Back to Basics: Estimating Protein Requirements for Adult Hospital Patients. A Systematic Review of Randomised Controlled Trials

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ABSTRACT

Aim: To review the supporting evidence for protein requirements in hospitalised adults, and compare the findings with commonly-used guidelines and resources. Methods: a systematic review was conducted based on a computerised bibliographic search of MEDLINE, EMBASE and CINAHL from 1950 to October 2011, as well as a citation review of relevant articles and guidelines. Studies were included if they were randomised clinical trials in hospitalised or chronically ill adults, comparing two or more different levels of protein intake. Information about study quality, setting, and findings was extracted using standardised protocols. Due to the heterogeneity of study characteristics, no meta-analysis was undertaken. Results: 116 papers were obtained in the search and 33 of these met all inclusion criteria. Five studies could not be obtained. The remainder reported outcome measures such as nitrogen balance, anthropometric measurements (including body weight, BMI, and mid-arm circumference), blood electrolyte levels and serum urea, which provide support for recommended protein intakes in various clinical conditions. The results were summarized and compared with current recommendations. Conclusion: high-level evidence to support current recommendations is lacking. The studies reviewed generally agreed with current guidelines and resources.

Keywords: Nutrition Assessment; Protein Metabolism; Dietary Protein; Nutrition Support

1. Introduction

Dietary protein is required by adults to supply the amino acids needed for the synthesis and maintenance of body proteins. In addition to making up the structures of muscles and organs, proteins fulfil a wide range of functions in the body including transportation, storage, detoxification, signalling, maintenance of pH and fluid homeostasis, hormone and enzyme activities, the body’s immune function, and as an energy source [1].

Proteins are synthesized and catabolised in a continuous turnover process. In health, equilibrium in the nitrogen balance, or the total nitrogen input minus the total nitrogen loss, is achieved by a normal dietary protein intake which replaces protein losses; any protein in excess of these needs is metabolized for energy [1]. Influences on protein turnover include exercise, diet and hormone effects. For example, thyroid hormone increases protein turnover rate; growth hormone stimulates anabolism; glucocorticoids decrease protein synthesis and stimulate catabolism [2] while anabolic steroids such as testosterone have the opposite effect, increasing protein synthesis and decreasing catabolism [3]. Insulin appears to inhibit muscle breakdown [4].

In healthy adults, a wide range of dietary protein intake is consistent with health as long as energy intake is sufficient. When protein intake is low, catabolism is inhibited if adequate carbohydrate or fat is present to use as an energy source as an alternative to breaking down protein [1]. Increasing energy intake, while keeping protein intake constant, improves nitrogen balance [1]. Conversely if there is inadequate energy contribution from another macronutrient source, even at very high protein intakes it is possible to starve to death [5] and a diet consisting solely of protein does not produce a better nitrogen balance than a protein-free low-energy diet (below 2500 kJ/day) [6]. Partly this is because the breakdown of protein for conversion to fat and glucose is not very efficient and the diet-induced thermogenesis is so much higher for pure protein diets (around 30% of the energy ingested) when compared with fat (6% - 14%) and carbohydrate (6%) [7-9]. This means that a larger total energy intake is required to maintain constant body weight.
when the diet is extremely high in protein.

Estimating requirements for protein is much more difficult than estimating requirements for energy, because the methodology is difficult to standardize and many different poorly-defined factors can influence the result, including wide variation in metabolic demand, body protein losses, growth patterns, activity, environment, diet (including micronutrients) and protein quality and digestibility [1]. As well as the total amount of protein required, the need for a balance of individual amino acids (the “biological value” of the protein) becomes important when diets are low in protein and energy, or where protein requirements are increased. Biological value of protein, however, is not a fixed or generalisable concept since metabolic demand can slowly adapt to protein intake, effectively altering the “value” obtained by different individuals [10].

Various countries’ recommendations for protein intake in healthy people [1,11,12] are based on nitrogen balance studies in young healthy people receiving protein of high biological value and digestibility. For adults older than 70 years, some countries’ recommendations are around 25% higher but this is controversial [1].

Recommendations for protein intake may be expressed as whole-number daily amounts of protein or in terms of grams per kilogram bodyweight, either grams of total protein or grams of nitrogen. In overweight and underweight people an adjusted weight value could be used, as with energy estimations (and for similar reasons) [13]. The nitrogen content can be estimated by dividing the protein amount by 6.25 (this assumes that protein has an average nitrogen content of 16 percent but this percentage may vary significantly depending on the amino acid profile of the diet [14]).

A recommended upper level is usually set for protein intake due to concerns that excessive protein might have detrimental effects on bone density (by increasing bone mineral loss due to increased renal acid load) and on kidney function (by increasing the amount of work the kidneys need to do in excreting waste) [11]. There is little strong evidence to support these concerns about the longterm effects of high protein intakes, however, and epidemiological studies using oral diets are confounded by the possible health risks associated with increased intakes of particular protein food sources (such as red or processed meats, or foods high in salt and saturated fat). For example, an analysis of over 20,000 healthy Greek participants in the EPIC study (European Prospective Investigation into Cancer and nutrition) [15] with mean five-year follow-up found that mortality correlated with increase in dietary protein intake, with a 13% increase in mortality risk per decile of protein intake. The correlation was stronger if carbohydrate intake decreased at the same time (controlled for total energy intake and other co-

founders); the mean protein intake in this study was 76 g (SD 24 g) per day. It is possible that this pattern of increased protein and decreased carbohydrate represents a shift from the protective traditional Greek diet and therefore does not mean that the increased mortality was a direct effect of protein intake per se. The Swedish Women’s Lifestyle and Health study of over 40,000 women [16] found a similar pattern of increased mortality risk (especially cardiovascular mortality) with increased protein and/or decreased carbohydrate intake, which the researchers attributed to the popularity of unhealthy low-carbohydrate/high-protein weight loss diets. Other large epidemiological studies have found no such relationship between protein intake and health outcome [17,18].

Protein requirements are altered in illness, by metabolic changes as well as by reduced intake and activity. Muscle activity inhibits protein breakdown and stimulates synthesis [19]. Atrophy of muscle, due to disuse, is a result mainly of increased breakdown but also a decrease in synthesis [20]; keeping the muscle passively stretched appears to inhibit this atrophy by reducing breakdown and increasing synthesis [21]. In trauma and infection, cytokines produced as part of the inflammatory response cause an increase in both protein synthesis and catabolism, but the increase in catabolism outweighs the increase in synthesis leading to net muscle breakdown [22,23]. (A loss of 1 kilogram of lean body protein tissue is equivalent to a loss of about 30 grams of nitrogen [24].) In cancer cachexia and in malnutrition, synthesis is decreased as well [25]. The ideal protein intake during illness therefore varies according to the disease state and should be evaluated on the basis of the patient’s outcome, rather than simple measurement of nitrogen balance or extent of catabolism. While optimal nutrition may reduce the extent of body protein losses, even very aggressive nutrition support cannot completely suppress inflammation-related catabolism [26].

A recent survey [27] of hospital dietitians in Australia and New Zealand found that most were using established guidelines or pocket book manuals to work out protein requirements for their patients. Few reported that they had ever referred to original research on this topic. A closer look at the recommendations in these guidelines [28-33] and manuals [34,35] reveals that some are completely unreferenced and others are “expert opinion” level of evidence. Many of the references are old, and some are studies of specific amino acids rather than total protein requirements; some of the guidelines cite only other guidelines or textbooks to support their recommendations. It appears that no recent systematic review has been conducted. The aim of this project was to develop a summary of the evidence base on protein requirements in illness, using a systematic review method-
ology focusing on randomised controlled trials to obtain the highest levels of evidence to support protein recommendations in adults during illness.

2. Methods

2.1. Search Strategy

This systematic review was conducted using the PRISMA Statement for guidance [36]. A search was conducted using four online databases (MEDLINE, EMBASE, CINAHL and Web of Science) from the earliest date available in each, using the search terms listed in Figure 1. A citation review of relevant practice guidelines and of other key articles was also conducted. No exclusion criteria were used for the initial search: all studies potentially of interest (based on title and abstract) were obtained in full-text form and then examined by two independent reviewers against the following inclusion criteria: study is a randomized controlled trial design, study population consists of hospitalized or ill adults, and study compares at least two different levels of dietary protein intake (see Figure 1). Studies other than randomized controlled trials were excluded to minimize the effects of the many confounders present in other study designs and to optimize the level of evidence being considered.

2.2. Quality Scoring

The quality and risk of bias of all included studies were rated by two independent reviewers, against the American Dietetic Association’s research quality criteria checklist [37]. Any discrepancies in rating were resolved by discussion, and final assessments were reported as “exceptional quality” (++), “high quality” (+), “neutral” (O), or “poor” (−) in accordance with the checklist scoring.

2.3. Statistical Analysis

No meta-analyses were performed. Chi square tests were used to assess whether lower-quality and higher-quality studies differed with respect to statistical power and choice of study outcome variables. A p-value of <0.05 was considered to be significant.

3. Results

Using the search outlined in Figure 1, 116 studies remained once duplicates were removed. Of this total, 38 met all inclusion criteria, that is, they were randomized studies of hospitalized or ill adults comparing two or more levels of protein. Five of the studies could not be obtained. The remaining 33 studies are listed in Table 1. They covered diagnostic groups including trauma/burns (n = 7 studies), critical illness and sepsis (n = 10), renal (n = 14), HIV/AIDS (n = 2) and liver disease (n = 2).

After rating of study quality, 23 studies were rated as high or exceptional quality, and ten were rated as neutral or poor quality studies. A summary table was prepared that included the findings from only high or exceptional quality studies (Table 2) as well as currently-used guidelines. Due to study heterogeneity, no meta-analyses were possible.

The most commonly-used outcome used in the included studies was nitrogen balance (including nitrogen input and excretion rates) which was measured in two-thirds of the studies. Other outcomes reported included anthropometric measurements such as body weight, Body Mass Index, waist-to-hip ratio and mid-arm circumference; laboratory tests such as urea excretion rates and glomerular filtration rates; and more general measures like quality of life, function, and nutritional status. Higher-quality studies were no more likely than lower-quality studies to use nitrogen balance as an outcome (p = 0.537) or to use more patient-focused outcomes such as quality of life or functional status (p = 0.407).

4. Discussion

This review was conducted in order to summarize current evidence on the protein requirements of hospitalized or
Table 1. Summary of protein requirements for adult hospital patients.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Daily protein requirement (g/kg)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>healthy people (RDI)</td>
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<tr>
<td>men all ages</td>
<td>0.83</td>
<td>WHO/FAO/UNU [1]</td>
</tr>
<tr>
<td>all ages</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>women additional for pregnancy (third trimester)</td>
<td>+0.43</td>
<td></td>
</tr>
<tr>
<td>additional for lactation</td>
<td>+0.35</td>
<td></td>
</tr>
<tr>
<td>in hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>elderly malnourished/pressure ulcers</td>
<td>1.25 - 1.5</td>
<td>DAA/DNZ [38], ESPEN [30], Cereda [39]</td>
</tr>
<tr>
<td>malnourished with glomerular filtration rate 30 - 60 mL/minute</td>
<td>1.1</td>
<td>Paridaens [40]</td>
</tr>
<tr>
<td>surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>general surgery</td>
<td>1.5</td>
<td>ESPEN [30]</td>
</tr>
<tr>
<td>gastrointestinal surgery</td>
<td>&gt;1.7</td>
<td>Smith [41]</td>
</tr>
<tr>
<td>intestinal failure</td>
<td>1.5 - 2.0</td>
<td>ESPEN [29,30]</td>
</tr>
<tr>
<td>gastroenterology general pancreatitis</td>
<td>1.0 - 1.5</td>
<td>ESPEN [29]</td>
</tr>
<tr>
<td>oncology general radiotherapy</td>
<td>1.0 - 2.0</td>
<td>ESPEN [29]</td>
</tr>
<tr>
<td>head and neck cancer cachexia during and after radiotherapy and chemotherapy</td>
<td>1.2</td>
<td>DAA [42]</td>
</tr>
<tr>
<td>Cossa [43], Isenring [44]</td>
<td></td>
<td></td>
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<tr>
<td>renal HIV stable</td>
<td>1.2 - 1.5</td>
<td>ESPEN [29, Charlin [46]</td>
</tr>
<tr>
<td>acute</td>
<td>1.2 - 1.6</td>
<td>ESPEN [29, Sattler [47]</td>
</tr>
<tr>
<td>chronic kidney disease stage 3, 4, 5 not dialyzed</td>
<td>0.75 - 1.0</td>
<td>CARI [48]</td>
</tr>
<tr>
<td>haemodialysis stable</td>
<td>1.2 - 1.4</td>
<td>CARI [49]</td>
</tr>
<tr>
<td>acute illness</td>
<td>0.9</td>
<td>Kloppenberg [50]</td>
</tr>
<tr>
<td>&gt;1.2</td>
<td>K/DQOI [51]</td>
<td></td>
</tr>
<tr>
<td>peritoneal dialysis stable</td>
<td>&gt;1.2</td>
<td>CARI [49]</td>
</tr>
<tr>
<td>acute illness</td>
<td>&gt;1.3</td>
<td>K/DQOI [51]</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>EDTNA/ERCA [52]</td>
<td></td>
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<tr>
<td>“conservative” management stage 5 acute illness</td>
<td>0.6 - 0.8</td>
<td>ESPEN [29], ADA [53], Ihle [54], Jungers [55], Locatelli [56], Mircescu [57], Williams [58], Teplan [59]</td>
</tr>
<tr>
<td>post kidney transplant—first four weeks</td>
<td>&gt;1.4</td>
<td></td>
</tr>
<tr>
<td>post kidney transplant—long term women</td>
<td>0.75</td>
<td>CARI [60]</td>
</tr>
<tr>
<td>men</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>liver fatty liver, cirrhosis, liver transplant, encephalopathy</td>
<td>1.2 - 1.5</td>
<td>ESPEN [29], Cordoba [61]</td>
</tr>
<tr>
<td>head trauma</td>
<td>&gt;1.5</td>
<td>Twyman [62], IOM [63]</td>
</tr>
<tr>
<td>general trauma and burns</td>
<td>&gt;1.2 - 2.0</td>
<td>ASPEN [31], Larsson [64]</td>
</tr>
<tr>
<td>burns &lt;15% body surface area</td>
<td>1.0 - 1.5</td>
<td>ACI [65]</td>
</tr>
<tr>
<td>15% - 30% body surface area</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>30% - 50% body surface area</td>
<td>1.5 - 2.0</td>
<td></td>
</tr>
<tr>
<td>&gt;50% body surface area</td>
<td>2.0 - 2.3</td>
<td>ACI [65], Serog [66]</td>
</tr>
<tr>
<td>rehabilitation phase</td>
<td>1.7 - 2.0</td>
<td>Demling [67]</td>
</tr>
<tr>
<td>critical illness and sepsis critically ill</td>
<td>1.2 - 1.5</td>
<td>ESPEN [29]</td>
</tr>
<tr>
<td>continuous renal replacement therapy &gt;2.0</td>
<td>Scheinkestel [69]</td>
<td></td>
</tr>
<tr>
<td>sepsis</td>
<td>1.2 - 2.0</td>
<td>ASPEN [31]</td>
</tr>
<tr>
<td>obese critically ill (permissive underfeeding: reduced energy intake) BMI 30 - 40</td>
<td>&gt;2 g/kgIBW</td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 40 &gt;2.5 g/kgIBW</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; IBW: Ideal Body Weight.
Table 2. Summary of included controlled trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Interventions</th>
<th>Results</th>
<th>p</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifton 1985 [72]</td>
<td>RCT, 2 weeks, n = 20 severe head injury inpatients</td>
<td>Isoenergetic EN ~3500 kCal Group 1: 1.5 g·P/kg Group 2: 2.6 g·P/kg</td>
<td>nitrogen intake (g/kg) Group 1: 0.24(0.04) vs. Group 2: 0.42(0.09) &lt;0.01 nitrogen loss (g/kg) Group 1: 0.36(0.08) vs. Group 2: 0.49(0.11) &lt;0.01 nitrogen balance, body weight, serum albumin, creatinine-height index, lymphocyte count NS</td>
<td>&lt;0.01</td>
<td>O</td>
</tr>
<tr>
<td>Demling 1998 [67]</td>
<td>RCT, 3 weeks, n = 15 rehabilitation inpatients post severe burns</td>
<td>Oral diet with supplement drink Group 1: 1.3 - 1.5 g·P/kg Group 2: 2.0 g·P/kg</td>
<td>protein intake (g/kg) Group 1: 1.4(0.1) vs. Group 2: 2.1(0.2) &lt;0.05 weight gain (kg/week) Group 1: 0.59(0.09) vs. Group 2: 1.22(0.05) &lt;0.05 able to complete physiotherapy without fatigue at week 2 (score/10) Group 1: 3(1) vs. Group 2: 6(1) &lt;0.05 able to complete physiotherapy without fatigue at week 3 (score/10) Group 1: 5(1) vs. Group 2: 8(2) &lt;0.05</td>
<td>&lt;0.05</td>
<td>+</td>
</tr>
<tr>
<td>Huang 1990 [73]</td>
<td>RCT, 2 weeks, n = 60 acute head injury inpatients</td>
<td>Non-isocaloric EN Group 1: 1.5 g·P/kg with energy 30 - 35 kCal/kg Group 2: 2.0 - 2.5 g·P/kg with energy 1.9 xBEE Group 3: 2.5 - 3.0 g·P/kg with energy 1.9 xBEE</td>
<td>nitrogen balance (g) Group 1: −13.8(0.5) vs. other groups (Group 2: −6.0(0.6); Group 3: −5.1(2.5); Group 4: −4.0(1.0); Group 5: −4.5(1.0)) &lt;0.001 urinary nitrogen loss (g) at day 8 Group 1: 14.3(1.4) and Group 2: 12.5(1.4) vs. other groups (Group 3: 23.3(3.2), Group 4: 25.1(1.5), Group 5: 30.7(1.5)) &lt;0.05</td>
<td>&lt;0.001</td>
<td>+</td>
</tr>
<tr>
<td>Larsson 1990 [64]</td>
<td>RCT, 8 days, n = 39 trauma or burn inpatients</td>
<td>Isoenergetic PN Group 1: 0 g·P/kg Group 2: 0.6 g·P/kg Group 3: 1.2 g·P/kg Group 4: 1.6 g·P/kg Group 5: 1.9 g·P/kg</td>
<td>nitrogen balance (g) Group 1: −3.23(0.59) vs. other groups (Group 2: −1.6(0.58))</td>
<td>&lt;0.001</td>
<td>+</td>
</tr>
<tr>
<td>Serog 1982 [66]</td>
<td>RCT, 12 days with crossover (3 days each), n = 24 severe burns inpatients</td>
<td>Isoenergetic EN ~4000 kCal Group 1: −2 g·P/kg Group 2: −4 g·P/kg</td>
<td>nitrogen intake (g) Group 1: 21.12(0.85) vs. Group 2: 40.07(1.35) &lt;0.001 nitrogen balance (g) Group 1: −0.09(2.89) vs. Group 2: +19.33(1.87) &lt;0.001 nitrogen output, weight, energy intake, energy expenditure, respiratory quotient NS</td>
<td>&lt;0.001</td>
<td>++</td>
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<tr>
<td>Twyman 1985 [62]</td>
<td>RCT, 10 days, n = 21 head injury inpatients</td>
<td>Isoenergetic EN ~3000 kCal Group 1: 1.5 g·P/kg Group 2: 2.2 g·P/kg</td>
<td>nitrogen balance (g) Group 1: −3.23(0.59) vs. Group 2: 1.6(0.58)</td>
<td>0.006</td>
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<tr>
<td>Wolfe 1982 [74]</td>
<td>RCT, 6 days with crossover (3 days each), n = 6 severe burns inpatients</td>
<td>Isoenergetic EN or PN ~40 kCal/kg Group 1: 1.4 g·P/kg Group 2: 2.2 g·P/kg</td>
<td>plasma leucine oxidation (μmol/kg) Group 1: 56 vs. Group 2: 76 &lt;0.05</td>
<td>&lt;0.05</td>
<td>O</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Group 1 (PN or EN)</td>
<td>Group 2 (PN or EN)</td>
<td>Critical illness</td>
<td></td>
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<td>-----------------------------</td>
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<tr>
<td>Groig 1987 [70]</td>
<td>RCT, 1 week, n = 9 septic inpatients on parenteral nutrition</td>
<td>isoenergetic PN ~2250 kCal</td>
<td>Group 1: 1.19 g/P/kg Group 2: 2.29 g/P/kg</td>
<td>protein oxidation (kCal/kg) Group 1: 4.7(0.6) vs. Group 2: 8.3(1.1) &lt;0.05</td>
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<td></td>
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<td>urea (mmol/L) Group 1: 7.3+/−2.8 vs. Group 2: 8.4+/−1.2 &lt;0.05</td>
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<td>nitrogen balance, glucose, fatty acids, insulin and triglycerides NS</td>
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<tr>
<td>McCowen 2000 [71]</td>
<td>RCT, 5 days, n = 40 inpatients on parenteral nutrition</td>
<td>Group 1: 0.9 g/P/kg with 15 kCal/kg Group 2: 1.5 g/P/kg with 20 - 25 kCal/kg</td>
<td></td>
<td>nitrogen balance (g) Group 1: −8.3(9.2) vs. Group 2: −0.6(4.8) &lt;0.03</td>
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<td></td>
<td></td>
<td></td>
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<td>infection rate, glucose, hospital LOS, mortality NS</td>
<td></td>
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<tr>
<td>Mesejo 2003 [68]</td>
<td>RCT, 14 days, n = 50 hyperglycaemic critically ill</td>
<td>isoenergetic EN ~1750 kCal Group 1: 1.14 g/P/kg Group 2: 1.25 g/P/kg</td>
<td></td>
<td>infection rate, ICU LOS, ventilator days, mortality, serum lipids, visceral proteins, full blood count NS ++</td>
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<tr>
<td>Scheinestein 2003 [69]</td>
<td>RCT, 6 days, n = 50 critically ill inpatients on CRRT</td>
<td>isoenergetic EN or PN Group 1: 2 g/kg for 6 days Group 2: 2 days each: 1.5 g/kg, 2 g/kg, 2.5 g/kg</td>
<td></td>
<td>protein balance day 4 (g) Group 1: −7.3(24.2) vs. Group 2: 0.4(9.2) 0.04 Scheinestein 2003 [69]</td>
<td></td>
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<tr>
<td>Smith 1982 [41]</td>
<td>RCT with crossover (1 week each), n = 8 malnourished gut surgery PN patients</td>
<td>isoenergetic PN ~1930 kCal Group 1: −1.2 g/kg Group 2: −2.2 g/kg</td>
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<tr>
<td>Askanazi 1984 [75]</td>
<td>RCT with crossover (1 week each), n = 8 malnourished gut surgery PN patients</td>
<td>isoenergetic PN ~1930 kCal Group 1: −1.2 g/kg Group 2: −2.2 g/kg</td>
<td></td>
<td>pH, PaCO₂, respiratory rate, V̇E, V̇R, Ṫ2PaCO NS</td>
<td></td>
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<tr>
<td>Charlin 2002 [46]</td>
<td>RCT with crossover (45 days each), n = 46 malnourished HIV positive outpatients</td>
<td>oral diet supplemented with extra foods or enteral formula Group 1: 1.19 g/P/kg Group 2: 1.56 g/P/kg</td>
<td></td>
<td>energy balance at end of first period (kCal/kg) Group 1: −2.1(8.2) vs. Group 2: 3.9(9.9) &lt;0.05</td>
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<td>urinary urea nitrogen at end of first period (g) Group 1: 5.6(2.6) vs. Group 2: 7.7(4.0) &lt;0.05</td>
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<td>nitrogen intake (g/N/kg) Group 1: 0.19(0.05) vs. Group 2: 0.25(0.07) &lt;0.05 ++</td>
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<td></td>
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<td>extra energy consumed as supplement (kCal/day) Group 1: 538 vs. Group 2: 274 not reported</td>
<td></td>
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<td></td>
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<td></td>
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<td>increase in protein intake (g) Group 1: 14.6 vs. Group 2: 37.4 NS</td>
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<td></td>
<td>albumin, serum total protein, bilirubin, ALP, GGT NS</td>
<td></td>
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<tr>
<td>Sattler 2008 [47]</td>
<td>RCT multi centre, 12 weeks, n = 59 stable HIV positive outpatients</td>
<td>oral diet (with isoenergetic supplement of maltose or whey protein) Group 1: 1.5 g/P/kg Group 2: 2.5 g/P/kg</td>
<td></td>
<td>protein intake at week 6 (g) Group 1: 1.68(0.6) vs. Group 2: 2.62(0.43) &lt;0.001</td>
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<tr>
<td></td>
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<td>protein intake at week 12 (g) Group 1: 1.40(0.56) vs. Group 2: 2.57(0.51) &lt;0.01</td>
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<td>carbohydrate intake at week 6 (g) Group 1: 6.29(1.75) vs. Group 2: 5.29(1.98) &lt;0.01</td>
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<td>fat intake at week 12 (g) Group 1: 1.62(0.69) vs. Group 2: 1.77(0.58) &lt;0.01</td>
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<tr>
<td></td>
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<td></td>
<td>change in triglycerides at week 12 (mmol/L) Group 1: +0.44(1.11) vs. Group 2: −0.18(0.70) 0.03 +</td>
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<tr>
<td></td>
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<td></td>
<td>change in CD4 lymphocytes at week 12 (cells/mL) Group 1: −5(124) vs. Group 2: +31(84) 0.03</td>
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<tr>
<td></td>
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<td></td>
<td>adverse gastrointestinal symptoms Group 1: 7/24 patients vs. Group 2: 15/17 patients 0.03</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>energy intake, carbohydrate intake at week 12, fat intake at week 6, weight, lean body mass, waist-to-hip ratio NS</td>
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</tr>
</tbody>
</table>

**HIV**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Group 1 (PN or EN)</th>
<th>Group 2 (PN or EN)</th>
<th>Critical illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlin 2002 [46]</td>
<td>RCT with crossover (45 days each), n = 46 malnourished HIV positive outpatients</td>
<td>oral diet supplemented with extra foods or enteral formula Group 1: 1.19 g/P/kg Group 2: 1.56 g/P/kg</td>
<td></td>
<td>energy intake, carbohydrate intake at week 12, fat intake at week 6, weight, lean body mass, waist-to-hip ratio NS</td>
</tr>
</tbody>
</table>

**Surgery**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Group 1 (PN or EN)</th>
<th>Group 2 (PN or EN)</th>
<th>Critical illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Askanazi 1984 [75]</td>
<td>RCT with crossover (1 week each), n = 8 malnourished gut surgery PN patients</td>
<td>isoenergetic PN ~1930 kCal Group 1: −1.2 g/kg Group 2: −2.2 g/kg</td>
<td></td>
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</tr>
</tbody>
</table>
### Back to Basics: Estimating Protein Requirements for Adult Hospital Patients. A Systematic Review of Randomised Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
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<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumenkrantz 1982 [76]</td>
<td>unclear if randomised, 2 - 4 weeks, n = 8 peritoneal dialysis outpatients</td>
<td>isoenergetic oral diet ~2500 kCal</td>
<td>Group 1: 0.4 g P/kg, Group 2: 0.75 g P/kg</td>
<td>nitrogen balance (g) Group 1: 0.35(0.83) vs. Group 2: 2.94(0.54) &lt;0.01</td>
<td>body weight change (kg) Group 1: 0 vs. Group 2: 2.1(1.4) &lt;0.02</td>
</tr>
<tr>
<td>Ihle 1989 [54]</td>
<td>RCT, 18 months, n = 72 renal outpatients</td>
<td>isoenergetic oral diet ~2500 kCal</td>
<td>Group 1: 0.4 g P/kg, Group 2: 0.75 g P/kg</td>
<td>time until start of dialysis, or death (months) Group 1: 7.1(4.8) vs. Group 2: 11.8(3.5) &lt;0.05</td>
<td>body weight, arm muscle circumference, serum total protein, albumin, calcium, phosphate, electrolytes, blood lipids, mean arterial pressure NS</td>
</tr>
<tr>
<td>Jungers 1987 [55]</td>
<td>RCT, 1 year, n = 19 renal outpatients</td>
<td>isoenergetic oral diet ~2500 kCal supplemented with keto-acids</td>
<td>Group 2: 0.6 g P/kg</td>
<td>nitrogen balance (g) Group 1: negative vs. Group 2: neutral to positive, not quantified</td>
<td>body weight, arm muscle circumference, serum total protein, albumin, calcium, phosphate, electrolytes, blood lipids, mean arterial pressure NS</td>
</tr>
<tr>
<td>Klahr 1994 [77]</td>
<td>RCT, multi-centre, 2 years, 840 renal outpatients</td>
<td>oral diet supplemented with ketoacids</td>
<td>Group 2: 0.58 g P/kg, Group 3: 1.3 g P/kg</td>
<td>decline in glomerular filtration rate (mL/min) between baseline and 3 years, all groups NS</td>
<td>protein intake (g/kg) Group 1: 0.90(0.14) vs. Group 2: 1.01(0.18) &lt;0.05</td>
</tr>
<tr>
<td>Kloppenburg 2004 [50]</td>
<td>RCT with crossover, 80 weeks, n = 50 haemodialysis outpatients</td>
<td>oral diet</td>
<td>Group 1: 0.9 g P/kg, Group 2: 1.3 g P/kg</td>
<td>nitrogen balance (g) Group 1: 0.90(0.14) vs. Group 2: 1.01(0.18) &lt;0.05</td>
<td>body weight, arm muscle circumference, serum total protein, albumin, calcium, phosphate, electrolytes, blood lipids, mean arterial pressure NS</td>
</tr>
<tr>
<td>Kopple 1969 [78]</td>
<td>RCT, 30 days, n = 19 pre-dialysis uraemic outpatients</td>
<td>oral diet</td>
<td>Group 1: 20 g protein (~0.3 g P/kg), Group 2: 40 g protein (~0.6 g P/kg), Group 3: 1 g P/kg</td>
<td>nitrogen balance (g) Group 1: negative vs. Group 2: neutral to positive, not quantified</td>
<td>mean uraemic index lower in Group 1 and Group 2 vs. Group 3, not quantified</td>
</tr>
</tbody>
</table>

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Continued

Kopple 1973 [79]  
unfirmed if randomised, crossover, 80 days, n = 8 uremic outpatients  
oral diet Group 1: 20 g protein (~0.3 g P/kg)  
Group 2: 40 g protein (~0.6 g P/kg)  
nitrogen balance (g) Group 1: −0.15(0.25) vs. Group 2: +1.16(0.20) <0.001  
urinary nitrogen (g) Group 1: 3.01(0.27) vs. Group 2: 3.84(0.22) not reported  
urea (mmol/L) Group 1: 16.1(3.0) vs. Group 2: 21.3(3.9) NS  
weight gain (kg) Group 1: −0.36(0.39) vs. Group 2: 0.62(0.19) <0.05  
creatinine, potassium, uric acid, pH, potassium intake, faecal nitrogen, faecal potassium, urinary creatinine, urinary uric acid, QOL score, appetite, reported symptoms  
renal survival (need for dialysis) Group 1: 27/230 patients vs. Group 2: 42/226 patients 0.059  
urinary urea Group 1: 14.94(6.03) vs. Group 2: 17.53(6.29) <0.01  
protein catabolic rate (g/kg) significantly lower in Group 1, not quantified  
not reported

Locatelli 1991 [56]  
RCT multi-centre, 2 years, n = 456 renal outpatients  
oral diet Group 1: 0.6 g P/kg  
Group 2: 1.0 g P/kg  
renal survival (need for dialysis) Group 1: 1/27 patients vs. 7/26 patients  
eGFR (mL/min/1.73 m²) Group 1: 15.4(5.0) vs. Group 2: 13.4(5.1) not reported  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02  
prealbumin (g/L) Group 1: 16.4(4.6) vs. other groups (Group 2: 21.6(9.7), Group 3: 22.4(8.9)) 0.02 ++  
transferrin (g/L) Group 1: 206.0(60.1) vs. Group 2: 254.9(41.8) vs. Group 3: 173.5(68.4) 0.01  
urinary urea (g/L) Group 1: 9.6(5.2) vs. Group 2: 14.4(1.9) <0.01  
nitrogen balance (g) Group 1: −1.6(0.9) vs. other groups (Group 2: 1.0(0.2), Group 3: 0.8(0.3)) <0.01  
urinary nitrogen (g) Group 1: 5.2(3.0) and Group 2: 5.3(1.2) vs. Group 3: 10.08(5.1) <0.05  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02  
nitrogen balance (g) Group 1: −1.6(0.9) vs. other groups (Group 2: 1.0(0.2), Group 3: 0.8(0.3)) 0.01  
urinary nitrogen (g) Group 1: 5.2(3.0) and Group 2: 5.3(1.2) vs. Group 3: 10.08(5.1) <0.05  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02

Mircescu 2007 [57]  
RCT, 60 weeks, n = 53 renal outpatients  
oral diet 30 kCal/kg  
Group 1: 0.3 g P/kg as vegetable protein supplemented with ketoacids  
Group 2: 0.6 g P/kg  
renal survival (need for dialysis) Group 1: 1/27 patients vs. 7/26 patients  
eGFR (mL/min/1.73 m²) Group 1: 15.4(5.0) vs. Group 2: 13.4(5.1) not reported  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02  
prealbumin (g/L) Group 1: 16.4(4.6) vs. other groups (Group 2: 21.6(9.7), Group 3: 22.4(8.9)) 0.02 ++  
transferrin (g/L) Group 1: 206.0(60.1) vs. Group 2: 254.9(41.8) vs. Group 3: 173.5(68.4) 0.01  
urinary urea (g/L) Group 1: 9.6(5.2) vs. Group 2: 14.4(1.9) <0.01  
nitrogen balance (g) Group 1: −1.6(0.9) vs. other groups (Group 2: 1.0(0.2), Group 3: 0.8(0.3)) <0.01  
urinary nitrogen (g) Group 1: 5.2(3.0) and Group 2: 5.3(1.2) vs. Group 3: 10.08(5.1) <0.05  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02

Paridaens 1995 [40]  
RCT, 6 weeks, n = 67 malnourished elderly inpatients with renal insufficiency  
isoenergetic EN ~2000 kCal  
Group 1: 0.72 g P/kg  
Group 2: 1.1 g P/kg  
Group 3: 1.6 g P/kg  
nitrogen balance (g) Group 1: −1.6(0.9) vs. other groups (Group 2: 1.0(0.2), Group 3: 0.8(0.3)) <0.01  
urinary nitrogen (g) Group 1: 5.2(3.0) and Group 2: 5.3(1.2) vs. Group 3: 10.08(5.1) <0.05  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02  
prealbumin (g/L) Group 1: 16.4(4.6) vs. other groups (Group 2: 21.6(9.7), Group 3: 22.4(8.9)) 0.02 ++  
transferrin (g/L) Group 1: 206.0(60.1) vs. Group 2: 254.9(41.8) vs. Group 3: 173.5(68.4) 0.01  
urinary urea (g/L) Group 1: 9.6(5.2) vs. Group 2: 14.4(1.9) <0.01  
nitrogen balance (g) Group 1: −1.6(0.9) vs. other groups (Group 2: 1.0(0.2), Group 3: 0.8(0.3)) <0.01  
urinary nitrogen (g) Group 1: 5.2(3.0) and Group 2: 5.3(1.2) vs. Group 3: 10.08(5.1) <0.05  
urea (mmol/L) Group 1: 17.7(5.5) vs. Group 2: 29.5(1.5) vs. Group 3: 46.7(25.4) <0.02

Rosman 1984 [80]  
RCT, 18 months, n = 228 renal outpatients  
oral diet Group 1: 0.4 g P/kg (for creatinine clearance 10 - 30 mL/min/1.73 m²)  
Group 2: 0.6 g P/kg (for creatinine clearance 31 - 60 mL/min/1.73 m²)  
Group 3: “usual diet”  
renal survival (persistent 20% increase in creatinine) Group 1: 60.0% and Group 2: 66.4% vs. Group 3: 21.8% of patients at 2 years <0.05  
weight (kg) at 18 months Group 1: 69 vs. Group 2: 71 vs. Group 3: 73 <0.05  
urinary protein (g) significantly lower in protein-restricted groups, not quantified  
urinary urea (mmol/L) at 18 months Group 1: 32 vs. Group 2: 34 vs. Group 3: 24 <0.05  
urinary creatinine (mmol/L) at 9 months Group 1: 9.2 vs. Group 2: 10.4 vs. Group 3: 10.6 <0.01  
diastolic blood pressure (mmHg) at 9 months Group 1: 90 vs. Group 2: 85 vs. Group 3: 90 <0.05  
ihemoglobin, haematocrit, creatinine, urea, phosphate, calcium, ALP, total protein, albumin, lipids, pH, bicarbonate, urinary sodium, urinary calcium, urinary phosphate NS

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Duration</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teplan 1994</td>
<td>RCT</td>
<td>3 months</td>
<td>n = 36</td>
<td>malnourished renal outpatients</td>
<td>isoenergetic oral diet Group 1: 0.74 g P/kg supplemented with keto-acids, Group 2: 1.2 g P/kg</td>
</tr>
<tr>
<td>Williams 1991</td>
<td>RCT</td>
<td>19 months</td>
<td>n = 95</td>
<td>renal outpatients</td>
<td>oral diet at least 30 kCal/kg Group 1: 0.6 g P/kg with low phosphate, Group 2: at least 0.8 g P/kg with low phosphate, Group 3: at least 0.8 g P/kg with no phosphate restriction</td>
</tr>
<tr>
<td>Cordoba 2004</td>
<td>RCT</td>
<td>14 days</td>
<td>n = 30</td>
<td>encephalopathic cirrhosis inpatients</td>
<td>oral diet with energy and protein intake doubled gradually over 4 weeks. Protein intake: Day 0: 0.95 g P/kg Day 28: 1.78 g P/kg</td>
</tr>
<tr>
<td>Kondrup 1997</td>
<td>Unsure</td>
<td>2 - 4 weeks</td>
<td>n = 11</td>
<td>malnourished cirrhosis inpatients without encephalopathy</td>
<td>oral diet with energy and protein intake doubled gradually over 2 weeks. Protein intake: Day 0: 1.04 g P/kg Day 14: 2.12 g P/kg</td>
</tr>
</tbody>
</table>

**Renal, continued**

- urea (mmol/L) Group 1: 14.7(6.2) vs. Group 2: 18.6(5.7) <0.05
- phosphate (mmol/L) Group 1: 1.28(0.38) vs. Group 2: 1.89(0.42) <0.05
- Whitehead quotient essential: non-essential amino acids ratio Group 1: 1.66(0.56) vs. Group 2: 1.94(0.42) +
- HDL cholesterol (mmol/L) Group 1: 0.26(0.07) vs. Group 2: 0.15(0.09) <0.05
- prealbumin, albumin, transferrin, TIBC, glucose, triglycerides, calcium, creatinine, pH, immunoglobulins NS
- protein intake (g P/kg) Group 1: 0.74 g P/kg supplemented with keto-acids, Group 2: 1.2 g P/kg NS
- phosphate intake (mg) Group 1: 815(43) vs. Group 2: 1000(47) vs. Group 3: 1315(57) not reported
- urinary urea (mmol) Group 1: 213(9) vs. other groups (Group 2: 283, Group 3: 283) <0.05
- protein catabolic rate (g/kg) Group 1: 0.71(0.02) vs. other groups (Group 2: 0.92(0.03), Group 3: 0.95(0.04)) 0.001
- urinary phosphate (mmol) Group 1: 17.9(1.0) vs. other groups (Group 2: 18.6(1.0) vs. Group 3: 22.5(1.0) <0.05
- mortality, dialysis requirement, creatinine, phosphate, weight, mid- arm muscle circumference, transferrin, immunoglobulins, bicarbonate, urinary protein, blood pressure, creatinine clearance NS

**Liver**

- catabolism at day 2 (g P/day) Group 1: 4.1(3.6) vs. Group 2: 3.5 (2.4) 0.04
- catabolism at day 14, protein synthesis, encephalopathy, albumin, bilirubin, ammonia, prothrombin activity NS

- nitrogen balance (g N/kg) Day 0: −0.02(0.08) vs. Day 28: +0.51(0.11) 0.001
- protein synthesis (g/kg) Day 0: 2.15(0.24) vs. Day 28: 2.81(0.35) 0.033
- nitrogen balance (g N/kg) Day 0: −0.08(0.24) vs. Day 14: 0.90(0.36) 0.027
- protein synthesis (g/kg) Day 0: 3.14(0.48) vs. Day 14: 3.88(0.44) 0.044
- amino acids (mmol/L) Day 0: 3.85(0.24) vs. Day 14: 4.82(0.21) 0.049
- glucose, lactate, fatty acids, ketones, growth hormone, IGF-1, TSH NS
- body weight at 12 weeks (kg) Group 1: 72.2 vs. Group 2: 75.9 <0.001
- nutritional status at 8 weeks (SGA “A”) Group 1: 11/29 patients vs. Group 2: 18/26 patients 0.020
- quality of life, not quantified 0.009
- physical function, not quantified 0.012
chronically ill adults. A limitation of all macronutrient studies is the effect of one macronutrient on total energy intake and/or the proportions of other macronutrients. For protein, in particular, this presents difficulties because protein requirement is affected by total energy intake. The effects of altering protein intake may therefore be confounded if energy intake is also changed. However, replacing protein with either carbohydrate or fat in isoenergetic studies may not be neutral as to effect. Of the 33 studies, 10 were not isoenergetic [39,41,44,46,64,71,73,75,80,81] and additionally a further three [58,59,77] did not provide sufficient detail to ascertain this. A number of the studies also failed to assess actual intake (as distinct from prescribed intake) [54,56,57,59,61,64,74,78,80]. This is not only relevant for oral diets where intake is voluntary, but also in non-volitional feeding (enteral or parenteral) where intake may be interrupted for various reasons including tube problems, medication administration, surgical procedures, and poor tolerance of the nutrition. Without such an assessment it is unclear whether the studies’ findings were actually the result of different protein intakes.

The value of clinical trial findings in predicting protein requirements may be compromised by the outcome measures chosen, if these are clinically meaningless or lacking in wide applicability. Accurate measures of protein synthesis and breakdown, using radiolabelled amino acids, are not in general use and were employed in only one of the studies reviewed. It could be argued that it is more meaningful to assess protein requirements in terms of more concrete, patient-focused outcome measures such as survival and function, however, most of the studies reviewed here were too small to be powered adequately for measuring any such outcome. More than two-thirds of the studies had 50 participants or fewer (five studies had fewer than ten sub-

Other conditions

- protein intake (g/kg) Group 1: 1.2(0.2) vs. Group 2: 1.5(0.2) <0.001
- energy intake (kCal/day) Group 1:1848(309) vs. Group 2: 1586(211) 0.02
- ulcer score at week 12 (using PUSH tool) Group 1: −10.7(3.4) vs. Group 2: 7.4(3.4) <0.05
- ulcer surface area at week 12 (mm²) Group 1: 1228(852) vs. Group 2: 701(835) <0.05 ++
- serum zinc (µmol/L) at 12 weeks Group 1: 4.17(3.99) vs. Group 2: 6.93(4.09) <0.03
- antibiotic therapy (days) Group 1: 103 vs. Group 2: 36 <0.001
- weight, BMI, serum total protein, albumin, transferrin, total cholesterol, lymphocytes, haemoglobin, geriatric nutritional risk score NS
- protein intake (g/kg) Group 1: 1.0 - 1.1 vs. Group 2: 1.1 - 1.3 0.001
- energy intake (kCal/kg) Group 1: 25 - 29 kCal/kg vs. Group 2: 28 - 31Kcal/kg 0.022 ++
- body weight at 12 weeks (kg) Group 1: 72.2 vs. Group 2: 75.9 <0.001
- nutritional status at 8 weeks (SGA “A”) Group 1: 11/29 patients vs. Group 2: 18/26 patients 0.020
- quality of life, not quantified 0.009
- physical function, not quantified 0.012
- protein intake (g/day) Group 1: 65(15) vs. Group 2: 83(15) <0.01
- intolerance of feeds Group 1: 16.9% of days vs. Group 2: 3.3% of days <0.05 ++
- urinary nitrogen, nitrogen balance, diarrhoea NS

P = protein; RCT = randomised controlled trial; PN = parenteral nutrition; EN = enteral nutrition; BEE = basal energy expenditure; IBW = ideal body weight; GCS = glasgow coma score; LOS = length of stay; ICU = intensive care unit; NS = not significant; ALP = alkaline phosphatase; GGTT = gamma glutamyl transferase; HDL = high-density lipoprotein cholesterol; BMI = body mass index; IGF-1 = insulin-like growth factor 1; TSH = thyroid-stimulating hormone; SGA = subjective global assessment of nutritional status; Note all values are serum levels unless otherwise stated.
jects). Only seven studies [44,47,50,56,61,68,80] included any sample size calculations. Of these, the studies rated as lower-quality studies were no more likely to be under-powered than higher-quality studies (p = 0.817).

Recommendations for protein intake vary according to clinical condition, but for some diagnostic groups there is little high-level evidence available. This is also the main limitation of this review, namely the small number of studies and the suboptimal quality of many of these. Five studies were not possible to obtain within the limited resources of this project. Of those obtained, one-third of studies were scored neutral or poor quality. In general, older studies were the most likely to score poorly due to inadequate description of randomisation, blinding and allocation concealment in particular, with newer work reflecting the contemporary emphasis on thorough reporting and careful study design.

At present, nutritional prescriptions are quite imprecise, based on wide recommended ranges and lacking in ways to evaluate the patient’s ongoing nutritional progress. Particularly in the case of protein requirements, there is a need for future research to inform these prescriptions, with adequately-powered well-controlled studies investigating a range of different intakes and assessing the results in concrete, patient-focused ways. The limited availability of high-level evidence for some of the diagnostic groups, and the significant heterogeneity within some groups (critical care in particular) indicates a need for further research in specific illnesses. However, it is reassuring to find that the studies included in this review do report protein intakes similar to those included in the guidelines and pocketbooks that dietitians are currently using to guide the nutritional care of their patients.

REFERENCES


Back to Basics: Estimating Protein Requirements for Adult Hospital Patients. A Systematic Review of Randomised Controlled Trials


[38] Trans-Tasman Dietetic Wound Care Group, “Evidence Based Practice Guidelines for the Dietetic Management of Adults with Pressure Injuries,” DAA and DNZ, 2011.


Back to Basics: Estimating Protein Requirements for Adult Hospital Patients. A Systematic Review of Randomised Controlled Trials


