



Diet therapy along with nutrition education can improve renal function in people with stages 3–4 chronic kidney disease who do not have diabetes: a randomised controlled trial

Maryam Hamidianshirazi^{1,2}, Maryam Shafiee³, Maryam Ekramzadeh^{2,4*}, Mahsa Torabi Jahromi³ and Farzad Nikaein²

¹Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

²Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

³Shiraz Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

⁴Division of Nephrology and Hypertension, Lundquist Institute, Harbor-UCLA Medical Center, Torrance, CA, USA

(Submitted 2 November 2021 – Final revision received 11 June 2022 – Accepted 27 June 2022 – First published online 7 July 2022)

Abstract

The current trial investigates the effect of renal diet therapy and nutritional education on the estimated glomerular filtration rate (eGFR), blood pressure (BP) and depression among patients with chronic kidney disease (CKD). A total of 120 CKD patients (stages 3–4) ($15 < \text{eGFR} < 60$) were randomised into an intensive nutrition intervention group (individualised renal diet therapy plus nutrition counselling: 0.75 g protein/kg/d and 30–35 kcal/kg/d with Na restriction) and a control group (routine and standard care) for 24 weeks. The primary outcome was the change in the eGFR. Secondary outcomes included changes in anthropometric measures, biochemistry (serum creatinine (Cr), uric acid, albumin, electrolytes, Ca, vitamin D, ferritin, blood urea nitrogen (BUN), and Hb), BP, nutritional status, depression and quality of life. The eGFR increased significantly in the intervention group compared with the control group ($P < 0.001$). Moreover, serum levels of Cr and the systolic and diastolic BP decreased significantly in the intervention group relative to the control group ($P < 0.001$, $P < 0.001$ and $P = 0.020$, respectively). The nutrition intervention also hindered the increase in the BUN level and the depression score ($P = 0.045$ and $P = 0.028$, respectively). Furthermore, the reduction in protein and Na intake was greater in the intervention group ($P = 0.003$ and $P < 0.001$, respectively). Nutritional treatment along with supportive education and counselling contributed to improvements in renal function, BP control and adherence to protein intake recommendations. A significant difference in the mean eGFR between the groups was also confirmed at the end of the study using ANCOVA ($\beta = -5.06$; 95% CI (-8.203, -2.999)).

Keywords: Renal function: Nitrogenous toxins: Protein-restricted diet: Education: Nutrition consult: Mental disorder

Chronic kidney disease (CKD) is a condition in which kidneys are damaged, leading to loss of filtration capacity and the aggregation of excessive fluid and waste products in the blood⁽¹⁾. The prevalence of CKD was less than 1% of the population in 1990, but it increased up to 12% in 2013, and it has now become a global health concern⁽²⁾. CKD is classified into stages 1–5 based on estimated glomerular filtration rate (eGFR)⁽³⁾. Over time, progressive CKD can end up with irreversible end-stage renal disease (ESRD)^(4,5). ESRD patients have many co-morbidities affecting their quality of life. The main nutrition-related goals in CKD are slowing down the disease progress and attenuating uremic toxicity. Maintaining good nutritional status also lowers

the risk of secondary complications, including CVD, anorexia, cachexia, bone disease, hyperlipidemia⁽¹⁾, oedema, anaemia and hypertension⁽⁶⁾. Besides, there is an association between depression and reduced kidney function and increased mortality in these patients^(7,8).

Medical nutrition therapy and medications are methods for controlling CKD. Medical nutrition therapy includes restriction in the intake of protein, Na, K, P and fluids⁽⁹⁾. Several studies have shown that restriction of protein and Na has a major role in controlling uremia and hypertension^(10–12). Yet, altering the dietary pattern and lifestyle of CKD patients is a real challenge⁽¹³⁾. A systematic review aiming to find benefits of multifactorial

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; SBP, systolic blood pressure.

* **Corresponding author:** Maryam Ekramzadeh, email mekramzade@gmail.com

provided by moderate intakes of fruits and vegetables in the intervention group⁽⁶²⁻⁶⁴⁾. Consequently, this intervention might have played a role in BP control⁽⁶⁵⁾.

Dietary protein and blood pressure. Reduced protein intake in the intervention group could lower BP through a decrease in the glomerular hydrostatic filtration pressure⁽¹⁰⁾.

Depression

The current study findings revealed remarkably better results regarding the attenuation of depression in the treatment group compared with the control group. The increment in the depression score might have been prevented in the treatment group through a decrease in BUN and Cr levels, an increase in eGFR, higher intake of soluble fibre and better amino acid profile in the context of high biological value protein consumption. According to the review of the literature, this has been the first study assessing the effects of dietary intervention on depression among CKD patients. Depression in CKD patients might be attributed to uremic intoxication⁽⁶⁶⁾, which could, in turn, exacerbate kidney failure and affect the feeling of well-being⁽⁶⁷⁾. It should be noted that increased contact with healthcare providers during the educational interventions may have a beneficial role in reducing depression in the patients of intervention group.

Nutrient intake

Based on the findings of the present study, modification in the treatment group's diet (lower protein, fat, Na and P intakes with adequate energy and higher carbohydrate and soluble fibre intakes) led to better outcomes amongst the CKD patients.

Protein source. Balancing the animal and plant sources of protein intake is of paramount importance in CKD. Despite the proper high biological value protein intake, reasonable servings of fruits and vegetables were considered in the daily diet of the intervention group without adversely affecting serum phosphorus and potassium levels⁽⁶⁸⁾.

Phosphorus. The significant reduction in phosphorus intake in the patients who adhered to the diet might probably be the result of the limited protein, legumes and nuts intake as well as the implementation of effective educational strategies related to dietary phosphorus sources. The patients in the intervention group were instructed to replace meat with egg white, which has the lowest phosphate:protein ratio. They were also asked to limit the foods with a high phosphate:protein ratio (such as cheese and egg yolk) and to avoid rich sources of phosphorus like legumes, nuts and inorganic phosphate additives⁽⁶⁹⁾.

Dietary fibre. Comparison of the two groups indicated that the intake of soluble fibre was significantly increased in the patients who had adhered to their diet. This finding could be reflective of adequate consumption of low biologic value protein while maintaining a good balance of serum potassium and phosphorus. Maximum tolerable fruit and vegetable intake (4/4 mean servings) together with moderate protein restriction (Table 3) was

also suggested in this regimen, which were desirable according to the study results.

Nutrition education and consultation

According to the findings of this research, better clinical improvement in renal function would be achieved if modified renal diets were supported by adequate nutrition education and consultation. An adequate diet tailored personally would be more desirable if accompanied by sufficient education about why and how to achieve that. In fact, psychological factors (knowledge, attitude and satisfaction) have been expressed as the most important determinants of adherence to treatment. In the current research, the participants were educated about a clear and distinct vision in renal diet with a distinguished definition of suitable food items through booklets (self-education) and educational classes and were periodically followed via phone contact during the study⁽⁷⁰⁾.

The current study had some limitations, the first of which being single measurements of serum Cr, BUN and skeletal muscle mass (SMM) during the study period (just before and after the study and not repeating the measurements for monitoring the trend). In addition, the urinary protein and urea were not measured. Considering the effect of increased contact with healthcare providers at intervention visits, which may play a supportive mental role in chronic diseases, it seems that lack of attention control group is another limitation. As the participants of this study were CKD patients without co-morbidities (diabetes, heart failure, etc.), results may not be generalised to people with CKD with complex chronic disease. Future studies are needed to evaluate the effects of renal diet therapy on inflammation and oxidative stress markers, muscle atrophy indices, and blood gas parameters for metabolic acidosis conditions. Assessing hard end points, such as progression to ESRD co-morbidities and survival, in combination with surrogate conventional biomarkers, is also suggested in long-term clinical trials.

Conclusions

According to our findings, nutritional treatment along with supportive education and counselling contributed to improvements in renal function and BP control.

In CKD, diet therapy can prevent disease progression and delay the initiation of renal replacement therapy through the modulation of the eGFR. Thus, commencing a nutritional treatment along with supportive education and consultation for better acceptance and adherence to the diet is recommended from the early stages of CKD. These comprehensive interventions can also impede the worsening of mental conditions associated with CKD-related depression.

Acknowledgements

The authors would like to thank Dr Nasrin Shokrpour at the Research Consultation Center of Shiraz University of Medical Sciences for improving the use of English in the manuscript.

This study was extracted from Maryam Hamidiashirazi's MSc thesis in Nutrition, which was financially supported by



the Vice-Chancellor for Research Affairs of Shiraz University of Medical Sciences (grant No. 97-01-84-19003).

Research idea and study design: M. H., M. S., M. E. and M. T.; data acquisition: M. H., M. S., M. E. and F. N.; data analysis/interpretation: M. H., M. E. and F. N.; statistical analysis: M. H., M. E. and F. N.; supervision or mentorship: M. S., M. E. and M. T. Each author contributed to the important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

The authors declare that there are no conflicts of interest.

References

1. Thomas R, Kanso A & Sedor JR (2008) Chronic kidney disease and its complications. *Prim Care* **35**, 329–344.
2. Bikbov B, Purcell CA, Levey AS, *et al.* (2020) Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* **395**, 709–733.
3. Levey AS, Coresh J, Bolton K, *et al.* (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* **39**, S1–S266.
4. Fox CS, Matsushita K, Woodward M, *et al.* (2012) Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* **380**, 1662–1673.
5. Fujii H & Joki N (2017) Mineral metabolism and cardiovascular disease in CKD. *Clin Exp Nephrol* **21**, 53–63.
6. Webster AC, Nagler EV, Morton RL, *et al.* (2017) Chronic kidney disease. *Lancet* **389**, 1238–1252.
7. Wang W-L, Liang S, Zhu F-L, *et al.* (2019) The prevalence of depression and the association between depression and kidney function and health-related quality of life in elderly patients with chronic kidney disease: a multicenter cross-sectional study. *Clin Interv Aging* **14**, 905.
8. Goh ZS & Griva K (2018) Anxiety and depression in patients with end-stage renal disease: impact and management challenges—a narrative review. *Int J Nephrol Renovasc Dis* **11**, 93.
9. Di Iorio BR, Di Micco L, Marzocco S, *et al.* (2017) Very low-protein diet (VLPD) reduces metabolic acidosis in subjects with chronic kidney disease: the “nutritional light signal” of the renal acid load. *Nutrients* **9**, 69.
10. Bellizzi V, Di Iorio B, De Nicola L, *et al.* (2007) Very low protein diet supplemented with ketoanalog improves blood pressure control in chronic kidney disease. *Kidney Int* **71**, 245–251.
11. Bellizzi V (2013) Low-protein diet or nutritional therapy in chronic kidney disease? *Blood Purif* **36**, 41–46.
12. Kleinknecht C, Salusky I, Broyer M, *et al.* (1979) Effect of various protein diets on growth, renal function, and survival of uremic rats. *Kidney Int* **15**, 534–541.
13. Banerjee T, Liu Y & Crews DC (2016) Dietary patterns and CKD progression. *Blood Purif* **41**, 117–122.
14. Brown TJ, Williams H, Mafrici B, *et al.* (2021) Dietary interventions with dietitian involvement in adults with chronic kidney disease: a systematic review. *J Hum Nutr Diet* **34**, 747–757.
15. Stengel B, Metzger M, Combe C, *et al.* (2019) Risk profile, quality of life and care of patients with moderate and advanced CKD: the French CKD-REIN cohort study. *Nephrol Dial Transplant* **34**, 277–286.
16. Morante JH, Sánchez-Villazala A, Cutillas RC, *et al.* (2014) Effectiveness of a nutrition education program for the prevention and treatment of malnutrition in end-stage renal disease. *J Ren Nutr* **24**, 42–49.
17. Aghakhani N, Samadzadeh S, Mafi TM, *et al.* (2012) The impact of education on nutrition on the quality of life in patients on hemodialysis: a comparative study from teaching hospitals. *Saudi J Kidney Dis Transplant* **23**, 26.
18. Ebrahimi H, Sadeghi M, Amanpour F, *et al.* (2016) Influence of nutritional education on hemodialysis patients' knowledge and quality of life. *Saudi J Kidney Dis Transplant* **27**, 250.
19. Chen S-H, Tsai Y-F, Sun C-Y, *et al.* (2011) The impact of self-management support on the progression of chronic kidney disease – a prospective randomized controlled trial. *Nephrol Dial Transplant* **26**, 3560–3566.
20. Sealed Envelope Ltd. 2001, Create a blocked randomisation list. <https://www.sealedenvelope.com/simple-randomiser/v1/lists>.
21. K/DOQI & National Kidney Foundation (2000) Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* **35**, S1–S140.
22. Cases A, Cigarrán-Guldrís S, Mas S, *et al.* (2019) Vegetable-based diets for chronic kidney disease? It is time to reconsider. *Nutrients* **11**, 1263.
23. Salomo L, Kamper A, Poulsen G, *et al.* (2017) Habitual dietary phosphorus intake and urinary excretion in chronic kidney disease patients: a 3-d observational study. *Eur J Clin Nutr* **71**, 798–800.
24. Nursal TZ, Noyan T, Tarim A, *et al.* (2005) A new weighted scoring system for subjective global assessment. *Nutrition* **21**, 666–671.
25. Cukor D, Rosenthal DS, Jindal RM, *et al.* (2009) Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int* **75**, 1223–1229.
26. Roozbeh J, Sharifian M, Ghanizadeh A, *et al.* (2011) Association of zinc deficiency and depression in the patients with end-stage renal disease on hemodialysis. *J Ren Nutr* **21**, 184–187.
27. Powles WE (1974) *Beck, Aaron T. Depression: Causes and Treatment*. Philadelphia: University of Pennsylvania Press.
28. Montazeri A, Vahdaninia M, Mousavi SJ, *et al.* (2011) The 12-item medical outcomes study short form health survey version 2.0 (SF-12v2): a population-based validation study from Tehran, Iran. *Health Qual Life Outcomes* **9**, 12.
29. Ware JE Jr, Kosinski M & Keller SD (1996) A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* **34**, 220–233.
30. Zal F, Mostafavi-Pour Z & Vessal M (2007) Comparison of the effects of vitamin E and/or quercetin in attenuating chronic cyclosporine A-induced nephrotoxicity in male rats. *Clin Exp Pharmacol Physiol* **34**, 720–724.
31. Pickering TG, Hall JE, Appel LJ, *et al.* (2005) Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the subcommittee of professional and public education of the American Heart Association council on high blood pressure research. *Hypertension* **45**, 142–161.
32. Levey AS, Stevens LA, Schmid CH, *et al.* (2009) A new equation to estimate glomerular filtration rate. *Ann Intern Med* **150**, 604.
33. Cortinovis M, Ruggenti P & Remuzzi GJN (2016) Progression, remission and regression of chronic renal diseases. *Nephron* **134**, 20–24.
34. Tsai C-W, I-Wen T, Hung-Chieh Y, *et al.* (2017) Longitudinal change in estimated GFR among CKD patients: a 10-year follow-up study of an integrated kidney disease care program in Taiwan. *PLOS ONE* **12**, 1932–6203.
35. Ikizler TA, Burrows JD, Byham-Gray LD, *et al.* (2020) KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis* **76**, S1–S107.