Randomized Controlled Trial of Nutritional Counseling on Body Composition and Dietary Intake in Severe CKD

Campbell, Katrina L.; Ash, Susan; Davies, Peter S. W.; Bauer, Judith D

Published in:
American Journal of Kidney Diseases

DOI:
10.1053/j.ajkd.2007.12.015

Randomized-controlled trial of nutritional counseling on body composition and dietary intake in severe chronic kidney disease

Katrina L Campbell PhD, Susan Ash PhD, Peter SW Davies PhD, Judith D Bauer PhD

Institute where the work was done:
Institute of Health and Biomedical Innovation, Queensland University of Technology (KLC, SA)
Department of Nutrition and Dietetics, Royal Brisbane and Women's Hospital (KLC, SA)
Wesley Research Institute, The Wesley Hospital (JDB)
Children's Nutrition Research Centre, Royal Children's Hospital, University of Queensland (PSWD)

Corresponding Author:
Katrina L Campbell PhD B Hlth Sc (Hons)
Department of Nutrition and Dietetics
King's College London
150 Stamford Street, London, SE1 9NH, UNITED KINGDOM

Phone: +44 2 07848 4269
Fax: +44 2 07848 4195
Email: katrina.campbell@kcl.ac.uk

Registered Trial: ACTRN012606000493549

Word count:
Abstract: 271
Manuscript body 3479

Running head: Nutrition intervention in pre-dialysis CKD
The authors have no conflict of interest to declare.

This study was funded in part by a Royal Brisbane and Women's Hospital Foundation Seeding grant, Queensland University of Technology Postgraduate Research Award (PhD scholarship) and an Institute of Health and Biomedical Innovation Research Scholarship.

Abstract

Background: Progressive reduction in renal function results in an increased risk of malnutrition. Despite this, there is little evidence informing the impact of nutrition intervention on pre-dialysis chronic kidney disease (CKD, Stage IV and V).

Study design: Randomized-controlled trial

Setting and participants: Fifty-six (Male 62%; age mean (SD) 70.7 (14.0) years) CKD outpatients,were randomly allocated to intervention (n=29) or control (n=27) by concealed computer-generated sequence.

Intervention: Intervention group were provided with individualized dietary counseling with regular follow-up, aimed at achieving an intake of 0.8-1.0g/kg protein and >125kJ/kg energy; or control, receiving written material only.

Outcomes: Body composition, nutritional status and dietary intake

Measures: Change in body composition (body cell mass, BCM, measured by total body potassium, in 40/56 participants), nutritional status (Subjective Global Assessment, SGA) and energy and protein intake (three-day food record).

Results: Over the 12 weeks, the control group lost BCM (-3.3% (95% CI -6.9 to 0.4)), whilst the intervention group maintained (0.60% (-2.9 to 4.1)). The overall difference in change between treatment groups for BCM 3.6% (-1.0 to 8.7) and energy intake 17.7kJ/kg/day (8.2 to 27.2) and improvements in SGA (X^2 (2) = 12.76 (P<0.01)), favoring the intervention treatment. A large response to treatment allocation was demonstrated in female participants, with little change observed in males for either group.

Limitations: Power to detect sex differences, change in BCM and potential bias in ascertainment of SGA**.**

Conclusions: Structured nutrition intervention may provide beneficial patient outcomes including limiting deterioration in nutritional status and increasing dietary energy intake when

compared with control treatment for patients in pre-dialysis. Further investigations are warranted to determine the impact of such interventions on body composition.

Index words: Nutrition intervention; chronic kidney disease; pre-dialysis; randomized-controlled trial; body cell mass; dietary counseling

Registered Trial: ACTRN012606000493549

Introduction

Malnutrition is present in up to 48% of patients at the time of dialysis initiation[1] and is an independent and significant predictor of morbidity and mortality.[2] In Stage 4 chronic kidney disease (CKD) (glomerular filtration rate (eGFR) 15-30 mL/min/1.73m^2) the focus of the medical treatment shifts to managing metabolic disturbances and preparing patients for renal replacement therapy (RRT).[3] requiring multidisciplinary care to manage symptoms, treat co-morbidities and prevent complications [3], including optimising nutritional status.[4]

Deterioration in nutritional status often predates the onset of RRT.[5, 6] Patients with advanced CKD who are not receiving nutritional management demonstrate the greatest deterioration in nutritional status before RRT initiation[7]. Considering this, there is a need for careful nutritional monitoring and appropriate dietary prescription and implementation of nutritional care at this time.[8]

Studies in severe CKD prior to RRT have focused on dietary prescription, in particular, restricting protein to below recommended dietary allowance with an aim to provide better metabolic control, and potentially delay the progression to dialysis initiation. A significant number of studies, including four meta-analysis[9-13] have investigated this relationship, yet, the efficacy of a low-protein diet to retard renal failure progression is conflicting and severely restrictive diets have poor compliance.[14, 15] It appears there may be no greater benefit of restricting protein below what is recommended for healthy adults.[16]

Implementation of nutrition intervention refers to the type, duration, content and location of the nutrition care. Evidence from the Modification of Diet in Renal Disease (MDRD) study demonstrate dietary compliance increases with self-management interventions involving

patients with ongoing feedback, monitoring and support.[17-19] The National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative (K/DOQI) guidelines for nutrition care prior to dialysis recommend frequent nutritional counselling and monitoring, especially in patients presenting with an inadequate intake and/or signs of malnutrition.[8]

To the authors knowledge, no controlled trial to date has been published to evaluate the effectiveness of implementation, with the aim to optimise nutritional status prior to dialysis, by promoting a controlled portion (0.8-1.0 g/kg), high energy (>125kJ/kg) intake.[4, 20] The purpose of this study was to determine if providing individual nutrition counseling with regular telephone follow-up improves body composition, energy intake and nutritional status compared with providing written material only.

Methods

Potential participants were approached upon consecutive entry into a pre-dialysis outpatient clinic at the Royal Brisbane and Women's Hospital. Eligible participants met the following criteria: adult (>18 years); eGFR <30ml/min CKD; not previously seen by a dietitian for Stage IV CKD; an absence of communication or intellectual impairment inhibiting their ability to undertake the intervention; an absence of malnutrition from a cause other than CKD; and not expected require RRT within six months. Participants were randomly allocated to receive either individualised nutritional counselling (intervention group) or written education material (control group) via a computer-generated number sequence, concealed to the recruiting officer until after baseline assessment.

The intervention, administered by a single dietitian, aimed to provide an individualised dietary prescription (including energy (125-146kJ/kg/day), and protein (0.75 - 1.0g/kg/day))[4], incorporating K/DOQI recommendations to provide intensive nutritional counselling with regular monitoring. The delivery of the intervention was guided by the medical nutrition therapy framework from the American Dietetic Association, and followed the structure provided in Figure 1.[21, 22] The intervention group were provided with an initial individual consultation at baseline, of up to 60 minutes duration, followed by telephone consultation, commonly 15 to 30 minutes duration, fortnightly for the first month, then monthly. The intervention utilised self-management principles: goal setting, menu planning, label reading and identification of foods containing protein, sodium etc, depending on requirements. Participants in the control group received generic nutrition information tailored for CKD (as provided in regular clinical practice).

The length of the intervention was 12 weeks following baseline assessment. No participants in either group voluntarily dropped out of the study following receipt of intervention, as per CONSORT flowchart in Figure 2.

Ethics approval was granted by the Royal Brisbane and Women's Hospital and Queensland University of Technology Human Research Ethics Committees and informed consent was obtained from each participant. The following outcome measures included were collected at baseline (week 0) and week 12.

Body composition measurements

The primary outcome of this study was the assessment of body composition by total body potassium counting (TBK), a measure of body cell mass (BCM) the body's functional metabolising tissue. TBK analysis was performed using a shadow shield whole-body counter (Accuscan, Canberra Industries, MA, USA), which requires the participant to lie supine on a bed that is moved under three sodium iodide detectors. Two 1100 second scans were performed on each participant with all personal metallic objects removed. The detectors count 1.46MeV gamma rays being emitted by the potassium-40 (40K). Background and sensitivity checks were completed daily and considered in each measurement. On the basis of repeated measurements of phantoms, the precision of TBK values from this apparatus was 2.3%. The minimal detectable difference of TBK is 4% [23] is considered to be valuable research tool for monitoring progress following nutrition intervention.[24]

Anticipated change in TBK was used to determine the sample size. Based on the premise that the minimum benefit that nutrition intervention will achieve is TBK maintenance, the control group in a previously reported study, demonstrated a reduction in TBK of around 5% (± 5)

over 12 weeks in Stage IV CKD (n=12). The sample size was calculated by comparing the two means (TBK maintenance vs. 5% loss). Based on 0.8 power to detect a significant difference (P = 0.05, two-sided), 20 patients were required for each study group. The aim was to recruit 60 participants to account for anticipated attrition and missing data.

Potassium is the primary intracellular cation and, as 98% of the body's potassium is located within the BCM,[25] it is possible to determine BCM from TBK analysis. BCM was calculated from TBK using the equation of Wang et al (2003): BCM (kg) = (TBK (g) x 9.18) / 39.1).[26] The measurement of TBK to estimate BCM has been validated in CKD.[27]

Nutrition assessment

Nutrition status was also assessed using Subjective Global Assessment (SGA). This tool provides a comprehensive appraisal of nutrition status assessing change in weight, gastrointestinal symptoms (anorexia, nausea, etc), food intake, and functional capacity; and physical examination, including subcutaneous fat and muscle stores.[28] The SGA global rating classifies patients into category A (well nourished), B (moderately, or suspected of being malnourished) or C (severely malnourished) and is a well validated tool for diagnosis and prognosis of nutrition status in CKD.[29] SGA assessment was ascertained by a single assessor, who was also the dietitian undertaking the intervention and dietary intake assessment.

Dietary intake

Dietary intake was assessed using a three-day food record. The participants were requested to estimate or measure all food and fluids consumed for those three days (two weekdays and one weekend day). Food records were verified by the dietitian with visual food models and household measures to ensure accuracy.

Food records were analysed using FoodWorks (Professional Version 3.02 Xyris Software, Brisbane, Australia) a computerized food composition database, based on the Australian Nutrient Database (AusNut, Department of Human Services and Health, Canberra). The software produced an average nutrient consumption per day by calculating the mean intake over the three days of recording. Mean protein and energy intake was calculated in units per kg of ideal body weight (calculated according to Ash et al 2006).[4]

Biochemistry

Biochemical analysis including albumin by BromoCresol Purple (normal range = 3.5 – 4.8 g/dL (35–48 g/L)), C-reactive protein (CRP, high sensitive, normal range 0 – 5 mg/L (0.0–0.5 g/dL), and creatinine (normal range 0.6 – 1.3 mg/dL (53-115mol/L)) was undertaken at a central laboratory. Estimated GFR was calculated using the abbreviated (4-variable) Modification of Diet and Renal Disease (MDRD) equation.[30]

Statistical analysis was carried out using SPSS Version 13 (SPSS Inc, Chicago, IL, USA) with the level of significance set at $p<0.05$. The analysis of the effect of the intervention proceeded as per treatment allocation, irrespective of how compliant participants were with the intervention protocol. Participants were excluded from the final analysis if they either died or moved onto RRT during the 12-week trial period (classed as 'renal death' or adverse event).

Each outcome measure was converted to a change score (Week 12 – Week 0). Assessment of change in outcomes by treatment group was analysis by analysis of covariance (ANCOVA), adjusting for baseline values. Baseline eGFR, body mass index (BMI), sex and co-

morbidities were identified as potential confounders and were added to each of the original ANCOVA models. Main effects and interactions were assessed. The final model only included covariates with a significant relationship.

Results

Sixty-six consecutive subjects were considered eligible upon entry into the pre-dialysis clinic during the recruitment period from September 2004 to September 2005. Informed consent was provided from 62 subjects (62/66, 94% consent rate), following this, six were excluded prior to baseline assessment (see CONSORT flowchart, Figure 2). Therefore, 56 patients (Male 62%; age mean (SD) 70.7 (14.0) years) received either intervention (n=29), or control (written material only, n=27). Data in Table 1 demonstrate there was no significant difference between participants allocated to either treatment or control group at baseline.

Of the 56 participants who received allocated intervention, no participants voluntary withdrew from the study, however, six were lost to follow-up (four died and two went onto receive maintenance dialysis, classed as "renal death" or an adverse event), and nine had missing BCM data during the intervention period. The baseline characteristics of the final sample with complete data were compared with participants who had incomplete BCM data, and those who reached renal death in Table 2. As demonstrated in Figure 2, there were more participants in the intervention group (5 of 29) experiencing adverse events than the control group (1 of 27). Of those who died, all four were from the intervention group; in three the identified cause of death was a cardiovascular event and one from an unknown cause. One from each group commenced dialysis, both due to issues in controlling blood pressure control. Of those who completed the intervention period, nine were withdrawn from BCM assessment (three from the intervention group, and six from control); four due to voluntary withdrawal from TBK and five were too large to comfortably undertake the measure due to size limitations of the TBK sensor.

The following results are from the analysis of the 50 participants who completed the study (intervention n=24, and control n=26).

Table 3 identifies mean change in BCM (absolute (kg) and relative (%)) and intake (energy and protein) over the treatment period. BCM change assessed in 82% (n=41) of the final 50 participants, showed a reduction in the control group and no significant change in the intervention group. The data was re-analysed with an estimate of BCM maintenance for all participants lost to follow-up. Relative (%) change in BCM persisted to be not statistically significant, with similar mean difference in change as demonstrated in Table 3 (unadjusted, 2.6% (-1.4 to 6.6) p=0.2; adjusted 3.7% (-0.4 to 7.8) p=0.07).

Energy intake significantly increased over the treatment period for the intervention group and decreased in the control group, with final intake values of 114.5 ± 25.6 k/kg and 102.7 ± 22.2 kJ/kg respectively. Conversely, mean protein intake did not change significantly between groups; however, the decrease in protein in the control group alone was significant. Final protein intakes were similar between the groups (intervention 0.98 ± 0.22 g/kg and control 1.00 ± 0.25 g/kg protein).

Most participants maintained their baseline nutrition status according to SGA over the 12-week treatment period. In the intervention group, 2 participants malnourished (SGA B) at baseline died, and the remaining 5 improved their nutritional status, resulting in no malnutrition in the intervention group at week 12. In contrast, the control group had an increase in the proportion malnourished from 2/27 (11%) at baseline, to 6/26 (22%, including

1 severely malnourished, SGA C) at week 12. This difference in change in SGA between the 2 groups was statistically significant X^2 (2) = 12.76 (P<0.01).

Table 4 evaluates clinical variables between treatment groups and change over the treatment period. There was negligible difference in change between groups for CRP, eGFR and weight. The mean difference in change in albumin reached statistical significance, reflecting a significant decrease in the control group.

Adjusted estimates for change in BCM and intake are also provided in Table 3. BCM was adjusted for baseline BCM, BMI and sex. Change in dietary energy and protein intake was adjusted for baseline intake, comorbidity and sex. Therefore, sex was identified as a consistent confounding variable in a models for each of the outcome variables (main effect p= 0.005 for BCM; interaction with treatment p=0.004 for both energy and protein intake). A significant sex interaction was identified for protein and energy intake when the interaction term was significant (p=0.004, for both), and remained so when the main effect of sex was included in the model and not significant (p=0.4 and p=0.5, respectively). This suggests an effect modification influencing the treatment outcomes. A descriptive comparison of response to treatment allocation comparing each gender is presented in Figures 3 to 5. These graphs indicate a large magnitude in change for females, in particular, with reductions in control group for BCM and energy intake, and negligible change for most outcomes in the males for each group.

Discussion

There is little literature to inform nutrition practice in CKD prior to dialysis. The outcome of this study supported the use of individualised self-management nutrition interventions with regular monitoring, as previously shown to achieve compliance in pre-dialysis CKD patients in the MDRD study. [17-19] However, in this study the benefits of this intervention appeared to be restricted to females, with no difference in change following intervention in the males in this sample.

Malnutrition results in a reduced body cell mass (BCM) and concomitant expansion of extra cellular mass. It is the loss of this metabolically active component of body mass which creates the negative effects seen with malnutrition.[31, 32] A strength of this study is the use of TBK to measure BCM, therefore this measure was not influenced by changes in fluid status or non-nutritional factors.[33] From the BCM data, the metabolically active tissue of the control group declined, and that of the intervention group was maintained. While this difference was not statistically significant, it was a clinically significant difference in BCM. Declines of this magnitude in BCM are associated with increased disability (reduced strength, immune and pulmonary function) and mortality.[34, 35] It is likely that a statistically significant difference was not evident due to the fact that the 3.5% mean difference in change observed was less than the 5% which the sample size was originally powered to detect.

As with BCM, change in SGA is not a commonly reported outcome measure in the CKD literature. SGA is most commonly used to determine the prevalence and prognostic significance of malnutrition.[29] In Stage IV and V pre-dialysis, SGA B or C are significant independent predictors of poor outcome and related to higher mortality and morbidity.[6, 36] Malnutrition in pre-dialysis appears to be a predictor of progression to dialysis, increased rate

of acute hospitalisations and death, independent of GFR.[36] Prior to this investigation, only one small intervention study (n=11) exists in pre-dialysis using SGA as an outcome measure. Patients received three-monthly nutrition intervention, and at 6 months, all well-nourished patients maintained nutritional status, and 2 of the 3 malnourished patients were reclassified as well-nourished.[37] This intervention was not randomised or as intensive as the investigation featured in this paper, however, further supports the importance of intervention and follow-up to promote at least maintenance of nutritional status in pre-dialysis.

Dietary energy intake appeared to be an important intermediate outcome driving nutritional status changes in the treatment groups, as particularly evidenced by change for females in Figures 3 and 4. Sufficient energy and quality protein intake is essential for the maintenance of nitrogen balance.[38] Although there is some evidence that protein intake >0.8g/kg may induce a faster rate of decline in GFR compared with low-protein diet,[39] there are clear risks with provision of a restricted-protein diet (<0.6g/kg/day) that may include simultaneous reduction in energy intake and nutrition status parameters (TBK, weight, albumin etc).[40, 41] In this study, the intervention promoting sufficient energy intake, whilst controlling protein intake, resulted in attenuating declines in nutritional status; a surrogate for potential improvements in mortality and morbidity outcomes.

Albumin significantly decreased in the control group and was maintained in the intervention group, resulting in a significant mean difference in albumin between the two groups at week 12. This magnitude of difference reflects the results of other nutrition support interventions in CKD.[42, 43]

In this study, there appeared to be significant effect modification by gender for each of the nutrition related outcomes, with no difference between treatment groups for males, while the females had a significant difference in change in all variables between groups.

The literature supports that nutritional markers predicting outcome can differ by sex. Observational studies, using TBK to monitor nutrition status over a longer period of CKD progression indicate a progressive reduction in BCM in females only.[44] In the MDRD study, GFR correlated with dietary energy intake in women but not in men.[45] Disparities have also been noted in an investigation to determine sex-specific associations between subjects with human immunodeficiency virus characteristics and change in body composition, in response to treatment.[46, 47] Finally, longitudinal and cross-sectional studies report a greater magnitude of change in fat-free mass in females with aging.[48, 49] A possibility is that the final phase of CKD decline prior to dialysis mimics a fast-track of the natural trajectory of FFM decline.[50]

Aside from the differences noted in the physiology between genders, the self-management focus of the treatment relies on patients self-efficacy and responsibility for their own care. Despite men and women reporting similar barriers to compliance with dietary prescription, women demonstrate better adherence to diets.[51] Studies have indicated that locus of control is age-dependant, with older males relying more heavily on chance and other factors, rather than themselves for change.[52] Females report a strong orientation toward self-management of health-care needs and were more likely to instigate behavior change.[52] This observed gender difference may have implications for practice and requires future research to determine if it is a reflection of a ‘true’ response.

This study had a number of limitations, which include; the sample size, which was under powered to detect statistically a clinically significant change in BCM, short treatment duration (12 weeks); exclusion of patients close to dialysis commencement (those who potentially may benefit the most from the intervention), and was isolated to a single center. In addition, there is potential bias in the ascertainment of the SGA as it was performed by the same person delivering the intervention.

There was missing primary outcome data and adverse events which may have introduced bias. However, as demonstrated in Table 2, there appeared to be no systematic bias when comparing the baseline characteristics of those who reached renal death, had missing BCM data to those who completed the study with full data. The most notable discrepancy between the groups existed for BMI and co morbidities. BMI was notably higher in the participants with no BCM outcome data (29.5 ± 7.6 kg/m^2) compared with those with full outcome data (26.9 ± 4.3 kg/m^2). This can be partially explained participants with a large waist circumference being excluded from the TBK analysis due to size restrictions. Co morbidity index was higher in the group that did not complete the study due to death or dialysis, indicating this group was at higher risk of these complications from baseline. This stage of CKD is associated with a 3.2- and 5.9-fold increased risk of death[53], and mortality rates close to 50% over 5 years[54]. Therefore, although the mortality rate in the intervention group in this study was high (4/29), it was to be expected in this kind of population.

By use of a rigorous design, this study demonstrated structured dietetic intervention may be effective in attenuating declines in nutritional status of pre-dialysis CKD patients. Utilising counselling via telephone follow-up limited the logistical barriers of patient contact, therefore

improving the ability for this research to be translated into practice. This study represents a foundation for which to build the evidence-base for models of dietetic care in pre-dialysis. Further recommendations for future research include conducting a cost-benefit analysis for the implementation of this service into pre-dialysis management and investigations into the benefit of nutrition intervention on improving body composition.

Conclusion

The provision of individual nutrition counseling and regular follow-up, with a focus on promoting intake produces beneficial patient outcomes. Declines in body cell mass in uraemia may be attenuated or reversed, supporting the development of optimal nutritional status in pre-dialysis CKD patients. However, the impact of intervention was significant only for females, who demonstrated a poorer response to the control treatment. The potential gender difference in response to treatment requires further investigation.

Acknowledgements:

We would like to acknowledge Dr Helen Healy at Director of Renal Medicine and Julie Hulcombe, Director of Allied Health at Royal Brisbane and Women's Hospital, for their in-kind support and contribution to the study; and Justin Scott (Queensland Institute of Medical Research) for statistical support.

Author Contributions: KLC was the main author of the manuscript, initiated the study, collected the data and carried out the statistical analysis and interpretation. SA and JDB initiated the study, supervised the project, assisted in the statistical analysis and interpretation and writing the manuscript. PSWD assisted in the statistical analysis, interpretation and writing of the manuscript.

References

1. Heimburger O, Qureshi AR, Blaner WS, Berglund L and Stenvinkel P: Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. Am J Kidney Dis 36: 1213-1225, 2000

2. Stenvinkel P, Barany P, Chung SH, Lindholm B and Heimburger O: A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. Nephrol Dial Transplant 17: 1266-1274, 2002

3. Bolton WK: Renal physicians association clinical practice guideline: appropriate patient preparation for renal replacement therapy: guideline number 3. J Am Soc Nephrol 14: 1406-1410, 2003

4. Ash S, Campbell KL, MacLaughlin H, et al.: Evidence Based Practice Guidelines for Nutritional Management of Chronic Kidney Disease. Nutr Diet 63: S35-S45, 2006

5. Barrett BJ, Parfrey PS, Morgan J, et al.: Prediction of early death in end-stage renal disease patients starting dialysis. Am J Kidney Dis 29: 214-222, 1997

6. Churchill D, Taylor, WD., Keshaviah, PR.: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol 7: 198-207, 1996

7. Ikizler TA, Greene JH, Wingard RL, Parker RA and Hakim RM: Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol 6: 1386-1391, 1995

8. National Kidney Foundation: K/DOQI clinical practice guideline for nutrition in chronic renal failure. Am J Kidney Dis 39: s1-s140, 2000

9. Fouque D, Laville M and Boissel JP: Low protein diets for chronic kidney disease in non diabetic adults (Cochrane Review). Cochrane Database Syst Rev, 2006

10. Fouque D, Wang P, Laville M and Boissel JP: Low protein diets for chronic renal failure in non diabetic adults (Cochrane Review). Cochrane Database Syst Rev, 2004

11. Pedrini MT, Levey AS, Lau J, Chalmers TC and Wang PH: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: A meta-analysis. Ann Intern Med 124: 627-632, 1996

12. Kasiske B, Lakatua J, Ma J and Louis T: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. Am J Kidney Dis 31: 954-961, 1998

13. Fouque D, Laville M, Boissel JP, Chifflet R, Labeeuw M and Zech PY: Controlled Low Protein Diets in Chronic Renal-Insufficiency - Metaanalysis. Br Med J 304: 216-220, 1992

14. Johnson DW: Dietary protein restriction as a treatment for slowing chronic kidney disease progression: The case against. Nephrol 11: 58-62, 2006

15. Aparicio M, Chauveau P and Combe C: Low protein diets and outcome of renal patients. J Nephrol 14: 433-439, 2001

16. Kellet E, Smith A and Schmerlaib Y: The Australian Guide to Healthy Eating - Background information for nutrition educators, Canberra ATC : Commonwealth Department of Health and Family Services, 1998

17. Milas N, Nowalk MP, Akpele L, et al.: Factors Associated with Adherence to the Dietary Protein Intervention in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 95: 1295-1300, 1995

18. Gillies BP, Caggiula AW, Chiavacci AT, et al.: Nutrition Intervention Program of the Modification of Diet in Renal Disease Study: A Self-Management Approach. J Am Diet Assoc 95: 1288-1294, 1995

19. Doleck TA, Olson MB, Caggiula AW, et al.: Registered Dietitian Time Requirements in the Modification of Diet in Renal Disease Study. J Am Diet Assoc 95: 1307-1312, 1995

20. Voss D: The CARI Guidelines: Nutriton and Growth in Kidney Disease. Nephrol 10: S177-S203, 2005

21. American Dietetic Association: Chronic Kidney Disease (non-dialysis) Medical Nutrition Therapy Protocol: Medical Nutrition Therapy Evidence-Based Guides for Practice. Chicago, American Dietetic Association., 2002

22. Wiggins K: Guidelines for Nutritional Care of Renal Patients. Renal Dietitians Dietetic Practice Group, American Dietetic Association Chicago: American Dietetic Association, 2002

23. Ellis KJ: Human Body Composition: In Vivo Methods. Physiol Rev 80: 649-680, 2000

24. Dolson GM, Ellis KJ, Johnson ML and Adrogue HJ: Incidence and consequences of total body potassium depletion in chronic hemodialysis patients. Front Biosci 1: 126-132, 2003

25. Moore F: Energy and the maintenance of the body cell mass. JPEN J Parenter Enteral Nutr 4: 228-260, 1980

26. Wang Z, Zhu S, Wang J, Pierson RN, Jr and Heymsfield SB: Whole-body skeletal muscle mass: development and validation of total-body potassium prediction models. Am J Clin Nutr 77: 76-82, 2003

27. Woodrow G, Oldroyd B, Wright A, et al.: The measurement of total body potassium in patients on peritoneal dialysis. Perit Dial Int 21: S163-167, 2001

28. Ottery F: Patient-Generated Subjective Global Assessment, in McCallum P, Polisena, C., (ed): The Clinical Guide to Oncology Nutrition. Chicago, American Dietetic Association, 2000, pp 11-23

29. Campbell KL, Ash S, Bauer J and Davies PSW: Critical review of nutrition assessment tools to measure malnutrition in chronic kidney disease. Nutr Diet 64: 23-30, 2007

30. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N and Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130: 461-470, 1999

31. Tchekmedyian N, Zahyna D, Halpert C and Heber D: Assessment and maintenance of nutrition in older cancer patients. Oncology (Huntingt) 6: 105-111, 1992

32. Cederholm T, Jagren C and Hellstrom K: Outcome of protein-energy malnutrition in elderly medical patients. Am J Med 98: 67-74, 1995

33. Cohn SH, Vartsky D, Yasumura S, Vaswani AN and Ellis KJ: Indexes of body cell mass: nitrogen versus potassium. Am J Physiol Endocrinol Metab 244: E305-310, 1983

34. Castaneda C, Charnley J, Evans W and Crim M: Elderly women accommodate to a low-protein diet with losses of body cell mass, muscle function, and immune response. Am J Clin Nutr 62: 30-39, 1995

35. Arora N and Rochester D: Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. Am Rev Respir Dis 126: 5-8, 1982

36. Lawson JA, Lazarus R and Kelly JJ: Prevalence and prognostic significance of malnutrition in chronic renal insufficiency. J Ren Nutr 11: 16-22, 2001

37. Cliffe M, Bloodworth LL and Jibani MM: Can malnutrition in predialysis patients be prevented by dietetic intervention? J Ren Nutr 11: 161-165, 2001

38. Kopple JD: Dietary protein and energy requirements in ESRD patients. Am J Kidney Dis 32: S97-104, 1998

39. Mandayam S and Mitch WE: Dietary protein restriction benefits patients with chronic kidney disease. Nephrol 11: 53-57, 2006

40. Meloni C, Morosetti M, Suraci C, et al.: Severe dietary protein restriction in overt diabetic nephropathy: benefits or risks? J Ren Nutr 12: 96-101, 2002

41. Castaneda C, Gordon PL, Uhlin KL, et al.: Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. Ann Intern Med 135: 965-976, 2001

42. Leon J, Majerle A, Soinski J, Kushner I, Ohri-Vachaspati P and Sehgal A: Can a nutrition intervention improve albumin levels among hemodialysis patients? A pilot study. J Ren Nutr 11: 9-15, 2001

43. Leon JB, Albert JM, Gilchrist G, et al.: Improving albumin levels among hemodialysis patients: A community-based randomized controlled trial. Am J Kidney Dis 48: 28-36, 2006

44. Brennan BL, Letteri JM, Cohn SH and Ellis KJ: Serial measurements of body composition and total body mineral content in dialysis and nondialysis patients with renal failure. Miner Electrolyte Metab 13: 451-461, 1987

45. Kopple J, Berg R, Houser H, Steinman T and Teschan P: Nutritional status of patients with different levels of chronic renal insufficiency. Modification of Diet in Renal Disease (MDRD) Study Group. Kidney Int 27: S184-194, 1989

46. Visnegarwala F, Raghavan SS, Mullin CM, et al.: Sex differences in the associations of HIV disease characteristics and body composition in antiretroviral-naive persons. Am J Clin Nutr 82: 850-856, 2005

47. Kotler DP, Thea DM, Heo M, et al.: Relative influences of sex, race, environment, and HIV infection on body composition in adults. Am J Clin Nutr 69: 432-439, 1999

48. Roubenoff R, Hughes VA, Dallal GE, et al.: The Effect of Gender and Body Composition Method on the Apparent Decline in Lean Mass-Adjusted Resting Metabolic Rate With Age. J Gerontol A Biol Sci Med Sci 55: M757-760, 2000

49. Newman AB, Haggerty CL, Goodpaster B, et al.: Strength and Muscle Quality in a Well-Functioning Cohort of Older Adults: The Health, Aging and Body Composition Study. J Am Geriatr Soc 51: 323-330, 2003

50. Kyle U, Genton L, Hans D, Karsegard L, Slosman D and Pichard C: Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. Eur J Clin Nutr 55: 663-672, 2001

51. Chung ML, Moser DK, Lennie TA, et al.: Gender differences in adherence to the sodium-restricted diet in patients with heart failure. J Card Fail 12: 628-634, 2006

52. Buckelew S, Shutty Jr M, Hewett J, Landon T, Morrow K and Frank R: Health locus of control, gender differences and adjustment to persistent pain. Pain 42: 287-294, 1990

53. Go AS, Chertow GM, Fan DJ, McCulloch CE and Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351: 1296-1305, 2004

54. Keith D, Nichols G, Gullion C, Brown J and Smith D: Longitudinal Follow-up and Outcomes Among a Population With Chronic Kidney Disease in a Large Managed Care Organization. Arch Intern Med 164: 659-663, 2004

55. Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40: 373-383, 1987

Table 1 Baseline characteristics (mean ± SD) of patients with pre-dialysis CKD randomised to Intervention (n=29) or Control (n=27) treatment

Baseline Characteristics	**Intervention (n=29)**	**Control (n=27)**	**p-value[a]**
Age	69.5 ± 11.7	70.9 ± 11.6	0.7
Sex, Male n (%)	17 (58.6)	17 (63.0)	0.8 [b]
eGFR (ml/min/1.73m^2)	23.1 ± 7.2	21.6 ± 6.1	0.4
Serum Creatinine (mg/dL) [c]	2.9 ± 1.0	3.0 ± 0.9	0.7
BMI (kg/m^2)	26.8 ± 4.7	27.6 ± 5.2	0.5
% weight change in 6 months [c]	-1.8 ± 3.6	-0.3 ± 2.8	0.1
Charlson co-morbidity index	6.5 ± 1.9	6.7 ± 1.9	0.7
BCM (kg)	31.6 ± 7.3	32.3 ± 8.1	0.8
Nutritional status n (%)			0.2 [b]
SGA A Well nourished	22 (75.9)	24 (88.9)	
SGA B Moderately malnourished	7 (24.1)	3 (11.1)	
Mean daily protein intake (g/kg)	1.07 ± 0.32	1.17 ± 0.35	0.3
Mean daily energy intake (kJ/kg)	101.8 ± 23.0	108.5 ± 25.2	0.3

eGFR = Glomerular Filtration Rate, BMI = Body Mass Index, BCM = Body Cell Mass, SGA = Subjective Global Assessment, QOL = Quality of Life

[a]Independent samples t-test,

[b]chi-square test for independence

[c] To convert GFR in mL/min to mL/s, multiply by 0.01667; serum creatinine in mg/dL to mol/L, multiply by 88.4

[d] from previously measured weight in medical notes

Table 2 Comparison of baseline characteristics (mean ± SD) of study participants who completed the study with full outcome assessment, missing body cell mass assessment and those reaching renal death prior to in pre-dialysis CKD (n=56)

	Complete outcome data (n=41)	Incomplete body cell mass (n=9)	Renal death[a] during trial (n=6)	p-value
Treatment group (n (%) in Intervention)	21 (51)	3 (33)	5 (83)	0.1
Age (mean ± SD)	69.7 ± 12.4	69.8 ± 10.0	71.6 ± 10.2	0.4
Sex % M	64.9	53.8	50.0	0.7
eGFR (ml/min/1.73m^2) [a]	22.5 ± 5.8	22.7 ± 11.3	20.6 ± 2.5	0.8
BMI kg/m2 (mean ± SD)	26.9 ± 4.3	29.5 ± 7.6	25.6 ± 3.5	0.2
% weight change in previous 6 months	-0.73 ± 3.1	-1.29 ± 4.0	-3.60 ± 3.1	0.3
Charlson co-morbidity index (mean ± SD)	6.2 ± 1.8	7.2 ± 2.0	8.5 ± 1.5	0.02
Nutritional status, n (%)				0.4
SGA A Well nourished	36 (88)	6 (67)	4 (67)	
SGA B Moderately malnourished	5 (12)	3 (33)	2 (33)	
Home setting, n (%)				0.4
Lives with partner	25 (61)	7 (78)	4 (67)	
Lives alone	11 (27)	1(11)	1 (16.5)	
Lives with family or carers	5 (12)	1 (11)	1 (16.5)	

* Renal death = refers to a composite of reaching dialysis or death prior to study close

eGFR = Glomerular Filtration Rate, BMI = Body Mass Index, BCM = Body Cell Mass, SGA = Subjective Global Assessment, QOL = Quality of Life

[a] To convert GFR in mL/min to mL/s, multiply by 0.01667

Table 3 Impact of nutrition counselling on nutrition-related outcomes, difference in mean change (95% CI) between treatment groups (control from intervention), both adjusted and unadjusted values

	Change in Intervention (n=24)	Change in Control (n=26)	Mean difference mean (95%CI)	p-value	Adj r^2
BCM (%) [a]					
Unadjusted	2.0 (-1.9 to 5.9)	-1.5 (-5.5 to 2.5)	3.5 (-2.1 to 9.1)	0.2	0.01
Adjusted (sex; BMI)	0.6 (-2.9 to 4.1)	-3.3 (-6.9 to 0.4)	3.6 (-1.0 to 8.7)	0.1	0.24
BCM (kg) [a]					
Unadjusted	0.5 (-0.7 to 1.8)	-0.5 (-1.8 to 0.8)	1.1 (-0.7 to 2.9)	0.2	0.01
Adjusted (sex; BMI)	0.1 (-1.1 to 1.1)	-1.2 (-2.3 to -0.0)	1.2 (-0.3 to 2.7)	0.1	0.32
Energy (kJ/kg)					
Unadjusted	11.4 (4.7 to 18.0)	-6.3 (-13.0 to 0.4)	17.7 (8.2 to 27.2)	<0.001	0.34
Adjusted (CI; sex) [b]	14.2 (7.6 to 20.8)	-7.9 (-14.3 to -1.6)	22.1 (12.8 to 31.5)	<0.001	0.63
Protein (g/kg)					
Unadjusted	-0.07 (-0.15 to 0.02)	-0.11 (-0.19 to -0.03)	-0.04 (-0.73 to 0.16)	0.5	0.56
Adjusted (CI; sex) [b]	-0.05 (-0.13 to -0.03)	-0.13 (-0.21 to -0.05)	-0.08 (-0.03 to 0.20)	0.1	0.44

BCM = Body Cell Mass; BMI = Body Mass Index; CI = Charlson Index[55]

[a] n=41

[b] (note treatment group*sex interaction $p<0.001$; main effect of sex, not significant)

Table 4 Change in clinical variables during 12-week randomised controlled intervention in pre-dialysis CKD by treatment group (intervention n=24, control n=26)

Clinical variable (ideal value)	Intervention n=24 (mean ± sd)		Control n=26 (mean ± sd)		Mean difference in change[a] (95% CI)
	Week 0	Week 12	Week 0	Week 12	
Weight (kg)	73.5±16.1	73.8±15.7	76.9±18.0	77.4±20.1	0.14 (-1.3 to 1.6)
eGFR (ml/min/1.73m^2) [b]	23.4±7.9	22.9±6.8	21.7±6.2	21.4±7.2	0.30 (-1.75 to 2.34)
Albumin (g/dL)[b]	3.9±0.5	4.0±0.5	3.9±0.4	3.7±0.5	-0.23 (-0.4 to -0.05) [c]
C-reactive protein (mg/L) [b]	6.9±8.6	5.6±4.0	8.1±14.7	17.9±38.2	-11.16 (-13.02 to 35.35)

[a] ANCOVA, change in control – intervention (adjusting for baseline values)

[b] To convert GFR in mL/min to mL/s, multiply by 0.01667; serum albumin in g/dL to g/L, multiply by 10; C-reactive protein in mg/L to mg/dL, divide by 10.

[c] $p<0.01$

Legends

Figure 1 Summarised protocol used in this study for the intervention of pre-dialysis CKD patients adapted from ADA intervention protocol

Figure 2: CONSORT flowchart of participant progression through randomized controlled trial of nutrition intervention in pre-dialysis CKD patients

Figure 3: Mean change (± 95% CI) in body cell mass (%) following a 12-week randomised controlled trial of nutritional counselling, split by sex (n=41);

Control- - - - - - - Intervention ———

Figure 4: Mean change (± 95% CI) in energy intake (kJ/kg) following a 12-week randomised controlled trial of nutritional counselling, split by sex (n=50);

Control- - - - - - - Intervention ———

Figure 5: Mean change (± 95% CI) in protein intake (g/kg) following a 12-week randomised controlled trial of nutritional counselling, split by sex (n=50);

Control- - - - - - - Intervention ———