" phosphate containing food additives which were briefly mentioned in the 2013 EFSA report.[285,286] These "other" phosphate containing food additives include lecithins (E 322); ammonium phosphatides (E 442); ribonucleotides (E 626-635); riboflavin-5'-phosphate (E 101(ii)) and modified starches such as monostarch phosphate (E 1410), distarch phosphate (E 1412), phosphated distarch phosphate (E 1413), acetylated distarch phosphate (E 1414), hydroxypropyl distarch phosphate (E 1442); and sodium aluminium phosphate, acidic (E 541). Beside ribonucleotides these other phosphate additives have been the subject of separate EFSA reports in recent years.[287-290]

Modified starches remain a particular concern because it is unclear from the label if a modified starch contains phosphate or not. This is because starch modified by acid or alkali treatment, bleached starch, physically modified starch and starch treated by amylolitic enzymes are not considered to be food additives. While physical or enzymatic treatment of starch would not result in any addition of

phosphate, five out of the twelve modified starches are reacted with or esterified with phosphoric acid or some form of phosphate and are considered to be food additives, however their specific name or E number is not be required to be indicated as per European food labelling legislation (Regulation (EU) 1169/2011). As a result they are an unknown quantity when it comes to dietary phosphorus load. The number and percentage of food products labelled with modified starches (E 1404-E1452) by name or E number out of the total number of food products present in the Mintel Global New Products Database between 2011 and September 2016 was 40,569 (8.8%) but you could only tell if it contained P in 1259 (2.9%) of them.[287] This report also noted kidney calcification in chronic toxicity studies in animals; however the authors felt that there was no toxicological significance for human health.[287] Modified starches containing phosphates remain difficult to discern on product labels due to the fact that they can be just labelled as "modified starch" and are a major concern for the renal population.

For national implementation of the modified renal diet, the consensus was to expand the list of phosphate additives and to advise patient to check labels for their presence. Patients are advised to check food labels carefully and to look for any ingredient that has 'phos' in the term such as di**phos**phate, sodium poly**phos**phate, calcium tri**phos**phate. They are also advised to check for lecithin and ribonucleotides and for the phosphate E numbers E322; (E338-341); E343; (E450-452); E442, (E626-635); E101(ii); E1410; E1412-1414); E1442), E541. Finally they are advised to pay particular attention to bread, rolls, cakes and biscuits and processed foods particularly meat products.

Food additives are a major concern to our patient and unfortunately food safely authorities in the European Union and in the United States seem reluctant to restrict phosphate additives or to demand that products are more clearly labelled.[291] We need Food Safety Associations to reconsider the adverse effects that phosphates may have and to require labelling.[160]

Our research provides some reassurance that our patients are successfully avoiding the main phosphate additives but this area requires further investigation and monitoring particularly in terms of clarifying the contribution of modified starches.

6.4 Future Research in this Field

Given the worldwide burden of the disease, the low cost of dietary interventions, the other potential benefits of dietary interventions aside from the treatment of hyperphosphataemia, this area of research should be prioritised. We lack high quality evidence to guide our practice, but our unfunded pragmatic clinical research suggests that with some support and funding, important research can take place in the clinical setting.

6.4.1 Testing Food Based Recommendations

We need more food based intervention studies.[292] Going forward renal nutrition guidelines need to include both food and nutrient recommendations. Nutrient recommendations need to be translated into food based recommendations and trialed for safety and efficacy. Undertaking these trials is undoubtedly challenging [277] but absolutely essential and necessary to demonstrate the effectiveness of dietary interventions and to improve dietary strategies in CKD and ESKD. [183,242] Barriers to this including funding and support.

6.4.2 Possible Adverse Effects of Phytate

Phytate binds phosphorus which makes it unavailable for absorption and this is beneficial in the renal population, however phytate also reduces the bioavailability of other micronutrients notably zinc and calcium.[293] Therefore we need further studies to investigate this, given the reported prevalence of zinc deficiency in CKD and ESKD.[294,295] We did not measure zinc levels in our trial but its duration would likely have been too short to demonstrate such an effect.

6.4.3 Describing Phosphorus Intakes

We need to re examine how we better describe phosphorus intake going forward. An approach that may be considered is to describe phosphorus in term of total phosphorus but to include how much of the phosphorus is phytate bound. Another approach may be to use molar ratio. Dietary phytate-to-zinc and phytate-to-iron molar ratios can be used to estimate the bioavailability of iron and zinc in individual foods or whole diets and to design food-based strategies to enhance bioavailability of zinc and iron.[293] Similarly dietary phytate-to-phosphorus molar ratios could be used to estimate the bioavailability of phosphate in individual foods or whole diets and to design food-based strategies to reduce bioavailability of phosphorus.

6.4.4 The Effect of Fat on Phosphorus Absorption

Further research should examine the effect of food matrix on phosphorus absorption, including the exploration of the possible effects of the fat content of dairy products on phosphorus absorption. A possible theory to explain why different dairy products affect serum phosphorus differently[76] might be that fat

may form a calcium–fatty acid complexes (calcium soap) [296] thus releasing phosphorus for absorption.

6.4.5 Phosphorus Management Pre Onset of Hyperphosphataemia

Contrary to current guidelines, animal studies continue to provide evidence that dietary phosphate should be restricted prior to the development of hyperphosphataemia.[297] Current recommendations no longer recommend controlling phosphorus intake prior to the development of hyperphosphataemia. The 2017 KDIGO guidelines make an ungraded recommendation (4.1.5) that in patients with CKD G3a–G5D, decisions about phosphate-lowering treatment (including diet), should be based on progressively or persistently elevated serum phosphate. This is based on a suggestion of harm, likely related to calcium based binders in two small short term studies[94,298] and may well represent a missed opportunity to manage CKD MBD.

In summary, our understanding of the regulation of phosphate is still evolving. [299] A better understanding of mechanisms of intestinal phosphorus is necessary to improve on existing therapies for phosphate management.[26] We need more research not only into effective dietary strategies [300] but also into whether it improves outcomes.[25]

6.5 Dietitian Led Research in the Healthcare Setting

To improve patient care we need to enable healthcare professionals to actively lead and contribute to research agendas. Healthcare providers such as the Health Service Executive (HSE) and Irish Universities need to work collaboratively to develop research in Irish hospitals. While this project is an exemplar of successful

partnership between frontline HSE and academia, future similar efforts are unlikely without increased resources. The Clinical Research Facilities funded by the Health Research Board are an important step, as is the HSE Action Plan for Health Research 2019-2029.[301]

With appropriate employer support and facilitation, training and access to research expertise such as that provided by the Clinical Research Facilities in Ireland, we have shown that it is possible to run rigorous, well designed pragmatic and clinically relevant randomised controlled trials. RCTs are the gold standard for establishing cause and effect and are the cornerstone of evidence based medicine.[302] Clinical staff are well placed to identify clinical priorities and are incentivised to implement their research findings, two aspects of research that are currently lacking. There is usually a significant time lag from research to implementation.[303] We were delighted, without funding, to run the trial in 2017 and roll out the change in practice in January 2020. This is in part because front line dietitians were involved from the beginning. Dietitians who currently work in dialysis units, identified the need, inputted into the intervention and trial design and implemented the trial protocols. They were dedicated to and invested in the area. With pragmatically designed trials and training, front line practitioners are ideally placed to undertake pragmatic research projects. This pragmatic approach is similar to that of the HiLo study by Myles Wolf which has been funded by the National Institutes of Diabetes and Digestive and Kidney Disease[44] and is the way forward.

Finally the HSE must create mechanisms for secondments or research time particularly for staff leading frontline research in the clinical setting.

6.6 Implementation of Research

In January 2019, a meeting was held to present the evidence base from the working group, the results of the feeding study and the multicentre randomised trial. We ran an interactive group session format was used to consider the results with nine dieticians and one consultant from the trial. We discussed how the trial added to the current evidence base, and if we would implement it. To reach a decision an anonymous survey monkey vote was taken by the nine participant dietitians. Four strongly agreed and five agreed that the modified diet (protein & phosphate sections) should be adopted as part of the national diet sheet. Any outstanding concerns to be addressed by the implementation working group were documented.

6.7 Implications of our Research

The revised low phosphorus diet is well tolerated, increases patient choice and provides comparable biochemical control to the standard diet. In addition, it has an improved nutrient profile in terms of fibre and is more in line with healthy dietary pattern such as the Mediterranean diet and the Lancet Commissions' universal healthy reference diet. Based on this research, the revised dietary advice is being incorporated into a revised national renal diet sheet for use across the Irish health service.

Finally this project highlights the paucity of well designed clinical trials in the area but also demonstrates the potential within our health service to conduct pragmatic research at the front line.

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Appendix 1 : Literature Search

Evidence for Dietary Phosphate Restriction in Chronic Kidney Disease and End Stage Kidney Disease

The author undertook a key word (in title & abstract) and MESH heading search in **PubMed** on 23-8-16

Concepts	CKD	DIET	PHOSPHATE
Keywords	chronic kidney disease OR CKD OR end stage kidney disease OR ESKD OR haemodialysis OR hemodialysis OR HD OR dialysis	Diet OR Dietary OR Additive OR Additives	Phosphate OR Phosphorus
MeSH	Renal Insufficiency, Chronic OR Kidney Failure, Chronic OR Renal Dialysis	Diet	Phosphorus, Dietary

A separate search filter developed by the University Of Texas was used for clinical trials rather than the clinical trial filter

Search: ((((((((((((Chronic Kidney Disease[Title/Abstract]) OR CKD[Title/Abstract]) OR End Stage Kidney Disease[Title/Abstract]) OR ESKD[Title/Abstract]) OR Haemodialysis[Title/Abstract]) OR Hemodialysis[Title/Abstract]) OR HD[Title/Abstract]) OR Dialysis[Title/Abstract])) OR ((("Renal Insufficiency, Chronic"[Mesh]) OR "Kidney Failure, Chronic"[Mesh]) OR "Renal Dialysis"[Mesh]))) AND ((((((Diet[Title/Abstract]) OR Dietary[Title/Abstract]) OR Additive[Title/Abstract]) OR Additives[Title/Abstract])) OR "Diet"[Mesh])) AND ((((Phosphate[Title/Abstract]) OR Phosphorus[Title/Abstract])) OR "Phosphorus, Dietary"[Mesh])) AND ("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR

"clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])) =229 results

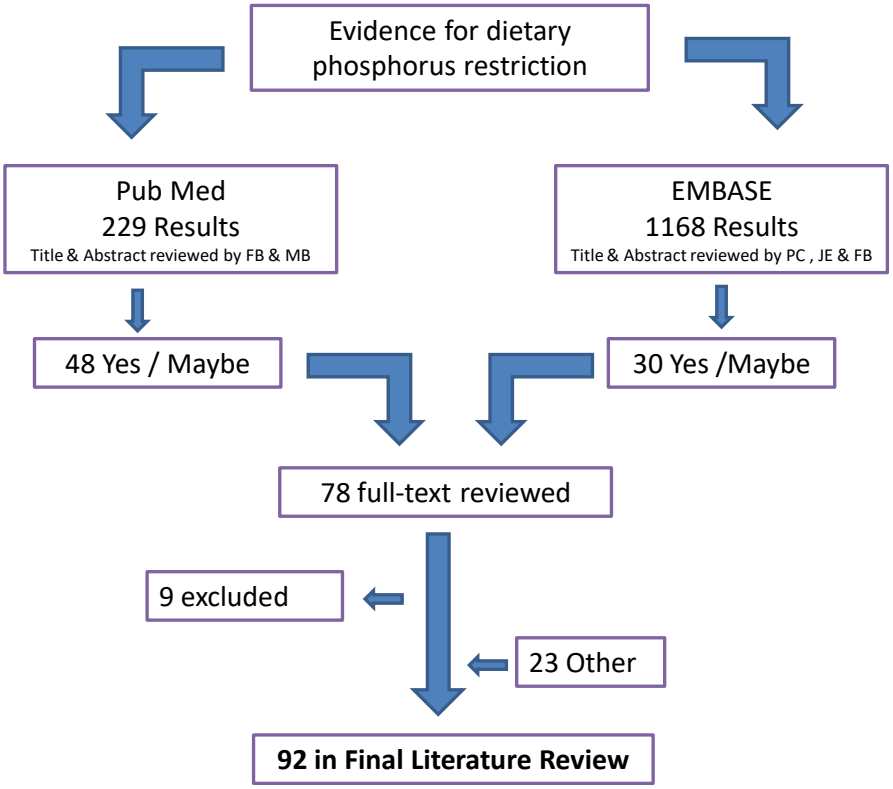
The author undertook an advanced search, searching as broadly as possible (mapping) in **Embase** on 23-8-16

CKD	AND DIET	AND PHOSPHATE
‘chronic kidney disease’ OR ‘end stage kidney disease’ OR ‘end stage renal disease’ OR ‘haemodialysis’ OR ‘hemodialysis’ OR ‘dialysis’	‘diet’ OR dietary OR additive OR additives OR ‘food additive’	‘phosphate ‘ OR ‘phosphates’ OR ‘phosphorus’ OR ‘ phosphate intake’

2430 results : Filters applied included age, study type and publication type 'chronic kidney disease'/exp OR 'chronic kidney disease' OR 'end stage kidney disease'/exp

OR 'end stage kidney disease' OR 'end stage renal disease'/exp OR 'end stage renal disease' OR 'haemodialysis'/exp OR 'haemodialysis' OR 'hemodialysis'/exp OR 'hemodialysis' OR 'dialysis'/exp OR 'dialysis' AND ('diet'/exp OR 'diet' OR 'dietary' OR 'additive' OR additives OR 'food additive'/exp OR 'food additive') AND ('phosphate'/exp OR 'phosphate' OR 'phosphates'/exp OR 'phosphates' OR 'phosphorus'/exp OR 'phosphorus' OR 'phosphate intake'/exp OR 'phosphate intake') AND ('clinical trial'/exp OR 'clinical trial' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'comparative study'/exp OR 'comparative study' OR 'controlled clinical trial'/exp OR 'controlled clinical trial' OR 'controlled study'/exp OR 'controlled study' OR 'cross-sectional study'/exp OR 'cross-sectional study' OR 'human'/exp OR 'human' OR 'major clinical study'/exp OR 'major clinical study' OR 'observational study'/exp OR 'observational study' OR 'prospective study'/exp OR 'prospective study' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)' OR 'retrospective study'/exp OR 'retrospective study') AND ('article'/it OR 'article in press'/it) = 1168 results

Criteria for incluson were any human clinical trial in the English language which added to our knowledge base on the effectiveness of dietary phosphate restriction in CKD and ESKD. Relevant studies conducted in subjects with normal kidney function were also included. Teams of two reviewers, independently and in duplicate, screened titles and abstracts and selected the trials they considered to be relevant or maybe relevant. Full text articles were reviewed and incorporated into a narrative summary and their implications thereafter discussed with the working group. Trials deemed relevant to the revision of dietary recommendations for phosphorus in CKD G3- 5D were selected for inclusion in the final review.


Evidence for dietary phosphorus restriction
Pub Med
229 Results
Title & Abstract reviewed by FB & MB
EMBASE
1168 Results
Title & Abstract reviewed by PC , JE & FB
48 Yes / Maybe
30 Yes /Maybe
78 full-text reviewed
9 excluded
23 Other
92 in Final Literature Review

Appendix 2: The Modified Diet Sheet

Your Guide to Controlling Phosphate

DIP HD Trial – Diet B

Irish Nutrition + Dietetic Institute Renal

Your doctor has put you on a low-phosphate diet because your kidneys are not working well enough to control the levels of phosphate in your blood. This leaflet tells you about a low-phosphate diet and which foods you can and cannot eat. It includes sample meal plans.

What is phosphate?

Phosphate is a mineral that helps to keep your bones strong and healthy. Your body gets phosphate from the foods that you eat.

Why do I need to control my phosphate level?

Normally, your kidneys manage the level of phosphate in your body. When your kidneys are not working properly, they cannot remove extra phosphate effectively. This causes the level of phosphate in your blood to rise. High levels of phosphate in the blood can weaken your bones and lodge in your eyes, joints, skin, heart and blood vessels. Over time this can lead to heart disease. Itchy skin may be a sign that your phosphate levels are too high.

To help control phosphate levels in your body, it is very important to eat a low phosphate diet.

Plain English Approved by NALA

Three steps to help reduce your phosphate levels

Step 1: Eat the right amount of protein for you.

Your dietitan will tell you which foods contain **protein** and how much of these you can eat each day. This is called your **daily allowance**. It is very important to keep to your protein and dairy food allowances as these foods are very high in phosphate. Keep reading to learn more!

Step 2: Avoid foods with added phosphate.

There is more about this on page 8.

Step 3: Don't eat foods that contain a large amount of phosphate.

There is a list of foods that contain phosphate on pages 9 and 10.

Step 1: Eat the right amount of protein for you

Why do I need protein?

You need to eat the right amount of protein each day to:

- build muscle, repair tissue and fight infection; and
- control the build-up of waste products in your blood.

Which foods contain protein?

High-protein foods include both animal and vegetarian proteins.

- Animal protein includes meat, fish, poultry, eggs and dairy products.
- Vegetarian proteins that are suitable for you include peas, chickpeas, kidney beans, butter beans, peanuts and cashew nuts.

Bread, cereals, rice, pasta and potato also have some protein but they contain less protein than the high-protein foods.

Protein

You need ____ **Protein** exchanges from the Meat, Fish, Poultry, Eggs, Beans and Nuts Food Group

1 Exchange = 1 of the following		
Cooked meat	25g / 1oz	Suitable meats include beef, steak, mince, lamb, pork
Cooked poultry	25g / 1oz	Suitable poultry includes chicken and turkey.
Cooked fish	25g / 1oz	Suitable fish include sole, cod, whiting, plaice, salmon, tuna. Eat fish twice a week.
Whole egg	1 whole egg	Limit to 3-4 whole eggs a week. Spread out over the week and only eat one egg a day.
Egg white	2 egg whites	Egg whites are very low in phosphate. You can add egg white to whole eggs to make scrambled eggs or omelettes.
Pulses (peas and beans)	100g/4oz (drained weight) pulses such as chickpeas, butter beans and kidney beans **or** 125g/5oz peas **or** 100g/4oz homemade houmous.	Choose pulses canned in water. Choose frozen peas and boil.
Nuts	25g/1oz peanuts **or** 25g/1oz peanut butter **or** 40g/1½oz cashew nuts.	No more than **1 portion** each day. Choose **unsalted** nuts.

Some points to note.

1. Please include **2** vegetarian protein exchanges a day.
2. You need to limit vegetarian protein to 2 exchanges each day. This is because vegetarian proteins are higher in potassium and phosphate than animal proteins.
3. You can also use ½ a protein exchange. (½ protein exchange = 50g **homemade** houmous **or** 62g peas **or** 12g peanuts **or** 1 egg white).
4. Most of the protein in your diet comes from these foods. Go for a variety of choices including fish twice a week.

The guide below gives you the weights of different portion sizes.

Please weigh out your cooked portion a few times so you get a good idea of what that size looks like.

1 cooked chicken breast	100-150g	4-6 oz
1 cooked pork chop	75-100 g	3-4 oz
2 to 3 thin slices cold meat	75-100 g	3-4 oz
4 dessertspoons of cooked minced meat	75 g	3 oz
1 cooked salmon fillet	100g	4oz
½ cup homemade houmous	100g	4oz

Dairy

You need **1 Dairy exchange** from the Dairy Food Group

1 Exchange = 1 of the following		
Milk	200mls/ 1 glass	This includes **all** the milk you use including what you add to your cereal or tea.
Yoghurt	125g/5oz	A small pot.
Hard cheese	25g/1oz	Suitable hard cheeses include Cheddar, Edam and Gouda.
Cottage cheese	75g/3oz	
Mozzarella	40g/1½ oz	Use grated or fresh mozzarella made with pasteurised milk.
Milk pudding	200g	1 cup rice pudding, custard or semolina.
Ice cream	200g	3 scoops or ⅓ pint block.
Soya milk	300mls	Check the ingredient to make sure it does not contain "phos".

In addition to your milk allowance, suitable milk substitutes are available on prescription. These include sno-pro and loprofin.

Bread and Cereals

You need **Bread / Cereal** exchanges from the Bread and Cereals Food Group

1 Exchange = 1 of the following		
Bread	1 slice bread.	Choose wholemeal or wholegrain sliced pan. Homemade soda bread (made without bran, wheat germ, phosphate containing raising agent or baking powder) is also suitable, but remember to count the milk.
Cereals	25g/1oz flake type, breakfast cereal or 1 wheat or oat cereal biscuit.	Choose options without chocolate coating or dried fruit for example Weetabix / Oatabix, Special K, Rice Crispies, Cornflakes or any similar own brand product.
Porridge	25g/1oz dry porridge oats.	⅓ cup.
Rice / pasta / noodles	3 dessertspoons (55g/2oz) boiled pasta, rice, noodles or couscous. (25g/1 oz uncooked)	Choose wholemeal or wholegrain instead of white. Make changes in fibre intake gradually.
Crackers	3 crackers or 3 oatcakes or 3 rice cakes.	
Others	½ pitta pocket or ½ tortilla wrap or 1 petit pan/ small soup roll.	

Dessertspoons are heaped cereal/dessertspoons using normal kitchen cutlery:

1 cup = 200mls plastic cup

Potatoes

Keep to **2 Potatoes** each day



- 1 potato = 100g/4oz
- Boil potatoes as per low potassium potato recipe.

If you do not eat potatoes, choose 2 extra exchanges from the bread and cereals food group.

Fibre and Fluid (liquids)

Peas, beans and whole grains such as wholemeal sliced pan are high in fibre. If you are not used to eating a lot of fibre, increase your intake of these foods slowly. Make one change every couple of days, not all at once.



You should drink fluid (from your allowance) when you are having a high fibre foods such as wholemeal bread. This is because fibre acts like a sponge, absorbing fluid from your bowel. Make sure to drink your full fluid allowance.

Summary of your daily allowances

For you, the right amount of protein is equal to

__ **Protein** exchanges + **1** **Dairy** exchange + **__** **Bread / Cereal** exchanges + **2** **Potatoes**

Step 2: Avoid food with added phosphates

How can I avoid phosphate additives?

Check food labels carefully, especially cakes, biscuits and processed foods. Look for any ingredient that has 'phos' in the term.

1. Check for "**phos**" such as di**phos**phate, sodium poly**phos**phate, calcium tri**phos**phate
2. Check for Phosphate E numbers E338, E339,E340, E341, E343, E450, E451, E452 and E541

Pay particular attention to bakery products, cakes, biscuits and processed foods. If a food contains phosphate, don't eat it.

Step 3: Don't eat foods that contain a large amount of phosphate

	Avoid	Choose instead
Meat	✗ Liver, kidney, pate Processed meats such as: sausages and ham.	✓ Beef, steak, mince, lamb and pork Chicken, turkey.
Fish	✗ Sardines, whitebait, monk fish, sea bass, bones of tinned fish.	✓ Sole, cod, whiting, plaice, salmon and tuna.
Dairy	✗ Processed cheese.	✓ Mozzarella, cottage cheese or hard cheese.
Pulses Nuts and Seeds	✗ Dried beans, baked beans, tinned and dried peas, hazelnuts, brazil nuts, almonds, pistachio nuts, walnuts. Seeds.	✓ Unsalted peanuts, unsalted cashew nuts. Chickpeas, butter beans and red kidney beans tinned in water.
Bread	✗ Bread made with baking powder or a raising agent containing phosphate, bread mixes, naan bread, sourdough bread.	✓ Sliced pan, baguettes, rolls, ciabatta, pitta bread, wraps. Soda bread (count the milk). Choose wholemeal varieties.
Crackers	✗ Crackers with phosphate containing raising agent.	✓ Crackers, oatcakes or rice cakes.

	Avoid	Choose instead
Cereals	× All bran, bran flakes, muesli, cereals containing nuts or chocolate, Ready Brek, wheat germ.	✓ Porridge, Weetabix /Oatabix, Special K, Rice Krispies, Cornflakes or any similar own brand product.
Baking Ingredients	× Baking powder, self-raising flour, bran, wheat germ.	✓ Yeast, white flour, wholemeal flour.
Drinks	× Cola drinks, Horlicks, Ovaltine, Complan, milk shakes, dried milk powder.	✓ Tea, lemonade, tonic water, Lucozade, ginger ale. Drinks you can dilute - check the label and choose those with a fruit juice content of **less** than 12%. Choose sugar free if overweight.
Treat Foods	× Chocolate, biscuits or cakes containing nuts, chocolate, baking powder or "phos" containing raising agent. Scones, cake mixes, waffles, muffins, instant dessert mixes, fudge, toffees, cereal bars.	✓ Oat-based biscuits, plain flapjacks, digestives, gingernuts, custard creams, jam rings, rich tea, marietta, lincoln, shortcake, pastry, doughnuts, jam tart crumbles, tarts, lemon meringue pie, cream, pancakes, jelly, boiled sweets, marshmallows, jellies, mints, turkish delight (no chocolate), Cream cheese.

Check all breads, biscuits, cakes and bakery products for phosphate additives.

If you are on other dietary restrictions such as a no added salt diet, a fluid restriction diet or a low potassium diet, please continue follow these restrictions. **If you following a low potassium diet, avoid rye crispbreads.**

Sample Meal Plan 1

Based on

6 **Protein** exchanges + 1 **Dairy** exchange + 6 **Bread / Cereal** exchanges + 2 **Potatoes**

		Protein	Dairy	Bread	Potato
Daily Allowance	Milk = 200mls		1		
Breakfast	1 Weetabix with 100mls milk from allowance 1 slice 100% wholemeal toast with spread and marmalade Tea with 25mls milk from allowance			2	
Mid-morning	1 apple				
Lunch	½ bowl chickpea soup and 2 slices wholegrain bread with spread 25g unsalted peanuts Tea with 25mls milk from allowance	1 ½		2	
Dinner	100g fillet chicken 62g peas 4 dessertspoons carrots 2 dessertspoons turnips 2 scoop mash Tea with 25mls milk from allowance	4 ½			2
Bedtime snack	Tea with 25mls milk from allowance 2 slice wholemeal toast with dairy spread and jam			2	

Sample Meal Plan 2

Based on

6 **Protein** exchanges + 1 **Dairy** exchange + 6 **Bread / Cereal** exchanges + 2 **Potatoes**

		Protein	Dairy	Bread	Potato
Daily Allowance	Milk = 100mls		½		
Breakfast	2 slices toast with peanut butter Tea with 25mls milk from allowance	1		2	
Mid morning	1 small pear				
Lunch	Omelette using 1 egg and 2 egg whites with tomato onion and ½ oz cheese and 2 slices wholemeal bread Tea with 25mls milk from allowance	2	½	2	
Dinner	Chilli Con Carne (1 portion) 110g wholegrain rice Apple crumble and cream Tea with 25mls milk from allowance	4		3	
Bedtime snack	3 crackers with dairy spread and an apple Tea with 25mls milk from allowance				

Your Meal Plan

Based on

__	**Protein** exchanges	+	1 **Dairy** exchange	+	__	**Bread / Cereal** exchanges	+	__ **Potatoes**

To be filled out with your Dietitian

		Protein	Dairy	Bread	Potato
Daily Allowance			1		
Breakfast					
Mid-morning					
Lunch					
Dinner					
Bedtime					

Dietitian: _____ Contact Details: _____

Appendix 3: SOP for the Multicenter RCT

Decreasing **I**ntakes & Absorption of **P**hosphorus in **H**aemo**d**ialysis Patients through Food Choices (**DIP HD**)

Standard Operating Procedures (SOP)

DIP HD SOP v4

Date: 4th April 2017

Contents:

2	Centres
3	Trial Resources
5	Pre Trial Preparation
7	Study Design
8	Trial Procedures
20	Appendices
28	References

CENTRES

Number	Multicentre	Abbreviation	Dietitians
1	Cork University Hospital	CUH	Fiona Byrne & Fiona Keohane
2	Beaumont Hospital	BH	Donagh Smith & Bernice Curtis
3	Cavan General Hospital	CGH	Pauline Connolly
4	Fresenius Northern Cross	FNC	Denise Mc Carthy
5	Beacon Drogheda	Beacon D	Karina Brennan
6	Beacon Sandyford	Beacon S	Joyce Earlie
7	Beacon Tallaght	Beacon T	Joyce Earlie
8	St. Vincent's University Hospital	SVUH	Sarah Wade
9	ater Misericordia University Hospital	MMUH	Barbara Gillman
10	Tallaght Hospital	TH	Halog Mellett
11	Midland Regional Hospital Tullamore	MRHT	Theresa Rennick
12	University Hospital Limerick	UHL	Maria Bowles
13	Mayo University Hospital	MUH	Celine Sands
14	Galway University Hospitals	GUH	Orla Slevin

TRIAL RESOURCES:

	Standard Care – Control Arm	Intervention Arm (n=100)
Diet Sheets These will also be emailed to each centre in case additional copies are needed	Standard Low Phosphate Diet Sheet v2, 80 will be printed in Cork Standard Low Phosphate Diet Sheet –DM v2 50 will be printed in Cork and posted to each unit	Revised Low Phosphate Diet Sheet 80 will be printed in Cork Revised Low Phosphate Diet Sheet -DM - 50 will be printed in Cork and posted to each unit
Recipe Booklet		Recipe Booklet 120 will be printed in Cork and posted to units
Diary	Food Diary: to be given the week before monthly bloods. 240 will be printed in Cork	
Patient Packs Bulk contents will be provided by the co-ordinating unit and given at the training day to any investigator driving to Cork	**110 Packs** 1. Small White Paper Bag 2. Diet Sheet (will be posted) 3. Weighing Scales	**110 Packs** 1. Large White Paper Bag 2. Diet Sheet (will be posted) 3. Recipe Booklet (will be posted) 4. Shopping card 5. Weighing Scales 6. 400g can of chickpeas (in water), 7. 400g can red kidney beans (in water) 8. 400g can butter beans (in water) 9. 25g portion peanuts (check & **source locally)** 10. 40g portion cashew nuts 11. O'Egg coupon
Large Zip bag	Large Zip bag for labels (to be given out with diaries in week 4)	
Patient Information Forms	To be printed locally at each centre	
Consent Forms	To be printed locally	
Baseline Data	Form 1 To be printed locally	
Biochemistry	Form 2 v2To be printed locally	
Tolerance	Form 3a to be printed locally	Form 3b to be printed locally
Education Log	Form 4 v2 To be printed locally	
Trial Deviations	Form 5 To be printed locally	
End of Intervention	Form 6 v2 To be printed locally	
Allocation Log	To be printed locally	
Databases	DIP HD Database Adverse Events	

ELECTRONIC DIP HD RESOURCE FILE

- Fiona will email a resource file to each unit with ethics form and documentation.

Diet Sheets / Booklets: Diet sheets & booklets have been colour printed in Cork and posted to each unit. In addition they have been sent electronically to each unit in case additional copies are needed.

1. Diet A
    a. DIP HD Diet A v2 (Standard Low Phosphate Diet Sheet)
    b. DIP HD Diet A –DM Version v2 (Standard Low Phosphate Diet Sheet DM)

This was posted to you. It is not marked v2 on paper copy.
Correction: Add name & contact details of Dietitian

2. Diet B
    a. DIP HD – Diet B (Revised Low Phosphate Diet Sheet)
    b. DIP HD – Diet B – DM Version (Revised Low Phosphate Diet Sheet DM)

Correction: to meal plan 2 in DIP HD Trial – Diet B & Diet B – DM version. The summary box has 7 protein exchanges not 6 & 8 bread /cereal with no potato; Add 1 to bread exchange column for bedtime crackers.

3. Recipe Booklet
4. Food Diary

Forms: To be printed locally at each centre

1. Patient Information Forms (Please use the version you submitted to your local ethics committee)
2. Consent Forms (Please use the version you submitted to your local ethics committee)
3. Baseline Data Form 1
4. Biochemistry Form 2 v2
5. Tolerance Form 3a&b
6. Education Log Form 4 v2
7. Trial Deviations Form 5
8. End of Intervention Form 6 v2
9. Allocation Log (individualised per unit)

Excel Databases

1. DIP HD Database (individualised per unit & emailed on 19-2-17)
2. Adverse Events (AE) Log

Documents

DIP HD SOP v4 includes Task Summary
DIP HD Information for Dialysis Staff
eMed generated report for DIP HD
Food Codes

References: [260] 2015 COFID User Guide

PRE TRIAL PREPARATION (WEEK -4 TO WEEK -1)

1. Establish Standard Care - **YOUR** current Practice

2. Study and familiarise yourself with the Revised Intervention Diet which was compiled by working group of RIG BUT DO NOT CHANGE YOUR PRACTICE

Summary of **Changes** Recommended in Revised Diet Sheet

1. **Inclusion of foods with reduced phosphorus bioavailability due to phytate content.**
   1.1. **Maximum** of 2 vegetarian protein exchanges are encouraged per day (max 1 nuts) and
   1.2. wholegrain cereals are encouraged

2. **Focus on more accurate protein prescription** of 1.1g protein/ kg IBW thus avoiding over prescription of protein which carries an obligatory protein load.
   2.1. LBV proteins & potatoes have been included in protein allowance
   2.2. % HBV changed to 50-70%
   2.3. Fish has been reduced to 25g per protein exchange
   2.4. Count 2 fruit & 2 vegetable portions as 4g protein

3. **Full avoidance of phosphate additives**

4. **Some focus on phosphorus to protein ratio.**
   4.1. Beef has lowest P: Protein ratio 7mg/g with oily fish having the highest ratio 11mg/g however consensus reached was not to focus on the ratio in this food group and to broadly follow healthy eating guidelines and to encourage variety
   4.2. Dairy products are restricted to 1 portion per day P: Protein ratio 20-30mg/g
   4.3. Egg white which have an extremely low ratio 1.1mg P/g protein are included

When trial finishes each patient should be advised to go back to following their regular renal diet

Extra notes

1. Pulses and nuts to be taken at a time where a patient is already taking binders – if they take binders tds with meals – then they should take them with these meals. If they take binders with meals and snacks – then they can take them at snack time.
2. The bread and cereals section of the diet sheet specifies homemade soda bread but if participant can source a bakery that makes suitable bread then that is fine.
3. 100g Pulses contain 10-15g carbohydrate (CHO)

4. Appendix 4 details the protein and carbohydrate content of bread & cereal exchanges

Recipe Book Notes:

1. Kallo very low salt beef stock (68.51mg K per 100ml serving) = 2.19mmoles potassium per portion. Consensus: Use ½ amounts of regular stock cubes for recipes for trial. Using ¼ strength for soup because of the increased volume of stock

2. The fluid content of the soup recipe does not include the water content of the vegetable or chickpeas

A full description of all changes and rational for the revised diet sheet was circulated on 30-1-17

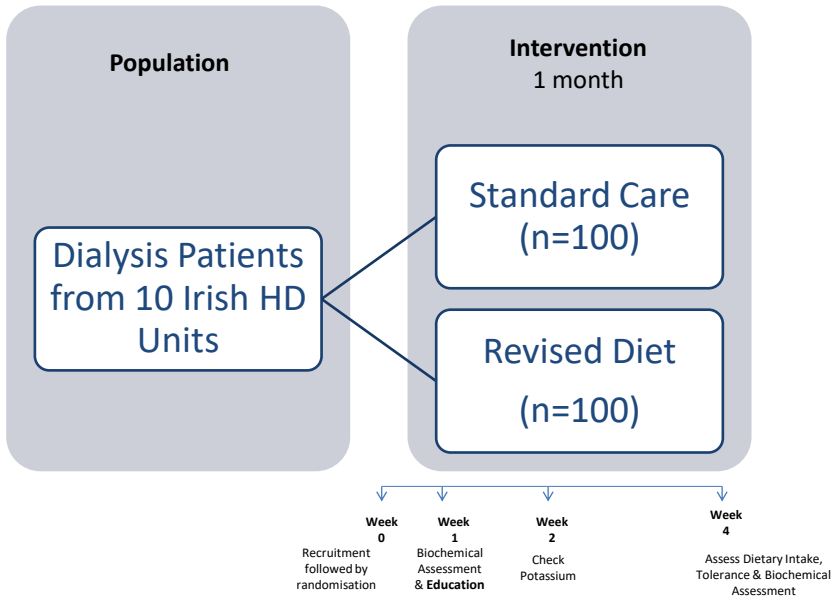
The Standard Care/ Current Diet Sheet

1. The standard care / current diet sheet has been retyped to match the font, layout and introduction of the revised diet sheet. The changes to the introduction were limited to NALA suggested changes.
2. The dietary information remains the same as the current RIG diet sheet.
3. The phosphate binder section has been removed.

Standard diet intervention (protein prescription, milk allowances and egg allowances) is as per your normal practice

Figure 1

Study Design



TRIAL PROCEDURES

3-4 WEEKS BEFORE TRIAL – SCREENING

1. Review all patients attending dialysis by first looking at lab values.
    a. Get the average of the last 3 available pre dialysis routine monthly phosphates.
    b. Instructions on how to generate an eMed report of biochemistry (by Oonagh Smith) were circulated on 20-1-17.

2. Ensure subjects fit the inclusion / exclusion criteria.

Inclusion criteria: >18 years

- Self reported Urine output less than 2 cups (400 ml) / day
- On maintenance haemodialysis for > 3 months
- Phosphate >1.6mmoles/L on average of last 3 routine monthly –as available- blood tests

The recruiter will take into consideration a patient's ability to make the required changes as well as likely compliance

Exclusion Criteria

- Hyperkalemia, defined as a predialysis serum K on routine monthly blood test of >6mmoles/l in the month preceding the trial.
- Parathyroidectomy
- Corrected serum calcium <2.2 or > 2.6mmol/L in the month preceding the trial.
- Acute concurrent illness, requiring hospitalisation in the 2 weeks prior to recruitment.

2-3 WEEKS BEFORE TRIAL: RECRUITMENT & CONSENT:

1. Allow for 2 visits per patient.

2. At the first visit tell the patient about the study. As per protocol and best practice, patients will be given the opportunity to take the information home to discuss with family or GP, should they wish to.

3. The procedure for signing consents should be as per local practice and should comply with requirements of local ethics boards. CUH practice (as per Professor Eustace) is to sign one form and make 2 photocopies. The original should be stored in the medical notes, a copy given to the patients and one kept in the trial file.

4. Once recruitment is complete: **Assign a study ID number** in order of recruitment. This will be a four digit number starting with the centre number then the subject number e.g. first patient recruited from Cork = 0101; the 12th patient recruited from Mayo = 1312

5. Add Entry on eMed "– **Enrolled on DIP HD Trial –DO NOT CHANGE CKD MBD medications, dialysis times or dialysate unless approved by the consultants**" Enter wherever notes are visible to all staff in your unit. Ideally doses of phosphate binders, vitamin D, calcimimetic, dialysis or dialysate should not be changed from 7 days before baseline bloods to end of intervention bloods. The end of intervention form 6 v2 will capture any changes to phosphate binders, vitamin D, calcimimetic, dialysis or dialysate and these can be corrected for in the statistical analysis.

6. Please record the numbers from your unit that were
    a. Screened
    b. Excluded as did not meet criteria
    c. Excluded other reasons
    d. Declined
    e. Recruited

1 WEEK BEFORE TRIAL (WEEK 0 IN FIGURE 1)

1. Create folder for each patient in which to put forms and other documentation.

2. Baseline data should be gathered the week before commencement of the trial using Form 1.

3. Assess baseline weight: the baseline weight will be the dry weight taken within 1 week of starting the intervention.

4. Measure height: this can be assessed in the month before the trial.

Height Measurement Protocol [304]

a) Individual should be barefoot / in thin socks and wearing light clothing so the positioning of the body can be seen.
b) Individual should stand on a flat surface, with weight distributed evenly on both feet, heels together, and the head positioned so that the line of vision is perpendicular to the body, known as the 'Frankfort Plane'.
c) The arms hang freely by the sides, and the head, back, buttocks and heels are in contact with the vertical board.
d) The individual is asked to **inhale deeply and maintain a fully erect position, while maintaining the head in the Frankfort position.**
e) The moveable head board is brought onto the topmost point on the head with sufficient pressure to compress the hair.
f) The height is recorded to the nearest 0.1cm.

5. Patient should be informed of the start date and given the opportunity to bring in a family member if they wish.

6. Check food scales against the calibrated scales you have received.

7. Create a list of patients recruited to the study and give to the consultants and to the dialysis staff. Ask Consultants and dialysis staff to let you know if there are any issues / concerns.

8. Baseline dietary assessment can take place the week before the trial or at the education day (1st day of trial).

9. Randomisation (must take place after dietary assessment) should take place as close to education as possible. This is because once a patient is randomised they must be included in the analysis of the arm they were randomised to even if they pull out before they start.

WEEK 1 OF TRIAL (WEEK OF BASELINE BLOODS)

ine bloods *Form 2* → Dietary assessment *Form 1* → **Randomise** → **Educate** *Form 4*→ order check K

Commence education the morning the monthly bloods commence. This is to maximise the length of time that patients are on the intervention. Education must be done **after bloods are taken** but you do not need to know the baseline results before you educate.

1. Take baseline bloods
2. Undertake baseline dietary assessment (if not done the previous week)
3. Randomise patient

Randomisation: *all reviewers / journal editors will enquire re randomisation procedures because it is essential to ensure allocation concealment and to ultimately minimise trial bias.*

- If mean (3 month) serum phosphate is below cut off of 1.9mmoles/l choose next numbered envelope from the **low** bundle
- If mean (3 month) serum phosphate is above cut off of 1.9mmoles/l choose next numbered envelope from the **high** bundle

Note: Due to the randomness of block sizes there are between 20 and 22 high phosphate envelopes and between 20 and 22 low phosphate envelopes being sent to each unit. This is more than you need.

The envelopes marked by the statistician are sequentially numbered with the following information: **centre** (shorthand for your unit) – **strata** (High/Hi/H or Low/Lo/L) – sequential envelope **number**. This is slightly different presentation to the allocation log's description of the envelope which (centre number followed by stata followed by sequential number), but contains the same information.

Please double check before you open the envelope that you are opening the **RIGHT** envelope.

Record the allocation on the allocation log. The allocation log is in the resources file – please print and add the data to the paper copy. At the end of the trial you will add this data to the main excel database.

Standard Care	Intervention Group
4. Calculate protein requirements 1-1.2g/kg IBW 70% HBV 5. **Educate re diet A**	Use usual intake from dietary assessment and protein requirements 1.1g/kg IBW 50-70% HBV to guide allowances. See appendix 1 for more detailed instruction **Educate re diet B**
6. Give Patient Pack for diet A	Patient Pack for diet B

7. Show subjects how to use food scales.

8. Emphasis importance of not discussing the trial in the unit.

9. Bring subjects attention to your contact details at the end of the diet sheet.

10. Tell patients their medications should only be changed by their consultants during the month of the trial.

11. Order check potassium (on all subjects) between 8 and 14 days after the patient starts the trial (i.e. day of baseline bloods). The time range is to allow subjects (on the intervention arm) time to make changes and increase their intake of fibre. Do not take bloods after an intradialytic period containing special occasion such as a birthday / St Patricks Day.

From Protocol "Blinding: *We will attempt to blind patients referring only to the diets as 2 different diets and avoiding the use of terminology such as old and new. We will reprint the diet sheet for both arms so they do not resemble current illustrated formats."*

WEEK 2 OF TRIAL

1. **Intervention Arm only**: Assess protein intake. Do 24hr recall with protein tot (at bedside), with reallocation of allowances if required. Record change in protein allowance as yes/ no (Form 4).

2. Remind all patients of importance of adhering to the intervention for the month.

3. Check if patient has had any issues (adverse events).

4. Check potassium levels. Record on Form 2 Biochemistry.

WEEK 4/5 OF TRIAL / THE WEEK BEFORE MONTHLY BLOODS

1. Remind patients of importance of adhering to the intervention for the last week.

2. Give food diary.

3. Give bag to collect labels and / or encourage them to take photograph of label including the ingredients.

4. Educate re weighed intake (use calibrated scales for demonstration). See Appendix 3 for UCC SOP by Dr. Carol Ni Chaoimh.

5. Decide with patients what days to record: non consecutive & and one dialysis , one non dialysis day (choose the days from within the last week of study , up to and including the day of the final bloods).

6. Arrange date for collection of food diary.

7. Ensure end of intervention bloods are ordered.

8. Order any additional bloods e.g. FGF23 if not routinely done monthly in your unit.

9. Check if patient has had any issues (adverse events).

WEEK 5/6 OF TRIAL / AFTER MONTHLY BLOODS ARE DONE

1. Collect food diary and clarify intake – go through the diary.
    a. Check all foods have been weighed.
    b. If food is not weighted use an alternative methods for estimating weight (see below).
    c. Seek clarity if you feel you will not have sufficient info to code the food.

2. Collect food labels / review any photographs of labels – noting in the diary if the food contained a phosphate additive.

3. Fill out Tolerance questionnaire.

4. Check if patient has had any issues (adverse events).

5. Fill in Form 6 End of Intervention form

MANAGING ADVERSE EVENTS:

1. Dietitian will check with the patient at each review (except first) if they have any problems. Any issues should be recorded on the adverse event log.

2. A list of patients recruited to the study will be given to the consultants and to the dialysis staff. They will be asked to let the Dietitian know if there are any issues / concerns.

3. If there are any adverse events, the dietitan will record on a database and ask the Consultant if in their opinion the event was related or unrelated to dietary intervention.

4. If considered related: record free text paragraph with details of event, contributory causes, investigations, treatment, outcomes.

5. If considered related and is severe: alert trial coordinator within 1 working day.

MANAGING HYPERKALAEMIA

1. Before Intervention starts
    a. If a patient has a high serum potassium in the weeks before the trial, after recruitment but before the trial starts, treat as normally would – review and advise.

2. From baseline bloods
    a. If potassium >6mmoles/l – review dietary intake to ensure complying with dietary advice Record on Form 4
    b. Withdraw from study if K ≥6.3mmoles (confirmed). Potassium should be repeated pre the next dialysis and only if the repeat level ≥ 6.3mmoles/l , will the patient will be removed from the study.

Management	Relevant Time Period
Recording adverse events	From education until you tell them to go back on normal renal diet
Managing hyperkalaemia	From baseline bloods until you tell them to go back on normal renal diet

MANAGING TRIAL DEVIATIONS

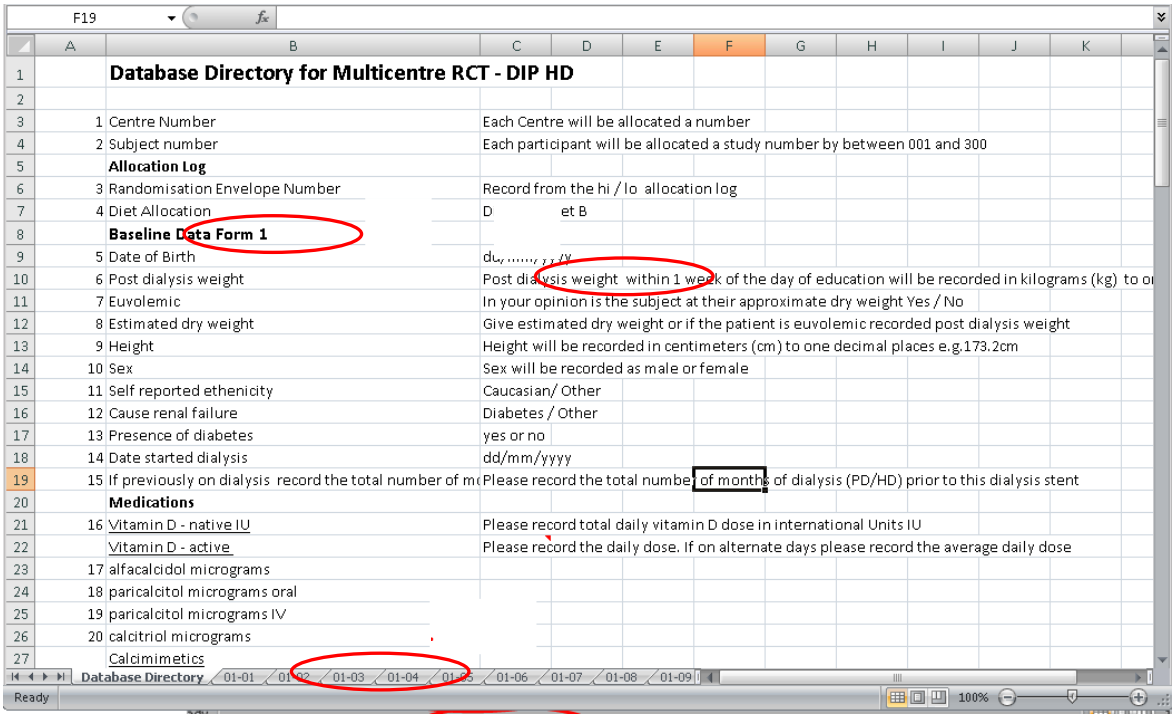
Please fill out any deviation from the trial protocol / SOP on Form 5 and submit to Fiona Byrne. If you would not consider the event a trial deviation but you think that it may affect outcome measures please make a “note to file” on the back of the trial deviation form/ attach to trial deviation form and return to me.

BLOOD DRAWS

All patients recruited into the study in your unit should have bloods taken in the same way.

DIP HD EXCEL DATABASE ENTRY

1. Each database has been individualised for your unit
2. The database directory sheet gives an explanation of each variable
3. The allocation log and data from Forms 1-6 (+ food diaries data) will be added to database.
4. There is one sheet in the excel file for each subject.
5. QC will include double entry of the main outcome measure – serum phosphate
6. Send Fiona first persons data entry (optional)



	A	B	C
1		**Database Directory for Multicentre RCT - DIP HD**	
2			
3	1	Centre Number	Each Centre will be allocated a number
4	2	Subject number	Each participant will be allocated a study number by between 001 and 300
5		**Allocation Log**	
6	3	Randomisation Envelope Number	Record from the hi / lo allocation log
7	4	Diet Allocation	D et B
8		**Baseline Data Form 1**	
9	5	Date of Birth	dd/mm/yyyy
10	6	Post dialysis weight	Post dialysis weight within 1 week of the day of education will be recorded in kilograms (kg) to o
11	7	Euvolemic	In your opinion is the subject at their approximate dry weight Yes / No
12	8	Estimated dry weight	Give estimated dry weight or if the patient is euvolemic recorded post dialysis weight
13	9	Height	Height will be recorded in centimeters (cm) to one decimal places e.g.173.2cm
14	10	Sex	Sex will be recorded as male or female
15	11	Self reported ethenicity	Caucasian/ Other
16	12	Cause renal failure	Diabetes / Other
17	13	Presence of diabetes	yes or no
18	14	Date started dialysis	dd/mm/yyyy
19	15	If previously on dialysis record the total number of m	Please record the total numbe of months of dialysis (PD/HD) prior to this dialysis stent
20		**Medications**	
21	16	Vitamin D - native IU	Please record total daily vitamin D dose in international Units IU
22		Vitamin D - active	Please record the daily dose. If on alternate days please record the average daily dose
23	17	alfacalcidol micrograms	
24	18	paricalcitol micrograms oral	
25	19	paricalcitol micrograms IV	
26	20	calcitriol micrograms	
27		Calcimimetics	

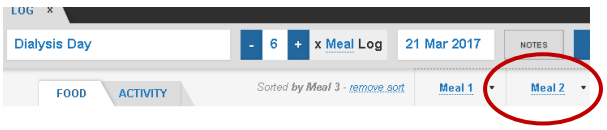
WEIGHED INTAKES – DATA ENTRY ON NUTRITICS

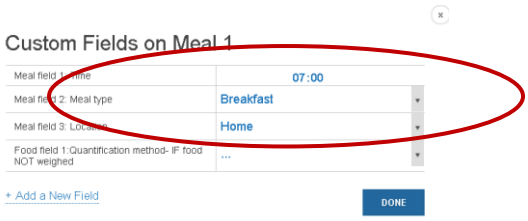
You can login at the link: www.nutritics.com/app

Username: **CUHResearch**
Password: **CUHResearch987**

Damian Kelly from Nutritics suggested watching 'Creating a Client', 'Creating a Diet Log' and 'Nutritics Research Edition' to get started. You can access the videos here. You can also access these through the programme online. Click menu on top right of screen →Choose tutorial videos from drop down menu. They are about 3 ½ minutes each.

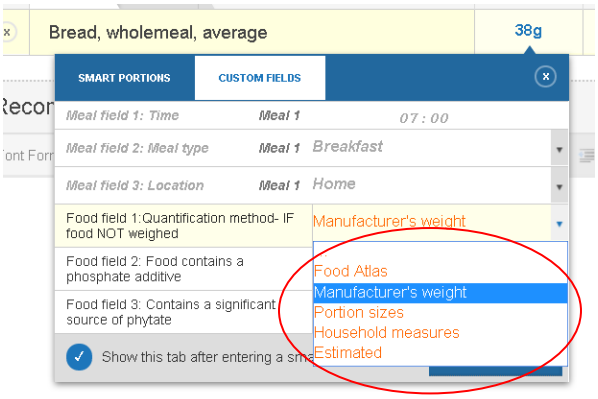
1. For each subject create a client.
2. Name the client: Enter the 4 digit subject ID in the ID box (no spaces or dashes).
3. Enter weight in kg – record the baseline weight.
4. Click on CREATE Log.
5. Name the log : Dialysis Day or Non Dialysis Day.
6. Change the date to the day that the food diary was recorded.
7. Click on Day log to change it to Meal log . Increase the number of meals (by clicking on the +/-) to match that of the subjects for that day.
8. **MEAL LEVEL CUSTOM FIELDS:** For each meal you will enter the time, meal type and location as custom fields. Click on Meal 1 to enter the 3 meal level custom field





- **Meal Field 1- Time:** enter the time recorded in 24hr clock.
- **Meal Field 2 - Meal type:** The definition of the eating occasion will be as the subject perceived it, as either a meal, snack or beverage. This will be entered as Breakfast, Midmorning snack, Lunch - light meal, Lunch - main meal, Mid-afternoon snack, Evening meal – light meal, Evening meal – main meal, Bedtime snack, Beverage.
- **Meal Field 3- Location** Subjects will record where they ate the meal. We will record this in nutritics as Home, Dialysis, Other

9. **FOOD LEVEL CUSTOM FIELDS:** All foods should be weighed, however if the food was not weighted, you will enter the alternative quantification method on nutritics
    9.1. **Quantification procedure for DIP HD :** Weighing should be encouraged as much as possible. If the weight is not available, use the following hierarchical approach to quantification which is based on methodology from North South Food Consumption Survey [260]



Use one of the following methods choosing method 1 first, then moving to 2 etc

1. Food photographic atlas: Fiona has copied 21 pages of the Nelson Food Standards Agency food atlas and has circulated to units. Do not use for foods that are easily described in terms of natural units e.g. biscuits, eggs, commercial sliced breads or where manufacturers weight is clear and unambiguous.
2. Manufacturer's weights: Obtain the amounts eaten by deriving them from weights printed on food packaging. These include confectionery, savoury snacks, chilled and frozen foods, franchised fast foods, canned or bottled goods and packaged bakery goods. To facilitate collection of such data, the researcher will ask subjects to collect all packaging of food and beverages consumed, and to bring them with them to dialysis. Subjects have also been asked to take photographs of label if for example the food was not finished.
3. Portion data
    a. IUNA online document http://www.iuna.net/wp-content/uploads/2013/09/Irish-Food-Portion-Sizes-Database.pdf /
    b. Food Standards Agency Food Portion Sizes 3rd edition
    c. Nutritics SMART portions (from published sources such as the MAFF handbook / USDA dataset or from in-house measurements)
4. Household measures quantified by the researcher by weighing the food or using portion data
5. Estimated food quantities based on the researcher's assessment of the amount likely to have been consumed, based on their knowledge of the respondent's general eating habits observed during the recording period.

9.2. **Food Field 2: Food contains a phosphate additives –** for processed / packaged food only. Not all processed / packaged foods contain phosphate additives and this is a significant limitation of McCance data which pools all food samples. To help us adjust the data (if determined to be a significant limitation) I am asking that you note whether or not a food contains phosphate additives (from ingredient list) when you are entering the data.

In the custom field which automatically appears after you enter a food weight please check the field "food contains phosphate additive" if the ingredient list has a phosphate additive. You can check this directly from label, from photograph of the label, online or in the supermarket.

9.3. **Food Field 3: Presence of phytic acid for relevant foods:** We will mark foods with a significant phytic acid/ phytate content only: We believe that phosphorus in foods with significant phytic acid is poorly absorbed and we want to be able to describe phosphorus intakes in terms of total intake and the percentage in foods with a high phytic acid content. To do this we need to mark / check all foods with a significant phytic acid content as we enter the foods.

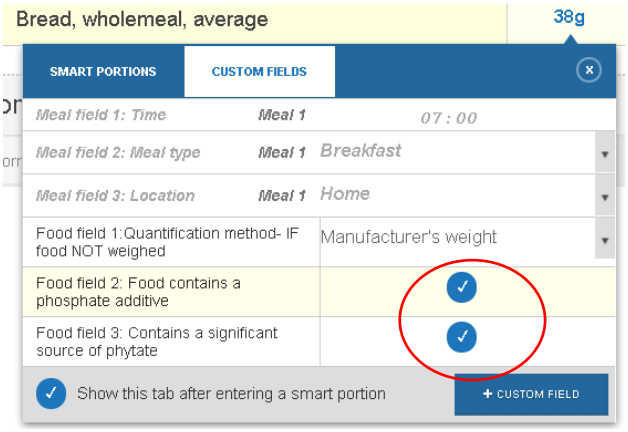
The main sources of phytate in the daily diet are cereals and legumes, including oil seeds and nuts [109].

We will take the list to contain

- Pulses
- Nuts
- Wholemeal / wholegrain breads, cereals, pasta, rice

The list of standardised food codes that I will send will already have this information added

<u>If you need to use a Mc Cance recipe /composite dish code that contains a phytate food please discuss with Fiona</u>

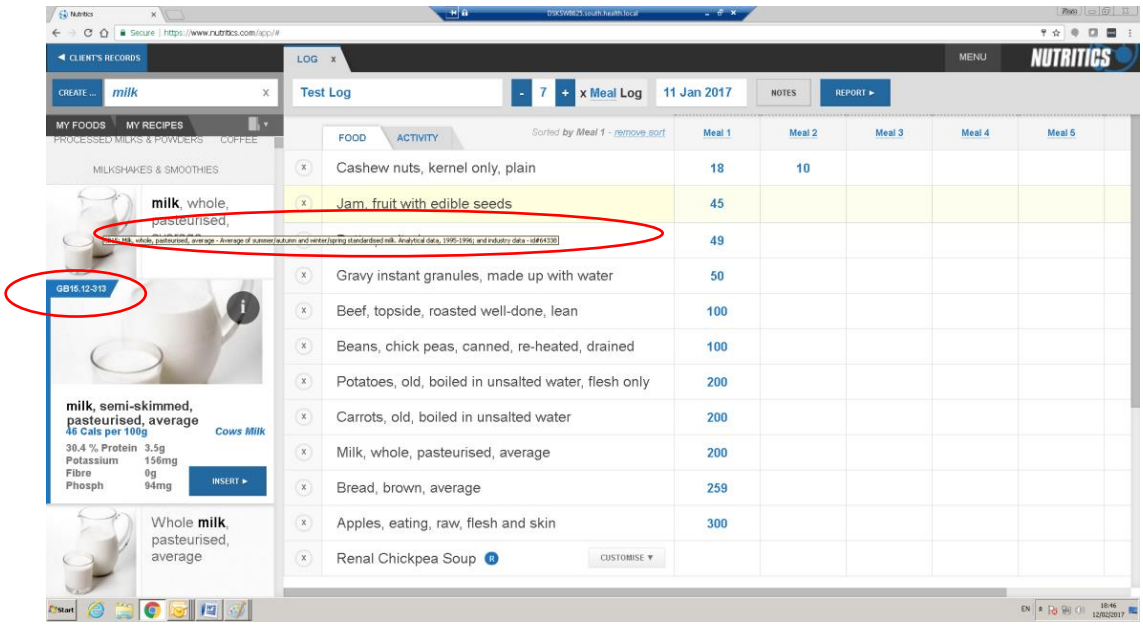


10. Binders will be added as a food code – one entry per meal

11. You will enter a second separate log under the same subject ID for the second day of the weighed intake

ANALYSIS OF FOOD DIARIES – FOOD DATA ENTRY

1. Databases to be used (these have been pre selected):
   1.1. Mc Cance & Widdowson 7 Data (Excellent sampling – robust methodology) = **GB15.** This database will always be your **first choice**.
      1.1.1. If you place the mouse on the picture the database GB15 will appear followed by a brief description of food.
      1.1.2. If you click on the food the database source and original food code will be displayed at the top left of the search



   1.2. Mc Cance & Widdowson 6 Data (GB08) should only be used where GB15 data does not exist.
   1.3. USDA is suitable for fresh produce if you put the mouse over the food name a popup bar start with US15 will appear
   1.4. Please read the 2015 COFID User Guide and the description of the development of an on-line Irish food composition database for nutrients [262] in the resource file.

2. Dietitians should choose food codes from Mc Cance & Widdowson 7 data that most closely matches the food recorded by the patient. Make sure to look at all options available on the list.

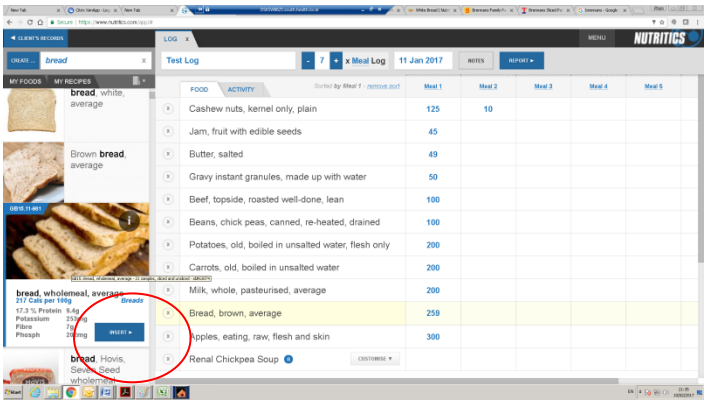
3. Fiona Byrne will provide units with a list of **standard food codes** for certain foods generated from the diet sheets including sliced pan; processed meats with no phosphate additives , double boiled potatoes, chickpeas , butterbeans and kidney beans with no added salt. As queries come in Fiona will add to the list.

4. **New Food Codes:** Any new food codes will be entered centrally by Fiona Byrne. We will communicate updates and new codes to coding team using Email info – keep the same thread with an excel database of new food codes attached.

5. **New Recipes:** Will be entered centrally by Fiona Byrne – please email Fiona with a copy of the recipe (scan / take a photo / type up).

6. If you have sent a query to the coordinating centre please make a note of same ie where the data gap is e.g. subject 3 ; day 2; lunch (e.g. in excel file) and tick off when entered into the diary. As queries come into Fiona she will also note and QC same.

7. Make sure when the food code pops up that there is data for phosphorus. Make sure the food has values for nutrients of key interest **<u>Phosphorus,</u>** Potassium, Fibre.



8. Special considerations coding for phosphorus
    a. Very important if food is boiled to capture this as P is leached
    b. Some food groups vary in use of additives e.g. biscuits but Mc Cance pools data. Encourage collection of packaging – it will help you to code the food and it means that you can check a custom field confirming whether phosphate additives were used in the food. This will help us to correct / adjust dataset afterwards if required. If patients are unable to bring in the wrapper ask them to take a photo of it with their smart phone.

9. QC
    a. When entering data – after each day recheck the food entered against the diary (1st line QC).
    b. Recommended QC Professor Mairead Kiely involves rechecking 10-12% entries. On completion of data entry, all diaries will be send to Cork for final QC checking by Fiona (2nd line QC)

10. Data entry should be undertaken by the research dietitian. If you are not in a position to undertake this work please contact Fiona.

TIME SHEET

Data we collect, on the time commitment this study took, will be essential in helping us to plan future studies. If you could take time at the end of each day (perhaps when you are doing your stats) to record the total hours time spent on study activities e.g. 2.5hrs. Excel Timesheet in the resources folder.

Appendix 1 of SOP
Instruction re calculating protein allowances including LBV.

There is very little evidence for HBV. In practical terms, 70% HBV achieves approx 28kcal/kg (www.irishkidneydiet.ie website data) and 50-70% allows flexibility to achieve energy. Pulses are not HBV and so when including 2 protein exchanges as pulses and nuts will not exceed 70% HBV

Practical Example:
IBW = 70kg
Protein requirement = 77g

1. Aim just under 70% milk & protein exchanges : Take 1 for milk and give the rest as protein exchanges ROUNDING DOWN i.e. 54g HBV = 1 Dairy + 6 protein exchanges (including vegetarian allowances) = 49g protein
2. Calculate remaining protein = 77g - 49 = 28g
3. Deduct 4 for fruit and vegetable 28g – 4g = 24g
4. Deduct 4 for potato = 24g – 4g = 20g
5. Divide the remaining protein as bread & cereal exchanges
6. **Adjust for normal dietary pattern/ patient preference / energy requirements**

Appendix 2 of SOP

Suggested for unit where all bloods done in one week & Dietitian works over 5 days 9-5pm

	Monday	Tuesday	Wednesday	Thursday	Friday	Sat	Sun
Morning	Subject 1	Subject 5	Subject 9	Subject 13	Subject 17		
Morning	Subject 2	Subject 6	Subject 10	Subject 14	Subject 18		
Afternoon	Subject 3	Subject 7	Subject 11	Subject 15	Subject 19		
Afternoon	Subject 4	Subject 8	Subject 12	Subject 16	Subject 20		

Appendix 3 of SOP
Weighed Intake Standard Operating Procedure for DIP HD
Dr. Carol Ní Chaoimh, Department of Food & Nutritional Science, UCC
Date: 19-1-17

Equipment required
Food diary, digital food scales, items (e.g. plate) for demonstration, plastic bag for food packaging

Food diary
The food diary contains:

- Subject identifiers: study ID and date of birth
- The dates of designated recording days
- Contact details for dietitian
- Instructions on how to complete the diary and use the scales
- Sample recording page
- Recording pages
- Sample recipe page
- Recipe pages
- Evaluation of the food diary
- Additional note pages.
- Back of the diary: reminder notes for filling in the diary

Designating recording days

- The diary will be given to participants in week 4, to be completed by week 5 **(before monthly bloods***)).*
- Diary is to be completed over two non-consecutive days, one to be a dialysis day and the other a non-dialysis day.
- These days are to be decided at the participant's appointment and recorded on the first page of the diary.

Dietary assessment protocol

1. Remind participant that a weighed food diary is being collected as part of the study.
2. Explain that all food and drink consumed over the two designated days needs to be recorded in the diary. Binders also need to be included in the diary.
3. It should be stressed to participants that what they eat during a recording day should be reflective of their diet in recent weeks and that the diary should not influence what they eat.

4. Instructions, including examples on how to complete the food diary are available at the beginning of the diary and should be used when explaining the methodology to the participant.

Instructions for completing the food diary

- Begin dietary recording at MIDNIGHT on your designated recording day.
- ALL food, drink and binders need to recorded in the diary, including snacks and drinks between meals.
- Use a NEW PAGE in the diary for each separate eating occasion.
- Use a NEW LINE in the diary for every item of food or drink that you consume.

- Complete the following on the top of the page for each eating occasion:
    - Date
    - Day of the week
    - Dialysis or non-dialysis day
    - Time
    - Type of meal
    - Location (Home/work/restaurant)
    - Phosphate binder

Instructions for weighing food and drink

- Check the **battery** in the scales on the day before recording
- Ensure that the scales is on a hard surface (counter/table) before weighing begins.
- Turn the scales on and wait until “0g” appears.
- Put the empty container, e.g. bowl/plate/cup, on the scales and press the on/tare button – the scales should now read “0g” with the container on it.
- Put the first food or drink item onto/into the container on the scales and write this weight, including a description of the food/drink in your diary. The description should include a brand name and cooking method, of applicable.
- Leaving the container on the scales, press the on/tare button – this should now read “0g” again.
- Now place the second food or drink item onto/into the container on the scales and write this weight down, including the description.

- Once all food and drink items have been weighed in the container and recorded in the diary, the container containing all the food items (or drink) can be taken off the scales.
- ***Leftovers:*** When you have finished eating, turn the scales on again and wait until "0g" appears. Put the container with any leftovers on the scales and write this weight down in the diary. Place a tick near leftover food/drink items. Describe leftovers in the space provided. Inedible food items such as bones and fruit peel should also be weighed as leftovers.
- ***Packaged food items:*** For items such as yogurt and desserts eaten from the pot, the pot should weighed before and after the contents have been eaten. Please keep packaging for food and drink items in the bag provided or take a photo of the label, including nutritional data and weight.
- ***Recipes:*** Recipes for homemade dishes should be recorded in the pages provided at the back of the diary. Give as much detail as possible including quantities of ingredients use, liquids added during cooking and cooking method. Weigh your portion and leftovers and record in the diary.

5. Participants should be encouraged to review the diary at the end of the recording day to check that all food/drink consumed was recorded. Any items forgotten should be recorded at this point.
6. At the end of the recording period, participants should complete an evaluation of the diary, including whether quantities/types of food were the same as usual and if different, reasons why, e.g. feeling unwell, eating out etc.
7. Participants should bring the diary and scales with them to their next appointment.

Diary review

The following items should be checked on receipt on the completed food diary as entries may need to be clarified by the participants:

- Go through the diary with the participant to check if any meals/foods were left out
- Check for blanks – at the top of the page, food items not weighed etc., leftovers etc.
- Clarify and illegible handwriting
- Ensure brand information is recorded
- Ensure recipes and portions of composite dishes are recorded
- Ensure that evaluation has been completed

Before entry into the nutritional analysis software (Nutritics), quantify the final weights of foods consumed (i.e. minus leftovers) and enter into the column titled "office use".

Quantifying leftovers: Generally, participants will weigh leftovers together on the original container on which the food was served. Subtract the empty container weight from the weight of the leftovers. If an adequate description of the leftovers is provided, this may be used to calculate the proportion of each food leftover. If a description is not provided, use the proportions of the food served.

Quantification protocol

Participants should be encouraged to weigh ALL food and drink items with the scales provided. However, some weights will have to be estimated using other methods.

The following quantification methods were used in the recent National Adult Nutrition Survey conducted by the Irish University Nutrition Alliance (IUNA):

(1) *Weighed by respondent/manufacturer weights)* - 46% of foods and drinks consumed were weighed. A further 10% of weights were derived from manufacturer‟s weights. To facilitate collection of such data, researchers asked respondents to collect all packaging of food and beverages consumed in a storage bag provided.

(2) *Food Atlas* - A photographic food atlas (Nelson *et al.,* 1997) was used to quantify 16% of foods and beverages consumed.

(3) *IUNA Weights* - Average portion weights that had been ascertained for certain foods by the IUNA survey team were used. This method was used to quantify 4% of foods and beverages consumed.

(4) *Food Portion Sizes* - "Food Portion Sizes" (Ministry of Agriculture, Fisheries and Food, 1997) was used to quantify 11% of foods and beverages consumed.

(5) *Household Measures* - Measures such as teaspoon, tablespoon, pint etc. were used to quantify 11% of foods and beverages consumed.

(6) *Estimated* - Food quantities were defined as estimated if the researcher made an estimate of the amount likely to have been consumed based on their knowledge of the respondent's general eating habits as observed during the recording period. This method was used to quantify 2% of foods and beverages consumed.

Other resources for quantification: The Irish Food Portion Sizes Database (www.iuna.net)

Appendix 4 of SOP: Renal Bread & Cereals

Food Name	**g**	**Measure**	**Source**	Kcal	**CHO**	**Protein**	**Na** mg	**K** mg	**P** mg
Bagels plain	45	1/2 medium	SMART / Tesco	123	26	4.5	248	59	54
Bread rolls white crusty	40	petit pain	SMART	105	22	3.7	160	66	42
Bread pitta white	33.5	1/2 oval	SMART	85	18.5	3	134	60	33.2
Bread wholemeal average	37	1 medium slice	SMART	80	15.5	3.5	148	94	75
Breakfast cereal cornflakes fortified	25	1 cup =23g	MMUH CUH	94	22.7	1.8	113	22	11.5
Breakfast cereal malted flake fortifie	25	1 cup =35g	CUH	93	20.9	3	95	54	44
Breakfast cereal wheat biscuits Weetabix type fortified	20	1 biscuit	SMART	66	14.5	2.1	52	79	52
Couscous plain cooked	55	3 dsp	MMUH	98	20.6	4	2.2	85	71
Cream crackers	21	3	SMART	93	14.6	1.9	81	45	21.6
Oat flakes rolled	25	1/3 cup	MMUH CUH	95	17.7	2.7	0.3	93	97
Oatcakes plain retail	33	3	SMART	149	20.7	3.1	263	118	126
Pasta white dried boiled in unsalted water	55	3 dsp	MMUH	93	20.5	3	0.6	63	48
Pasta wholewheat spaghetti dried boiled in unsalted water	55			74	15.1	2.9	2.8	45	68
Rice cakes plain low salt	27		SMART	97	21.4	2	23.5	75	83
Rice brown easy cook boiled in unsalted water	66	2.5 dsp= 55g adjusted	MMUH	104	23.3	2.1	0.7	66	93
Rice white basmati easy cook boiled in unsalted water	66	3 dsp		91	21.3	2.3	2.6	10.6	25.1
Rice white basmati raw	25			88	20.9	2	0.3	19.3	25.3
Rice white long grain easy cook boiled in unsalted water	55			80	19.1	1.7	3.3	9.9	21.5
Rice white long grain easy cook raw	25			87	20.6	1.8	0.5	39	39.8
Tortilla wheat flour soft	30	1/2 medium	SMART	86	16.2	2.3	187	37.8	64
		AVERAGE		**92.5**	**19.3**	**2.6**	**66.8**	**56.9**	**54.8**

Rice & pasta overrepresented

HD Task Summary v2

Week	Task
3-4 weeks pre trial	Screen
2-3 weeks pre trial	Inform → consent → Assign study number
1 week pre trial	Baseline data *Form 1*
Week 1 trial	Baseline bloods *Form 2* → Dietary assessment *Form 1* → **Randomise** → **Educate** *Form 4*→ order check K
Week 2 trial	Assess protein (Diet B) *Form 4* → encourage compliance *Form 4* → check adverse events → check K (10 ± 2 days) *Form 2*
Week 4/5 trial	Food diary education →set diary dates (pre end of intervention bloods) →encourage compliance → check adverse events
Week 5/6 trial	Clarify diary → check tolerance *Form 3a/b* → check adverse events → return to renal diet → End of Intervention bloods & data *Forms 2&6*

Diet A - CURRENT RIG DIET **Diet B - REVISED RIG DIET**