The Cons of Protein Restriction in Low Clearance Patients

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- History of several decades of use of protein restriction in CKD
- Originally a palliative treatment for advanced CKD prior to availability of long-term dialysis and kidney transplantation
- Reduced uraemic toxins –control symptoms and extend survival in absence of RRT

A LOW-NITROGEN DIET WITH PROTEINS OF HIGH BIOLOGICAL VALUE FOR SEVERE CHRONIC URÆMIA

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MECHANISMS OF DISEASE

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Dietary Protein Intake and the Progressive Nature of Kidney Disease:

The Role of Hemodynamically Mediated Glomerular Injury in the Pathogenesis of Progressive Glomerular Sclerosis in Aging, Renal Ablation, and Intrinsic Renal Disease

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- With advent of dialysis, focus of protein restriction moved to slowing of CKD decline
- Robust debate regarding validity of this approach and interpretation of evidence
- Great variety in practice world wide

- **Are low protein diets effective, practical, safe in real life clinical practice?**

“Required” protein intake in health

- World Health Organization recommends [2007]:
- Median daily protein requirement for healthy adults is 0.66 g protein/kg body weight
- 97.5th percentile of population requirements, i.e. the ‘safe’ level of protein intake, being 0.83 g/kg/day

Recommended protein intake in CKD

- UK Renal Association Clinical Practice Guideline on Nutrition in CKD
  - Minimum prescribed daily protein intake in CKD Stage 4 or 5 not on dialysis of 0.75–1 g/kg ideal body weight
- The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for evaluation and management of CKD
  - Recommends modest lowering of protein intake to 0.8 g/kg/day in adults with GFR<30 ml/min/1.73 m2
  - Avoiding high protein intake (>1.3 g/kg/day) in CKD patients at risk of progression

What are “low protein diets”

- Low protein diets (LPD) ~0.6 g/kg/day
- Very low protein diets (VLPD) ~0.3 g/kg/day
- Supplementation with essential amino acids or ketoacid analogues (SVLPD)
- Quality of protein
  - high biological value with a high percentage of essential amino acids to reduce the risk of malnutrition
  - plant vs animal protein possibly having differing effects on CKD progression

MDRD study

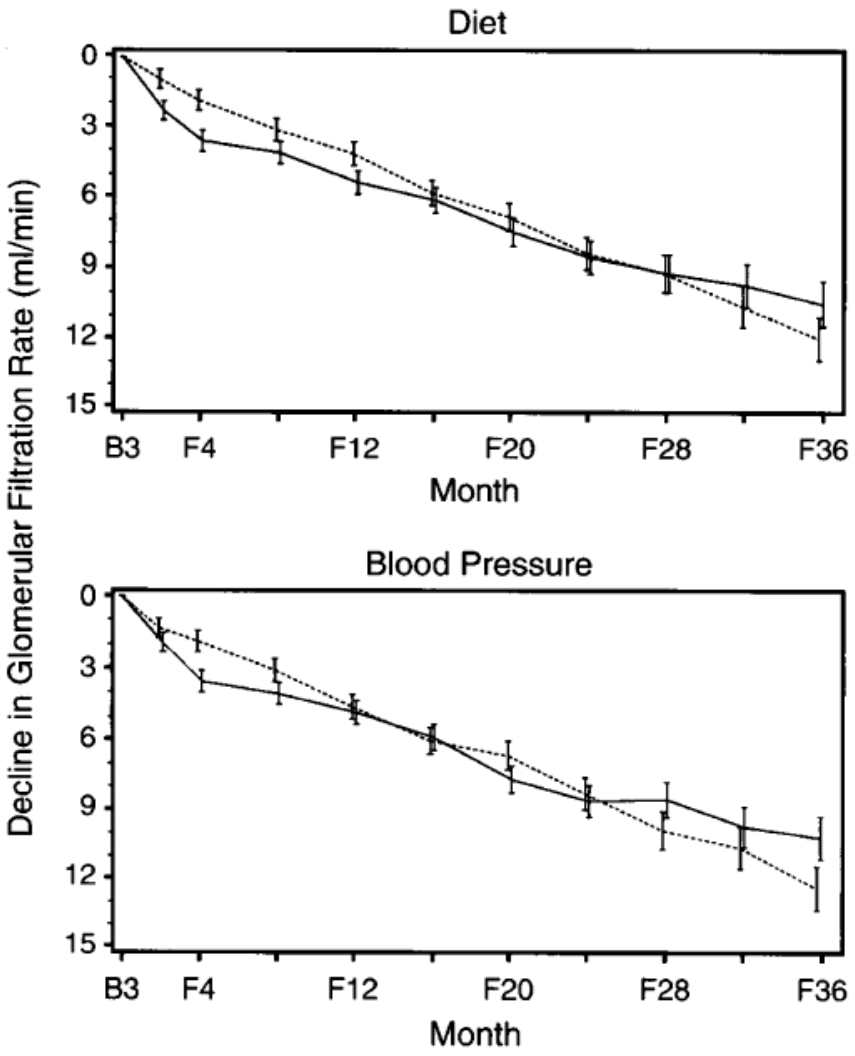
- The largest and most robust randomized trial of protein restriction is the Modification of Diet in Renal Disease (MDRD) study [1994].
- Study of >800 patients, investigated the effects of hypertension control and protein restriction on the progression of CKD
- GFR measured by ^{125}I-iothalamate clearances over a 2.2-year period in two sub studies.

- Study A randomized patients with GFRs of 25–55mL/min/1.73 m2 in a two-by-two factorial design to
  - normal protein intakes of 1.3 g/kg/day or reduced protein intake (0.58 g/kg/day)
  - and to mean blood pressures (BPs) of 107 or 92mmHg.
- Study B, patients with GFRs of 13–24mL/min/1.73 m2 were randomized to
  - a low-protein intake of 0.58 g/kg/day or a very low-protein intake of 0.28 g/kg/day plus keto acid/amino acid supplementation
  - two target BPs

MDRD study – summary results

- Study A - no difference in GFR decline between the normal and low-protein groups
- Study B - a non-significant ($P<0.07$) trend to a faster decline in GFR in the low-protein group than the very low-protein group
- Longer-term follow up of the MDRD study participants failed to find any benefit of protein restriction on CKD progression [Levey Am J Kidney Dis 2006; 48: 879–888].
- The MDRD study has been subject to a number of secondary analyses with varying conclusions, but the intention-to-treat primary outcome analysis showed no benefit of dietary protein restriction.

MDRD study A


Diet
Blood Pressure
Decline in Glomerular Filtration Rate (ml/min)
0
3
6
9
12
15
B3
F4
F12
F20
F28
F36
Month

MDRD study B

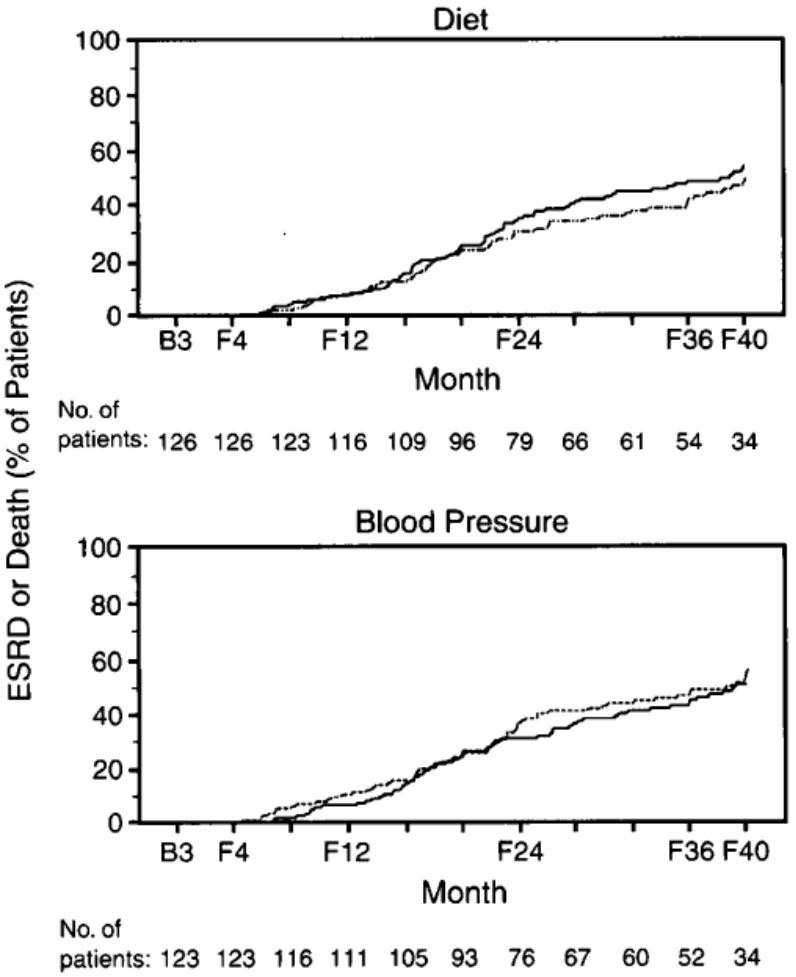


Figure 4. The Occurrence of End-Stage Renal Disease (ESRD) or Death in Patients in Study 2.

Evidence: Studies and limitations

- The majority of low protein studies, even when randomized, are relatively small and results variable
- Potential for publication bias with non-publication of ‘negative’ trials - is suggested by funnel plots in meta-analyses by Fouque [2000] Fouque et al. [2009] and Kasiske et al. [1998]

- Fouque meta-analysis 2000 in non-diabetic CKD patients, using ‘renal death’ as the outcome measure suggested reduced risk of renal death with protein restriction
- Updated Fouque analysis 2009 suggested a 32% decrease in renal death with protein restriction. Varying protein restrictions are included, making it unclear what an optimal diet would be.
- A meta-analysis by Kasiske et al in 1998 combining studies of non-diabetic and a smaller number of diabetic patients found a significant but small effect of protein restriction on the rate of progression

- Cochrane systematic review in 2007 by Robertson et al in patients with diabetic nephropathy - non-significant slowing of progression with protein restriction
- Pan et al in 2008 published a meta-analysis of eight RCTs in patients with diabetic nephropathy and found no impact on decreasing GFR (although noted the modest duration of some of the studies).

Study End Points

- A key methodological issue is validity of endpoints
- Some studies, including MDRD, used ‘gold standard’ measurements of kidney function
- Many others use blood test indicators
- Serum creatinine and urea (or eGFR) have limitations of accuracy and are affected by nutritional changes, giving a false appearance of a beneficial effect of LPDs on kidney function

- Other study endpoints reflect clinical outcomes such as start of renal replacement therapy and patient survival.
- But …. decisions about the timing of the start of RRT are at the clinician's discretion.
- Possibility changes in serum urea and creatinine due to protein restriction lead to delay in decision to start dialysis in protein restricted patients, in the absence of effect on kidney function.
- Clinician bias possible in non-blinded trials

Applicable to 21st Century Practice?

- Many studies of protein-restricted diets quite old
- Approaches to managing patients with CKD, affecting progression, have changed significantly
- Important changes in the management of hypertension
  - tight BP control targets
  - widespread use of angiotensin-converting enzyme (ACE) inhibitors / angiotensin receptor blockers in hypertensive / proteinuric patients

- In one meta-analysis only 9/108 diabetic patients received an ACE inhibitor [Pedrini, Ann Intern Med 1996; 124: 627–632].
- Unclear if any additional benefit would result from protein restriction in a patient with optimal management of hypertension on a maximum dose of ACE inhibitor

Protein restriction in the Elderly?

- Older patients dominate CKD populations but not clinical trials – do trial results apply?
- Already have lower protein intakes and physiological muscle loss - further reduction could lead to critical functional changes
- Cognitive deficit and financial limitations - difficult to effectively and safely follow a complex protein-restricted diet

LPDs and Ethic / Cultural Groups

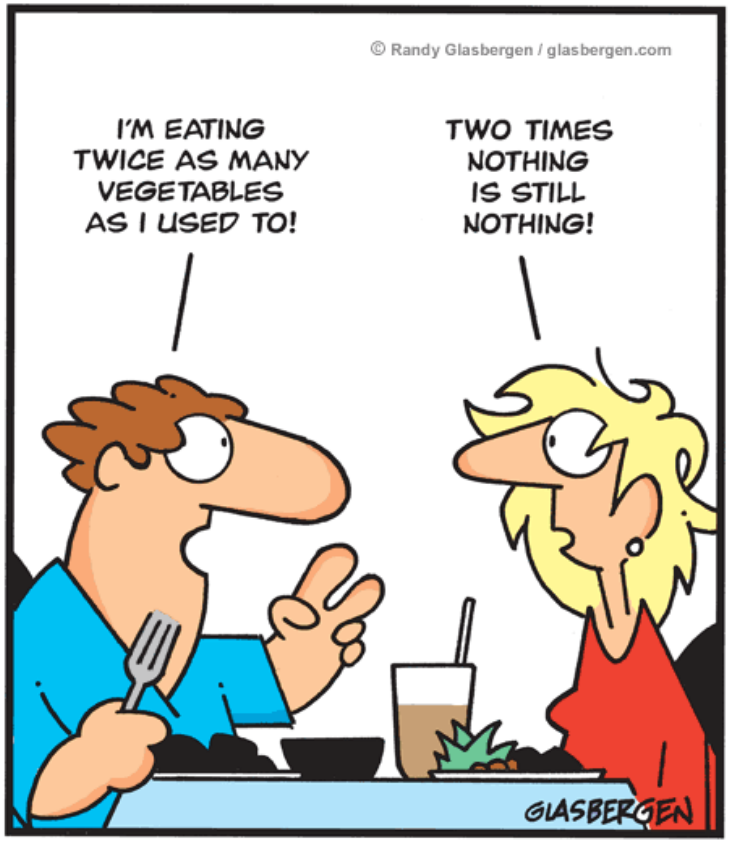
- Ethnic and cultural dietary variations between CKD populations – are results of protein restriction trials are applicable on an international basis (as the KDIGO CKD guideline notes)
- Providing intensive dietetic monitoring may be difficult in countries with lower healthcare resources.

Other potential mechanisms of LPDs

- In addition to putative effects on glomerular hyperfiltration, other effects of protein restriction could slow CKD progression (and contribute to positive study results)
- Reduced hydrogen ion generation with improved acidosis has been observed with protein restriction
- Correction of acidosis (achieved by sodium bicarbonate supplements) may slow CKD progression
- Protein restriction changes intake of other nutrients, e.g. reduced Na and phosphate intake – could slow progression
- Additional benefits of protein restriction - or could be replicated more easily without protein restriction?

Practicalities / tolerability of LPDs

- Huge general population confusion and anxiety about food and “healthy eating”
- Difficulties in adhering to CKD dietary restrictions
- Often multiple other (conflicting) dietary constraints
- Impact of dietary restrictions on quality of life



Concordance in studies

- Cianciaruso et al. [2008] RCT of the effects of protein intakes of 0.55 g/kg/day versus 0.8 g/kg/day on metabolic changes. Despite careful participant selection, only 53% subjects concordant in the 0.8 g/kg/day group and only 27% in the 0.55 g/kg/day group
- MDRD study: 35% and 46% of patients were adherent to the LPD and only 25% to the SVLPD despite extremely intensive dietician input that could not be replicated on a long-term basis in practice
- Satisfaction with the prescribed diets in MDRD increased slightly over time in the usual protein group, but declined with protein restriction, and especially with the very low-protein diet, with satisfaction correlating to dietary adherence

- In a 2008 editorial, Kopple estimated from personal experience that only 15% of patients with CKD can comfortably follow a protein-restricted diet.
- A study by Garneata et al. [2016] suggested a benefit from a ketoanalogue-supplemented very low-protein vegetarian diet. However, after screening and a run-in period to determine dietary compliance, only 14% of patients were eligible for randomization, indicating compliance difficulties and that any benefits arising from complex protein-restricted diets would only be applicable to a small subgroup of patients

- Per protocol vs ITT (can/do LPD diets work in those who are compliant – likely small proportion of patients, if any??)
- Any “benefits” claimed by some studies thus likely to be even less likely / affecting fewer patients in clinical practice with less motivation or monitoring than in trials

Safety of protein restriction

- Malnutrition / PEW is a frequent complication of CKD with strong adverse prognostic significance
- It has been suggested that a protein intake of 0.6–0.8 g/kg ideal body weight is sufficient to maintain stable protein stores in CKD
- This requires maintaining adequate energy intake (30–35 kcal/kg/day ideal body weight) and may become inadequate during intercurrent illness, which is common in our complex CKD patients.
- Protein intake falls spontaneously as GFR decreases without restriction

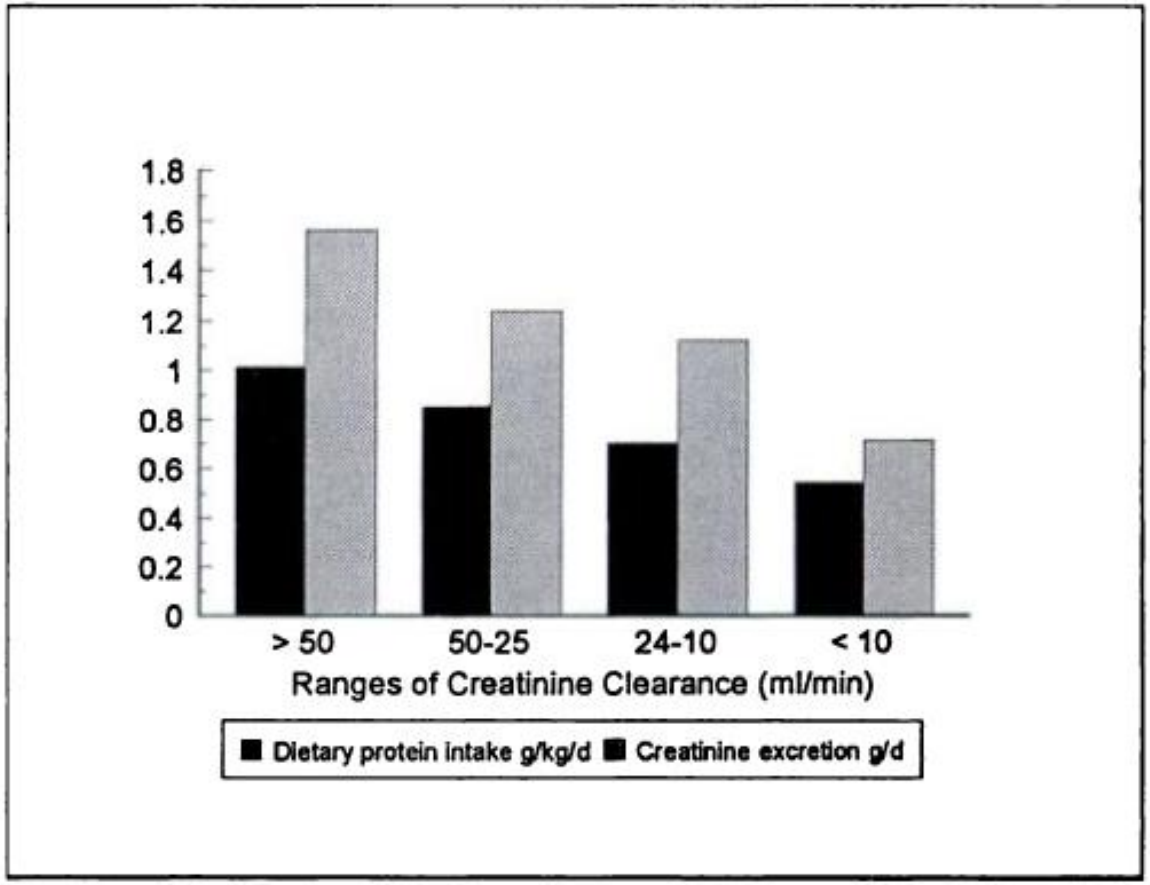


Figure 1. Average values of dietary DPI and total daily creatinine excretion of patients monitored during the study, classified according to different levels of CrCl.

Ikizler JASN 1995-6-1386

Safety - MDRD

- The MDRD study concluded that low and very low-protein diets are safe with no clear development of malnutrition, but…..
- Several nutritional indices declined and dieticians found it difficult to maintain energy intake requirements in patients with protein restrictions

- Cross-sectional analysis of MDRD showed correlations of declining protein and energy intake and a number of nutritional markers with lower GFR - concluding that very careful monitoring is required for patients receiving a low-protein diet
- A follow up of MDRD Study B demonstrated higher long-term mortality in the very low-protein group with ketoacid supplements than the comparator low-protein group

- Thus there is the potential for metabolic or dietary changes or intercurrent illness to occur, causing protein depletion in patients on a low-protein diet, and clinical experience shows that nutritional loss is more difficult to reverse in CKD patients.
- There are reasons for caution regarding adverse effects of protein restriction, although evidence of risk is not conclusive.

Dietetic impacts on CKD progression

- Dietary input crucial in maintaining health and slowing CKD progression by:
- Salt restriction
- Fluid intake
- Potassium restriction enabling optimal use of ACEi / ARB
- Nutritional support (maintaining nutrition where RRT start not otherwise indicated)
- …….but not protein restriction

Conclusions

- There is no convincing evidence that protein restriction slows CKD progression in humans
- It is unclear whether any purported benefits would apply to patients receiving modern standards of CKD care (BP control and RAS blockade)
- There are many demands made of patients with CKD, and major dietary restrictions have an important negative effect on quality of life

- A very small proportion of patients will be able to comply with the prescribed diet
- Any benefits should be balanced against impacts on quality of life and potential risk.
- Pragmatically, intensive monitoring required for (possible) efficacy and safety not practical in real life practice

- Dietetic management plays a crucial role in many aspects of care in patients with CKD
- However there is not an adequate evidence base to support addition of protein restriction to that list