



Nutrition in Chronic Kidney Disease Stages 3 to 5: Balancing Protein Restriction Against Protein-Energy Wasting

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Received: 10 January 2024; Accepted: 25 April 2024; Published: 26 July 2024

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Abstract

Dietary protein restriction has been offered in chronic kidney disease for decades to postpone dialysis, while protein-energy wasting is among the strongest predictors of death in the same patients. The randomised evidence resolves less of that tension than the guidance implies. A Cochrane review of 17 studies in 2,996 participants found that a very low protein intake probably reduces the number reaching kidney failure against a low intake, at a risk ratio of 0.65 (95% CI 0.49 to 0.85), while making little or no difference to death at 1.26 (0.62 to 2.54). Comparing a low intake with a normal one, neither death at 0.77 (0.51 to 1.18) nor kidney failure at 1.05 (0.73 to 1.53) moved. The complication is on the harm side. Final body weight was reported in three of the 17 studies, in 89 participants, with an interval spanning six kilograms in each direction. Twelve studies reported no wasting at all and three reported small numbers. Quality of life was not formally assessed in any study. Wasting affects 11 to 54 per cent of patients at these stages and carries a hazard ratio for death of 1.40 (1.04 to 1.89), yet the trials recruited metabolically stable patients. The trade-off in the title is therefore between a measured benefit and an unmeasured harm, in a population the trials largely excluded.

Keywords: Chronic kidney disease; Protein restriction; Protein-energy wasting; Evidence quality; Guidelines

Introduction

Two propositions govern nutritional care in chronic kidney disease before dialysis, and they pull in opposite directions. The first is that reducing dietary protein reduces the filtered load and postpones the need for renal replacement therapy, a proposition under study for several decades [1,2]. The second is that loss of body protein and energy reserves, formalised as protein-energy wasting, is among the strongest predictors of death in the same population [3,4].

Both are supported. Neither is straightforwardly compatible with the other, because the intervention that addresses the first restricts the intake that protects against the second [5,6]. Guidance resolves this by restricting protein only in patients described as metabolically stable and by monitoring nutritional

status alongside [7,8].

This review examines what the randomised evidence establishes on each side of that balance, and where the two bodies of evidence fail to meet.

Objective

This review sets out to establish four things from the published literature. First, which outcomes protein restriction moves and which it does not. Second, how the published intake thresholds compare with one another. Third, how thoroughly the harms of restriction were measured in the trials that established the benefit. And fourth, whether the population carrying the wasting risk is the population the trials enrolled.

Literature Review

What the randomised evidence shows: A systematic review identified 17 studies with 2,996 analysed participants and follow-up from 12 to 50 months, in adults with non-diabetic disease at stages 3 to 5 who were not receiving dialysis [2]. Comparing a very low intake with a low one, the number reaching kidney failure was probably reduced at a risk ratio of 0.65 (95% CI 0.49 to 0.85), reported as 165 fewer per 1,000, at moderate certainty [2]. Death in the same comparison showed little or no difference at 1.26 (0.62 to 2.54), also moderate certainty [2].

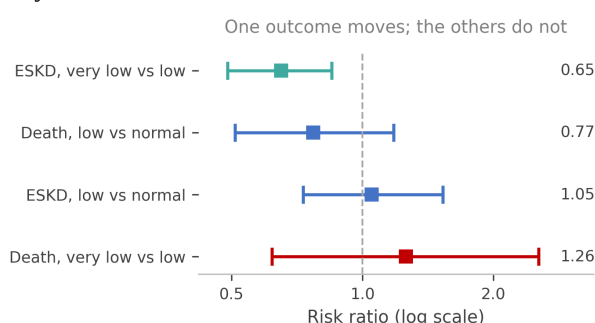


Figure 1: Pooled risk ratios by comparison and outcome [2]

What did not move: Comparing a low intake with a normal one, there was probably little or no difference in death, at 0.77 (0.51 to 1.18) across five studies and 1,680 participants with no measurable heterogeneity, and there may be little or no difference in reaching kidney failure, at 1.05 (0.73 to 1.53) across six studies and 1,814 participants at low certainty [2]. Whether either comparison affects the filtration rate remains uncertain, at a standardised mean difference of 0.18 lower (0.75 lower to 0.38 higher) for the low against normal comparison and 0.12 (0.27 lower to 0.52 higher) for very low against low, both at very low certainty [2]. So one of six pooled outcomes reached a conventional threshold [2].

Table 1: The pooled outcomes as published, with their certainty ratings [2]

Table 2: What the trial base answers and what it leaves open [2]

Comparison and outcome	Estimate	Certainty
Very low vs low, kidney failure	RR 0.65 (0.49-0.85)	Moderate [2]
Very low vs low, death	RR 1.26 (0.62-2.54)	Moderate [2]
Low vs normal, death	RR 0.77 (0.51-1.18)	Moderate [2]
Low vs normal, kidney failure	RR 1.05 (0.73-1.53)	Low [2]
Low vs normal, GFR	SMD -0.18 (-0.75-0.38)	Very low [2]
Very low vs low, GFR	SMD 0.12 (-0.27-0.52)	Very low [2]
Final body weight	MD -0.40 kg (-6.33-5.52)	Very low [2]

Why the question stayed open: The trial that framed the field randomised patients to protein and blood pressure targets and did

not demonstrate a significant benefit of restriction on the rate of decline in its primary analysis, a result that left the proposition neither established nor abandoned [1]. Successor trials were smaller, used varied targets and varied comparators, and reported the filtration rate more often than a clinical endpoint, which is the structural reason the pooled certainty ratings sit as low as they do rather than any single study being poor [1,2]. Thirty years of trials have not produced the one adequately powered comparison against ordinary intake that the question requires [2].

The thresholds do not agree with each other: Published intake targets for these stages span roughly fourfold. Guidance for metabolically stable adults without diabetes sets a low intake at 0.55 to 0.60 g/kg/day, or a very low intake of 0.28 to 0.43 g/kg/day taken with keto acid analogues, graded 1A for the kidney failure and death outcome and 2C for quality of life [7]. With diabetes present the same guidance gives 0.60 to 0.80 g/kg/day [7]. Other bodies set 0.80 g/kg/day for diabetes in kidney disease, and 0.75 to 1.00 g/kg/day in earlier disease [9,10]. A figure quoted without its source therefore carries little information (Figure 3).

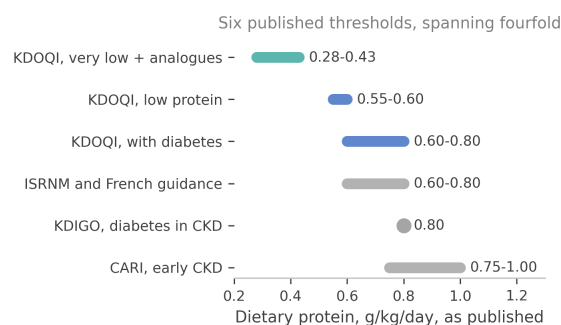


Figure 3: Published intake thresholds for these stages, as stated [7,9,10]

Where the wasting risk sits: Protein-energy wasting was given a consensus definition in 2008 and has been validated as a mortality predictor in several cohorts [5,11]. Prevalence rises as function falls, from under 2 per cent at stages 1 and 2 to 11 to 54 per cent at stages 3 to 5, and 28 to 54 per cent among 16,434 adults on maintenance dialysis (Figure 2) [3]. Across wasting stages 0 to 4 the hazard ratio for death was 1.40 (1.04 to 1.89) in 1,487 patients not on dialysis, and 3.03 (1.69 to 5.26) in 1,068 receiving haemodialysis [3]. The prevalence range is wide because the criteria applied differ between studies, which is itself a limitation of the estimate [3,11].

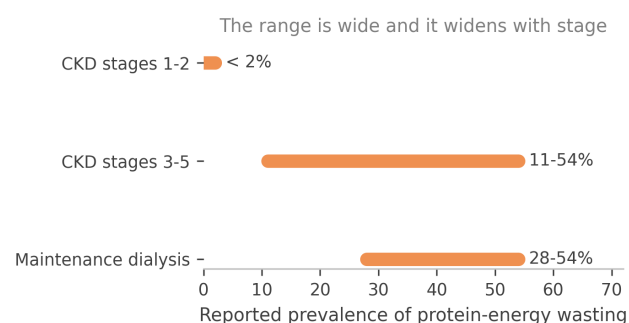


Figure 2: Reported prevalence of protein-energy wasting by stage [3]

The honest complication: The harms of restriction were the least measured outcomes in the review that established its benefit. Final body weight was reported in three of the 17 studies, in 89 participants, giving a mean difference of 0.40 kg lower with an interval from 6.33 kg lower to 5.52 kg higher at very low certainty, which excludes nothing of clinical interest [2]. Twelve studies reported no protein-energy wasting at all and three reported small numbers with it [2]. Quality of life, the outcome most directly affected by adhering to a restricted diet for years, was not formally assessed in any of the 17 studies [2]. The review's own conclusion was that studies of adverse effects and quality of life are required before these approaches can be recommended for widespread use [2].

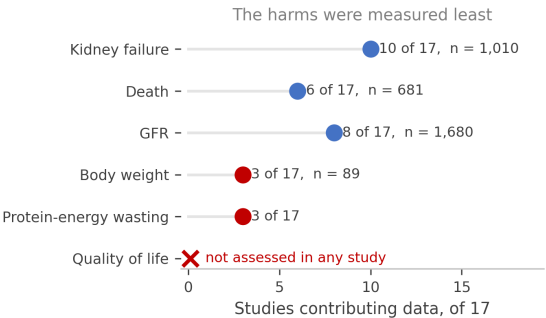


Figure 4: Studies contributing data to each outcome, of 17 [2]

Guideline grade and review certainty diverge: The same literature carries a strong 1A recommendation for restriction on the kidney failure and death outcome in one document and a low to moderate certainty rating in the other, and a 2C grade for quality of life against an outcome not assessed in any trial (Figure 5) [2,7]. Both readings are defensible, because a grade weighs the consistency of direction while a certainty rating weighs imprecision and risk of bias, but they should not be quoted interchangeably [2,7,12].

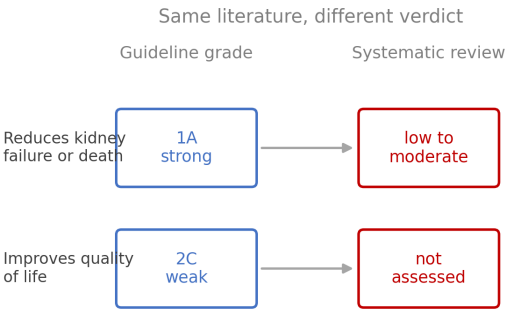


Figure 5: The same evidence under two appraisal systems [2,7]

Question	Status in the reviewed evidence
Does restriction delay kidney failure?	Very low vs low only, RR 0.65 [2]
Does it reduce death?	No difference in either comparison [2]
Does it cause weight loss?	3 studies, 89 patients, uncertain [2]
Does it cause wasting?	12 studies reported none [2]
Does it affect quality of life?	Not assessed in any study [2]

The population mismatch: Restriction is recommended for patients described as metabolically stable, and the trials recruited accordingly [2,7]. Wasting, by definition, is the state of not being metabolically stable [5]. The group in whom the trade-off is genuinely difficult is therefore largely outside the randomised evidence, and the guidance addresses them by exclusion rather than by data (Figure 6) [2,7,13]. Observational work in patients with established wasting is not a substitute, because intake falls as part of the syndrome and reverse causation is expected [3,13,14].

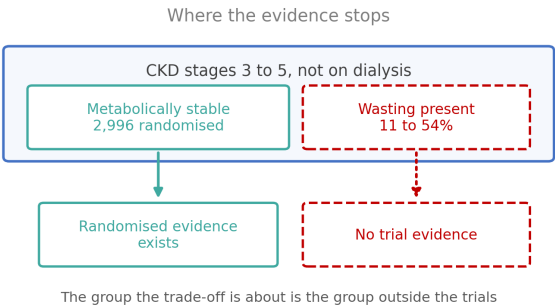


Figure 6: Where the randomised evidence stops [2,5,7]

Adherence is the mechanism of both effects: Long-term adherence to restricted intake is difficult to sustain and difficult to verify, and measured intake in trials differed from prescribed intake by a smaller margin than the prescriptions themselves [2,15]. In the low against normal comparison the achieved difference in calculated intake was 0.32 g/kg/day, and in the very low against low comparison 0.25 g/kg/day, both narrower than the gap between the assigned targets [2]. The same shortfall that dilutes the benefit also limits the harm, so the two are not independently adjustable [2,15,16].

What the supporting literature adds: Reviews of nutritional management in this setting describe the same tension and reach similar conclusions about the strength of the underlying data [6,17,18]. Work on the mechanisms of wasting attributes it to inflammation, acidosis, hormonal disturbance and reduced intake acting together, which is why supplementation alone does not reliably reverse it [11,19,20]. Sarcopenia and muscle mass measurement in this population have been reviewed separately and use criteria that overlap incompletely with the wasting definition, so prevalence figures from the two literatures should not be pooled [21,22,23]. Plant-dominant and Mediterranean patterns have been proposed as ways to lower intake while preserving diet quality, and their feasibility rather than their efficacy is what has been studied [24,25,26].

The trial that drives the one positive result: A randomised study of a ketoanalogue-supplemented vegetarian very low protein regimen against a conventional low protein diet in advanced disease reported a difference in progression, and it sits among the studies contributing to the pooled kidney failure estimate [32]. Its design features are the ones that limit generalisation: participants were selected for willingness and ability to sustain a demanding regimen, and the comparator was already restricted

[2,32]. A benefit measured against a restricted comparator does not establish a benefit against ordinary intake, which is the comparison the low against normal analysis addressed and found null [2].

Other syntheses of the same trials: Meta-analyses using the filtration rate as the outcome rather than kidney failure have reported slower progression with restriction, and one found the effect in non-diabetic and type 1 diabetic patients but not in type 2 [33]. A separate synthesis reached a broadly similar direction [34]. These do not contradict the review relied on here so much as answer a different question, because a surrogate outcome measured over a shorter horizon behaves differently from a clinical endpoint, and the certainty attached to the surrogate in the Cochrane assessment was very low for exactly that reason [2,33,34]. Where syntheses of one literature disagree, the outcome each chose usually explains it [2,33].

Assessment in practice: Comparisons of wasting criteria against composite nutritional scores report only moderate concordance, so which patients are counted as affected depends on the instrument used [11,27,28]. Guidance on assessment recommends using more than one measure and repeating it rather than relying on a single determination [7,29]. Reviews of the dialysis literature report higher prevalence and stronger mortality associations than the pre-dialysis literature, which is consistent with severity but also with differing ascertainment [3,30,31].

Table 3: Why figures from this field are not directly comparable

Source of variation	Consequence for comparison
Wasting criteria applied	Prevalence 11 to 54% at same stages [3]
Threshold cited	Targets span 0.28 to 1.00 g/kg/day [7,9,10]
Appraisal system	1A against low to moderate certainty [2,7]
Population enrolled	Metabolically stable only [2,7]

Energy is the other half of the prescription: Restricting protein while energy intake is inadequate produces net protein breakdown, so guidance pairs the protein target with an energy target and with monitoring of nutritional status rather than issuing it alone [7,14]. That pairing is what makes the intervention conditional, and it is also the part least likely to survive transfer from a trial with dietetic support to routine care, where contact is intermittent [14,16,17]. Reviews of the field treat the availability of skilled dietetic input as a precondition for restriction rather than an adjunct to it [7,17,18]. None of the pooled estimates describes what happens when the precondition is absent [2].

Acidosis, inflammation and the limits of intake: Wasting in this population is attributed to metabolic acidosis, chronic inflammation, hormonal disturbance, reduced appetite and comorbidity acting together, not to intake alone [11,19,20]. That

is why supplementation does not reliably reverse it and why an intake target cannot be the whole of the response [11,13]. It also means the two arms of the title trade-off are not symmetrical: intake is the lever for progression but only one of several inputs to wasting, so lowering it has a predictable effect on one side and a partial effect on the other [13,19,20].

What a trial in the unstable group would need: Such a study would recruit patients meeting the wasting criteria rather than excluding them, and would report body weight, muscle mass, wasting status and quality of life as primary outcomes alongside progression [2,5,7]. The obstacles are practical rather than conceptual: the instruments disagree about who is affected, so entry criteria are contested, and the follow-up needed for a clinical endpoint exceeds what adherence to a demanding regimen has been shown to sustain [2,15,27,28]. Until it exists, the honest description of current guidance is that it is a reasonable extrapolation, not a finding [2,7].

Method

This is a narrative review of published literature. Sources were assembled by searching the indexed literature for randomised trials, systematic reviews, consensus definitions and clinical practice guidance concerning dietary protein intake and nutritional status in adults with chronic kidney disease at stages 3 to 5 not receiving dialysis, giving precedence to pooled randomised evidence and to guidance that states its own grading [2,7].

Effect estimates are reproduced as their authors published them, with the interval and the certainty rating attached, because in this field the rating carries as much information as the point estimate. Where a review recorded an outcome as unmeasured, that is stated rather than left as an absence [2].

No new patient data were collected and no search protocol was registered, so this is not a systematic review. Intake figures are reported as the thresholds published in trials and guidance, not as recommendations for any individual.

Concluding Remarks

The benefit of protein restriction in these stages rests on one outcome in one comparison: fewer patients reaching kidney failure on a very low intake against a low one, at moderate certainty. Death did not move in either comparison, and the filtration rate remains uncertain. That is a narrower base than the strength of the recommendation suggests.

The harm side is not weakly supported so much as barely measured. Three studies and 89 patients contributed body weight, twelve studies reported no wasting, and no study assessed quality of life. An absence of reported harm across trials that did not look for it is not evidence of safety, and the review that produced the benefit estimate said so directly.

The unresolved question is not whether to restrict protein in metabolically stable patients, which the evidence supports within its limits, but what to do in the 11 to 54 per cent who are not stable. Those patients carry the mortality risk and sit outside the trials. Answering it requires studies that recruit them and measure weight, wasting and quality of life as outcomes rather than as omissions.

Study Limitations

The pooled estimates draw on trials spanning several decades, during which staging definitions, blood pressure targets and the availability of disease-modifying therapy all changed, so the applicability of older trials to current practice is uncertain. Prescribed and achieved intakes differed in most studies, which attenuates both benefit and harm by an unknown amount. Wasting prevalence figures rest on differing criteria and are not poolable. The diabetic and non-diabetic literatures are separate and the randomised evidence reviewed here excludes diabetes.

Acknowledgements

The authors thank the review group whose summary of findings recorded which outcomes were not measured, without which the asymmetry described here would be invisible.

Funding

No dedicated funding from public, commercial or charitable sources supported the preparation of this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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Citation: Salminen-Vaara E, Ostrowski B, Cardoso-Lima N. "Nutrition in Chronic Kidney Disease Stages 3 to 5: Balancing Protein Restriction Against Protein-Energy Wasting." *J Clin Nutr Heal* (2024);5: 001-006