

# Protein Restriction and Body Composition in Renal Disease

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**Objective:** To study the effect of low-protein diet (LPD) on body composition (BC).

**Study Design:** A systematic review of the literature investigating BC during LPD treatment using total body potassium, dual energy X-ray absorptiometry, bioelectrical impedance analysis, and anthropometry.

**Patients:** Studies reporting data of patients treated with LPD 0.3–0.75 g/kg/day and a renal function of glomerular filtration rate (GFR)  $\leq 20$  mL/min, creatinine clearance  $\leq 25$  mL/min, on serum creatinine  $\geq 500$   $\mu$ mol/L were included in the review. Fourteen studies with a total number of 666 subjects were found eligible.

**Results:** All studies except two concluded that treatment with LPD does not affect BC negatively. However, LPD should not be introduced in patients with a complicating disease, e.g., acidosis, septicaemia, and surgical treatment; neither should it be continued in patients who are unable to adhere to a diet prescription. Furthermore, LPD should be introduced with great caution in patients with an expected time to dialysis of  $\leq 4$  months due to an initial reduction of body weight and/or fat-free mass. Monitoring of treatment with LPD must be emphasized, including BC measurements and evaluation of protein and energy intake. These conclusions do not apply to patients with diabetes mellitus, because this diagnosis was excluded in a majority of reviewed studies.

**Conclusion:** There is no strong evidence that LPD impairs BC in patients with GFR  $\leq 20$  mL/min.

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MUSCLE ATROPHY IS A SERIOUS complication of advanced chronic renal failure (CRF) before and during dialysis, and can be related to nutrient intake (malnutrition) as well as to the metabolic and endocrine disorders associated with renal failure.<sup>1,2</sup> The potential benefit of low-protein diets (LPDs) for uremic patients has long been debated. Diet modification in uremia should both relieve uremic symptoms, correct some of the complications seen in kidney failure (e.g., osteodystrophy, hyperkalemia, and metabolic acidosis), and preserve or improve the nutritional status of patients.<sup>3</sup> Critics of LPD call attention to the lack of nutritional assessment in

intervention studies of LPD, and to these studies' primary focus on the benefits of LPD.<sup>4</sup>

Measurement of nutritional status is complicated, and the interpretations have limitations. The physiologic changes which occur in renal disease may affect many of these measurements,<sup>5</sup> e.g., by fluid retention and alterations in the distribution of intracellular water (ICW) and extracellular water (ECW).

The influence of nutritional and non-nutritional factors in CRF is reflected in resultant changes in body composition. The aim of this systematic review was to summarize and discuss studies of body composition in patients with chronic renal disease treated with LPD in stages 4 (excluding those with a glomerular filtration rate [GFR]  $> 20$  mL/min) and 5, according to the Kidney Disease Outcomes Quality Initiatives (KDOQI).<sup>6</sup>

## Measurement of Body Composition

The numerous methods for assessing body composition vary with respect to precision, accuracy, and utility. They range from simple methods such as anthropometry and bioimpedance (BIA)

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to computed tomography (CT) and dual energy X-ray absorptiometry (DEXA), which have become increasingly available. There are also more costly and labor-intensive methods for the measurement of body fluids and for analyses of atomic components such as potassium and nitrogen.

Body composition can be assessed by different body composition models. *At a molecular level*, body mass is divided into two-component models measuring fat mass and fat-free mass (FFM), or into multicomponent models ( $\geq 3$  components). In the latter models, FFM is divided into additional components, e.g., bone mineral, total body water (TBW), or total body protein. *At a cellular level*, body mass is divided into three components: extracellular solids, extracellular fluid, and cells. The cells can be further partitioned into fat and body cell mass. *At a whole-body level*, the basis for assessment of body composition is body weight, with a description of anthropometric measures such as circumference, skinfolds, and length. In addition to these models, there is an atomic and a tissue-organ level for determining body composition.<sup>7</sup>

Most commonly, the estimation of body composition has focused on body fat (BF). However, the importance of prediction of FFM is increasing because of its relationships to morbidity, mortality, physical performance, and caloric requirements.<sup>7</sup>

The major constituents of FFM are muscle, bone, vital organs, and extracellular fluid. Indirect techniques for measuring FFM rely on the assumptions that FFM has a constant density, and that its major constituents are present in fixed ratios, whereas the direct techniques estimate body composition without assumptions. The errors in body-composition measures are larger for predicted values than for observed values.

These findings in this review are based on studies using the following measurements of body composition:

- Whole-body counting/total body potassium (TBK);
- Dual-energy X-ray absorptiometry;
- Bioelectrical impedance analysis; and
- Anthropometry.

## TBK

Total body potassium can be used as a measure of cellular mass, because 95% to 98% of body

potassium is present in the intracellular space. Since fat tissue is essentially free of potassium, TBK may be used to estimate FFM. The TBK:FFM ratio was originally considered a constant set at 68.1 mmol/kg FFM,<sup>7</sup> but varies, e.g., with age, and in particular with changes in the ECW to ICW ratio.

Naturally occurring potassium is distributed in three isotopic states, of which potassium-40 (<sup>40</sup>K) represents 0.0118% of TBK and decays at a well-defined rate. Total body potassium is estimated by measuring the gamma emission of naturally occurring <sup>40</sup>K in a whole-body counter.

The measurement of TBK is a reference method to estimate body cell mass (BCM; muscle, visceral organs, blood, and brain). By using assumptions for an average K:N ratio in wet tissue and intracellular potassium concentration, BCM was originally defined as  $BCM \text{ (kg)} = 0.00833 \times K \text{ (mmol)}$ . Subsequent research indicated that  $BCM \text{ (kg)} = 0.0092 \times K \text{ (mmol)}$  may be more appropriate.<sup>8</sup> The BCM is the component of FFM that is most likely to change in disease over short periods of time (days or weeks).<sup>7</sup>

There are difficulties in estimating BCM from TBK in renal failure because low, normal, and high ratios of intracellular K to intracellular protein were all described.<sup>3,5</sup> In a study of 102 nondialyzed men and women with renal failure, the content of K in muscle was increased in relation to alkali-soluble protein in muscle, which indicates protein loss. However, the ratio of K to fat-free solids was normal.<sup>9</sup> The ratio of K to intracellular water was reduced in the same study. This finding reflects an accumulation of intracellular water. The reduced intracellular K concentration can be a consequence of altered membrane permeability, a disordered function of the sodium-potassium exchange mechanism, or disturbances associated with acid-base disorders.<sup>10</sup> Generally, a decrease of TBK reflects a diminishing BCM. It may be questioned whether this also applies to uremic patients. However, bearing in mind the results of Bergström et al. regarding muscle K content,<sup>9</sup> TBK should be considered a reliable method for evaluating body cell mass in uremia, as long as the patient is clinically stable.

## DEXA

Dual-energy X-ray absorptiometry provides a measure of bone mineral content (BMC), body fat (BF), and lean tissue mass (LTM), and is

becoming the preferred reference method for estimating body composition. During examination, the body is simultaneously scanned with two different low-energy X-rays. Detectors on the opposite side of the body measure the energy that is not absorbed, referred to as *attenuation*. Different tissues have characteristic attenuations at certain energy levels, e.g., soft tissues, which contain mainly water and organic compounds and therefore restrict the flux of X-rays less than bone. By using algorithms, it is possible to estimate the proportions of lean tissue and fat, based on the soft-tissue composition adjacent to the bone.

One concern in the use of DEXA is the potential interference from fluid accumulation, because DEXA cannot differentiate between ECW and BCM.<sup>7</sup> Other concerns include the method's reliance on computer software and pixel interpretation, which vary by manufacturer, and inherent assumptions regarding levels of hydration or tissue density, which can bias body composition estimates, e.g., in dialysis patients.<sup>11</sup>

## BIA

Bioelectrical impedance analysis is used to estimate TBW and FFM by measuring the resistance of the body to a small alternating electric current. The impedance values of resistance and reactance are converted into estimations of body composition, using regression equations validated against a criterion body-composition method. The equations describe statistical relationships that are reasonably accurate for estimating body composition found in a particular population, but large errors for individuals limit its clinical use. Variations between populations are due to differences in body size, shape, electrolytes, water distribution, or other aspects of the body's composition in health and disease. Each equation is applicable only to subjects who closely match the reference subjects for each equation.<sup>7</sup>

The equations rely on the assumption that the major constituents of FFM are present in fixed ratios. These assumptions are likely to be incorrect in CRE, where abnormalities in body water content and distribution pose a particular problem.<sup>12</sup> The largest contributors to whole-body resistance are the forearms (28%) and legs (33%), compared with the trunk (9%).<sup>13</sup> Hence, alterations in body water associated with dependent

edema, as in renal disease, may result in significant body resistance changes.

*Single-frequency* impedance measures TBW, and estimates FFM based on the "hydration law," i.e., the ratio of TBW to FFM equals 0.73. *Multifrequency* impedance measurements can differentiate TBW into ICW and ECW, and are especially used in research and clinical settings in end-stage renal disease and dialysis prescription.<sup>7</sup>

## Anthropometry

Anthropometry methods measure the size and proportions of the human body, and are used to assess total and regional body composition. The methods are relatively easy to perform, but require an experienced investigator. They can be performed quickly, and the equipment is inexpensive.

Measurements of skinfold thicknesses (e.g., biceps, triceps, and subscapular skinfold) are used to estimate BF through equations, preferably with consideration given to age and sex. The thickness of subcutaneous tissue at different sites of measurement changes proportionately with weight gain or loss, though anthropometry applied through predictive equations is unlikely to provide accurate measures of changes in total body composition. The correlation between skinfold thickness and %BF is  $r = 0.7 - 0.9$ .<sup>7</sup>

In anthropometry, FFM is estimated from the difference between body weight and BF.

Arm muscle circumference (AMC) or middle arm muscle circumference (MAMC) is calculated by measuring the middle arm circumference (MAC) and the triceps skinfold thickness (TSF) according to the equation:  $AMC \text{ (cm)} = MAC - (0.314 \times TSF)$ . A reduction in arm muscle area is interpreted as a loss of muscle protein or somatic protein mass. Arm muscle area (AMA) is calculated according to the equation  $AMA \text{ (cm}^2\text{)} = [MAC - \pi \text{ TSF (cm)}]^2 / 4$ .

Skin turgor and hydration may affect subcutaneous skinfold thickness. Measurements of dialysis patients should be conducted after dialysis, when the patient is at dry weight. The measurements should not be performed in the arm with a vascular access.<sup>5</sup>

## Methods

### Literature Search

A search was conducted with no date limitation on November 17, 2006 in PubMed, the

Cochrane Central Register of Controlled Trials and Protocols, the Public Library of Science (Plos), and the International Network of Agencies for Health Technology Assessment (INAHTA.org).

The search terms were grouped in to three topics separated by “AND” as follows:

- (renal insufficiency OR kidney failure OR uremia OR uremic OR kidney diseases)
- AND
- (“protein reduced” OR “low protein” OR “protein restricted” OR diet, protein restricted OR “conservative treatment”)
- AND
- (body composition OR muscle OR malnutrition OR nutrition\* OR nutrition assessment OR potassium/metabolism OR whole-body counting OR body water/metabolism OR anthropometry OR adaptation, physiological OR densitometry, X-ray OR skinfold thickness OR electric impedance OR “bioelectrical impedance”).

The search was limited to studies of humans aged  $\geq 19$  years, published in English.

### Eligibility Criteria

We included studies reporting on original data on the measurement of body composition during treatment with LPD. Accepted LPD treatments include protein levels from 0.3 g/kg/day (supplemented with essential amino acids or keto-analogues) to 0.75 g/kg/day. Renal function was defined as a mean GFR of  $\leq 20$  mL/min as measured by iothalamate clearance or Cr EDTA, or calculated with the formula of Modification of Diet in Renal Disease (MDRD) or of Cockcroft and Gault, or creatinine clearance (CrCl)  $\leq 25$  mL/min, or a mean serum creatinine  $\geq 500$   $\mu\text{mol/L}$ . Studies presenting data on TBK, DEXA, BIA, or anthropometry were included. Studies focusing on body composition in patients with a certain renal diagnosis were excluded.

### Data Extraction and Synthesis

There were no protocols or reviews by the Cochrane renal group, PloS, or INAHTA.org specifically concerning body composition and treatment with LPDs.

The search in PubMed, using the above-described search terms, resulted in 146 items. Every item’s abstract and Mesh-terms were

reviewed for type of predialysis diet intervention and type of assessment method for body composition or nutritional status. If any uncertainty remained as to whether the study should be included or not, the article was retrieved and evaluated. One hundred thirty-two items were subsequently excluded. Reasons for exclusion were:

- Body composition or nutritional status was not assessed in the study ( $n = 14$ ).
- Body composition or nutritional status was assessed, but not presented in numbers, or with a method not eligible for this review ( $n = 20$ ).
- The mean renal function of study patients exceeded eligibility criteria for this review ( $n = 17$ ).
- Recommended protein intake was  $>0.75$  g/kg/day ( $n = 3$ ).
- Noneligible patient groups were used, e.g., dialysis patients, patients with acute renal failure, patients with LPD + resistance training, or patients with LPD + intermittent dialysis treatment ( $n = 47$ ).
- The focus of the study not relevant, e.g., nitrogen requirement, metabolism of essential amino acid, or vitamin requirements in predialysis patients ( $n = 17$ ).
- The article was a review, or a presentation of a planned study or earlier publicized study ( $n = 13$ ).
- The article was not found ( $n = 1$ ).

The studies included may have used additional methods for measuring body composition or nutritional status. The studies may also have presented measurements of body composition in patients with chronic renal failure in other stages than those defined in this review. The results of those methods and measurements are not included in this presentation.

### Grading Methodical Quality of Studies

The studies’ designs were categorized according to the three levels of evidence of Levey et al.<sup>6</sup> and according to the ranking system of Lukaski<sup>7</sup> for the precision (interobserver or intra-observer differences) and accuracy of methods assessing skeletal muscle mass in humans.

### Results

The results of the data extraction of the 14 eligible studies are summarized in Table 1, and

include a number of references.<sup>2,3,12,14–24</sup> The studies of Attman et al.<sup>3</sup> and Attman<sup>15</sup> were analyzed together, after discussion with the authors. Gradings of the studies' designs and body-composition methods are presented in Table 2.

The total number of subjects with LPDs included in this review was 666. In seven studies, the subjects were prescribed a supplemented, very low protein diet (SVLPD).<sup>3,16,17,19,22–24</sup> In four studies, the subjects were prescribed either SVLPDs or conventional LPDs (0.6 g protein/kg).<sup>2,14,18,20</sup> In two studies, subjects were prescribed a conventional LPD only.<sup>12,21</sup> The average GFR was 14 mL/min, and ranged from 6 to 20 mL/min. The average creatinine clearance was 12 mL/min, and the mean serum creatinine was 680  $\mu$ mol/L. The mean age of subjects was 47 years. The study of Cupisti et al.,<sup>19</sup> with an age range of 18 to 76 years, is not included in this estimate because of a lack of information on patient age. The age range was not reported in all studies, but in the eight studies where it was reported, it ranged from 18 to 76 years, with a predominance of patients at  $\leq 70$  years (Table 1). All studies except two<sup>21,24</sup> excluded subjects with diabetes mellitus (DM).

All studies except four measured change in body composition over time. These four studies compared patients treated with LPD with either healthy age- and gender-matched controls or with age-, gender-, and GFR-matched controls on a standard diet at a given time before or at the start of dialysis treatment.<sup>12,14,18,24</sup> The measurements of change in body composition were mainly performed quarterly or semiannually in the remaining studies. The mean follow-up time in all but one of the prospective studies was  $\geq 12$  months.<sup>20</sup>

In general, there were no major changes of body composition over time in subjects treated with LPD, though the largest study showed statistically significant reduced values for several anthropometric measurements.<sup>2</sup> All studies except two drew the conclusion that treatment with LPDs is safe.<sup>12,22</sup> However, four studies<sup>2,16,17,22</sup> found an initial reduction of body weight (BW) or FFM in patients starting LPD, with stabilization after 3 to 4 months or recovery to initial values in some but not all cases.

There were no significant differences in body composition between groups with or without LPD treatment, though slightly reduced values could be seen in the LPD groups. This was espe-

cially the case in the study by Woodrow et al., where many LPD patients were below the lower centiles for TSF and MAC compared with controls.<sup>12</sup>

## Discussion

The studies included in this review generally concluded that treatment with LPDs does not affect body composition negatively. The validity of this conclusion depends on the representative accuracy of the patient group studied, as well as on methodological considerations in body composition measurements, diet prescription, and general management.

### Representative Accuracy of the Studies

The disease features and male:female ratio are similar in the studies, and acceptably reflect the predialysis population with regular nephrology follow-up, with the exception of DM, which was an exclusion criterion in a majority of studies. There are additional diagnoses and treatment groups excluded in one or several of the studies (e.g., nephrotic syndrome, malignancy, or steroid therapy treatment), but not to the same extent as with DM. The intrastudy patient features are similar, but differ in comparison from the predialysis population in general with respect to the lower mean age. The patients included in all studies but one<sup>2</sup> were selected, and may in these aspects differ from the overall predialysis population. There were also differences between studies in diet intervention, i.e., SVLPD and conventional LPD.

### Methodological Considerations: Body-Composition Measurements

The necessary considerations when evaluating body composition with TBK, DEXA, BIA, and anthropometry in renal disease were discussed earlier. However, a few studies evaluated their results from a methodological point of view, notably with specific aspects of body composition in renal disease.<sup>3,24</sup> The methodological considerations apply in particular to studies measuring body composition with BIA. The BIA analysis provides cheap and quickly obtainable measures of body composition even with unskilled operators, but shows poor validity in patients with CRF. With the BIA technique, results should be evaluated

**Table 1.** Data Extraction

Authors, Year, Reference Number	Design	Study Group	Prescribed Diet and Intervention	BCA	Results	Comments
Attman et al., 1980: <sup>3</sup> Body composition during long-term treatment of uremia with amino acid supplemented low-protein diet. Attman, 1986: <sup>15</sup> Long-term treatment with low-protein diet in uremia.	Prospective, nonrandomized clinical trial. Outcome measure: mean change in body composition over time within group treated with LPD as well as comparison of LPD group with reference population of healthy subjects.	Results based on n = 53. Detailed description of n = 31, 22 ♂ and 9 ♀, with mean age of 43.5 y, range of 18–66 y. GFR <10 mL/min, uremic symptoms, and S-creatinine >600 μmol/L. Exclusion: diabetics.	SVLPD, 20 g protein/day, 35–45 kcal/kg, 1-year diet treatment. Body composition measurement at 0, 3, 6, 9, and 12 mo.	TBK TBW BW	TBK slightly ↓ and TBW normal or ↑ in LPD group at baseline compared with healthy subjects. No change in mean body weight during treatment. Patients are able to maintain their body cell mass after ≥12 mo with SVLPD (no significant change in TBK or TBW). In patients with significant ↓ in TBK there was an association with nonadherence to diet or complicating disease, e.g., acidosis, septicemia, and surgical treatment.	Diet introduced at nephrologic ward, thereafter follow-up every 1–4 weeks by nephrologist and dietitian. Adherence to diet evaluated in subgroup (n = 17) by 4-day records of food intake at 3-mo intervals. In these, adherence was good (mean intake, 0.3 g/kg/day). Unclear for rest of study group. Calculated differences in means during follow-up were adjusted for sex and age, etc. Unclear method for estimation of GFR. Unclear if subjects with proteinuria had extra supplementation.
Chauveau et al., 1999: <sup>16</sup> Outcome of nutritional status and body composition of uremic patients on a very low-protein diet.	Prospective, nonrandomized clinical trial. Outcome measure: mean change in body composition over time within group treated with LPD as well as comparison of LPD group with 10 control subjects	n = 10, 6 ♂ and 4 ♀. Age: 57.1 ± 9.3 y; range, 39–70 y. GFR: <sup>51</sup> Cr-EDTA 13.2 ± 4.8 mL/min. No diabetics included. Controls: n = 10, 6 ♂ and 4 ♀. Age: 54.6 ± 6.9 y. Recruitment base unclear, but controls were chosen to match	SVLPD, 0.3 g/kg/day, vegetable origin. Proteinuria >3 g/day → supplementation of 1 g HBV protein for each gram lost, 35 kcal/kg/day, 1-year diet treatment. Body composition measurement at 0, 3, 6, and 12 mo.	DEXA (whole-body scan and regional analysis). Anthropometry (TSF, AMC, BW).	Tendency to lower BW, LBM, and BF in LPD group (NS) compared with controls at baseline. First 3 mo on diet: ↓ LBM (P < .01), thereafter gradual increase, without reaching initial values at 1 y = 2.3% loss of LBM. Mean limb-trunk lean	Dietary assessment: quarterly dietary records. DPI estimated from UUN excretion monthly. Adherence to diet: reduced protein intake both with diet diary (0.29 ± 0.05 g/kg/day) and UUN excretion. Energy

	similar in BMI, age, and gender.	with respect to BMI, age, and sex.	Monthly visits to dietician and physician.		tissue ratio ↓ from $0.87 \pm 0.12$ at baseline to $0.83 \pm 0.11$ at end of follow-up ( $P < .05$ ). Total BF mass and % body fat ↑ significantly. BW ↓ first 3 mo on diet, thereafter increased and reached initial values after 12 mo. Anthropometry not significantly modified.	intake $29.8 \pm 8.8$ kcal/kg/day at 1 y. No change in hydration status during follow-up. Included subjects' spontaneous dietary protein. Energy intake was low at inclusion. Physical activity remained unchanged in all patients. All patients clinically stable during 1-year survey.
Chauveau et al., 2003: <sup>17</sup> Body composition in patients on a very low-protein diet: a two-year survey with DEXA.	Prospective, nonrandomized clinical trial. Outcome measure: change in nutritional status during 2-y treatment with SVLPD.	n = 13, 8 ♂ and 5 ♀. Age: $55 \pm 12$ y; range, 39-70 y. GFR: $^{51}\text{Cr-EDTA}$ $15 \pm 4.7$ mL/min. Exclusion: patients with severe comorbid conditions, incapable of adapting to diet or close monitoring. No diabetics included.	SVLPD 0.3 g protein/kg/day, vegetable origin. Proteinuria >3 g/24h: 1 g supplementation with HBV protein for each lost g. Energy: 35 kcal/kg/day. Body composition measurement at 0, 3, 6, 12, 18, and 24 mo Monthly visits to physician and dietitian.	DEXA (whole-body scan and regional analysis) BW	LBM: ↓ first 3 mo ( $P < .05$ ), thereafter progressive ↑ resulting in a significant increase of 2 kg ( $P < .05$ ) after 24 mo, in total no significant change in LBM per overall follow-up ( $P = .2$ ). No significant change in total BF or %BF between baseline and 24 mo after starting diet. No significant change of BW from baseline to 12 or 24 months after starting diet.	Dietary assessment: 1st y: 4-day food record quarterly. 1st and 2nd y: UUN excretion. Adherence to diet: DPI according to food diary 1st y: $0.39 \pm 0.15$ g/kg/day. Similar intake estimated from UUN excretion 2nd y. Energy intake ≈ 30 kcal/kg/day according to food diary during 1st y.

(continued)

**Table 1.** Data Extraction (Continued)

Authors, Year, Reference Number	Design	Study Group	Prescribed Diet and Intervention	BCA	Results	Comments
Cupisti et al., 2004: <sup>14</sup> Nutritional status and dietary manipulation in predialysis chronic renal failure patients.	Cross-sectional study of body composition in patients with LPD diet for $\geq 6$ mo compared with healthy subjects comparable for age and gender.	n = 70, 43 ♂ and 27 ♀. Age: ♂ = $51.7 \pm 11.5$ y, and ♀ = $49.6 \pm 13$ y, range unclear. GFR: $< 15$ mL/min (calculated as average of creatinine clearance and urea clearance). Exclusion: age $> 75$ y, nephrotic syndrome, recent acute illness, chronic heart failure, DM, liver disease, malignancy, steroid or immunosuppressive therapy. Diet therapy for $\geq 6$ months, mean $45 \pm 38$ mo. Controls: n = 52, gender distribution unclear but comparable to LPD group according to authors. Age: ♂ = $48.4 \pm 10.8$ , and ♀ = $49.4 \pm 9.7$ . Recruitment: healthy department staff.	46 subjects LPD (0.6 g/kg/day). 24 subjects: SVLPD 0.3 g/kg/day, vegetable origin. Energy intake, 30–35 kcal/kg/day. Patient follow-up every 3–6 mo according to residual renal function and comorbid condition.	BIA Anthropometry (TSF, MAMC, and BW)	In both male and female subjects, BIA and anthropometric parameters were similar in CRF patients and controls, except for a lower phase angle in 3 CRF males. Anthropometric values were within normal reference ranges for age and gender. Patients with advanced CRF had no evidence of severe malnutrition.	Dietary assessment: UUN excretion. Adherence to diet: protein intake according to UUN excretion was $0.56 \pm 0.09$ g/kg/day in LPD group, and $0.36 \pm 0.06$ g/kg/day in SVLPD group. No values concerning energy intake.

<p>Cupisti et al., 2004:<sup>18</sup> Skeletal muscle and nutrition assessment in chronic renal failure patients on a protein-restricted diet.</p>	<p>Cross-sectional study of body composition in patients with LPD diet for <math>\geq 6</math> mo compared with healthy subjects comparable for age and gender.</p>	<p>n = 28, 16 ♂ and 12 ♀. Age: <math>45 \pm 11</math> y, range unclear. GFR: <math>&lt;15</math> mL/min. Exclusion: <math>&gt;60</math> y, nephrotic syndrome, chronic heart failure, DM, liver or primary muscle disease or malignancy, treatment with steroids or benzodiazepine. Controls: n = 28, 16 ♂ and 12 ♀.</p>	<p>14 patients on 0.6 g/kg/day, 30–35 kcal/kg. 14 patients on SVLPD 0.3 g/kg/day, vegetable origin. 30–35 kcal/kg.</p>	<p>BIA Anthropometry (TSF, MAC, MAMC, BW)</p>	<p>Anthropometric and BIA variables were similar in all three groups. Data suggest preserved muscle mass in patients treated with LPD after 6 mo.</p>	<p>Average of creatinine clearance and urea clearance was used to estimate GFR. DPI estimated from UUN excretion. Adherence to diet: <math>0.56 \pm 0.08</math> g/kg in LPD 0.6 g/kg group, and <math>0.37 \pm 0.09</math> g/kg in SVLPD group. No values concerning energy intake.</p>
<p>Cupisti et al., 1990:<sup>19</sup> Nutritional state of severe chronic renal failure patients on a low-protein supplemented diet.</p>	<p>Prospective, nonrandomized, clinical trial. Outcome measure: effect of SVLPD on nutritional status in patients with severe renal insufficiency.</p>	<p>n = 51, 32 ♂ and 19 ♀. Age: range, 18–76 y; no data on mean age. GFR: creatinine clearance <math>7.8 \pm 3.5</math> mL/min. Exclusion: nephrotic grade proteinuria (<math>&gt;3.5</math> g/24h), DM, systemic disease and noncompliance with diet. Controls: anthropometric measurements are compared with 77 subjects, recruitment unclear.</p>	<p>SVLPD 0.3 g/kg/day, vegetable origin. Energy intake 35 kcal/kg/day. Follow-up of diet: <math>13.5 \pm 6.8</math> mo.</p>	<p>Anthropometry (TSF, MAMC, BW)</p>	<p>No significant changes in MAMC. A tendency to <math>\uparrow</math> TSF in males. <math>\uparrow</math> BW (<math>P &lt; .05</math>). No apparent differences between diet group and controls, although statistical test not presented.</p>	<p>Adherence to diet: daily urinary urea output 2–3 days. Goal: <math>&lt;60</math> mg/kg and s-urea in range of normality. N intake and output measured in 14 cases and assessed as satisfying. No information on energy intake. No information on frequency of outpatient visits during study period. No information about controls. Included patients had free or 0.6 g/kg diet before study; no details presented.</p>

(continued)

**Table 1.** Data Extraction (Continued)

Authors, Year, Reference Number	Design	Study Group	Prescribed Diet and Intervention	BCA	Results	Comments
Feiten et al., 2005: <sup>20</sup> Short-term effects of a very-low-protein diet supplemented with ketoacids in nondialyzed chronic kidney disease patients.	Prospective, controlled, clinical trial. Randomized assignment to either LPD or SVLPD. Outcome measure: effect of 4-mo treatment with LPD and SVLPD on nutritional status.	n = 24, 15 ♂ and 9 ♀. Age: LPD = 43.9 ± 16.3 y. SVLPD = 49.7 ± 11.3 y, range unclear. GFR: creatinine clearance ≤25 mL/min/1.73m <sup>2</sup> ; in LPD group: 18.8 ± 2.9 mL/min; and in SVLPD group: 16.7 ± 5.3 mL/min. Exclusion: catabolic illnesses, DM, autoimmune disease, malignant hypertension.	All subjects: 1 month of 0.6 g/kg/day, 50% HBV. 12 subjects: 0.6 g/kg/day, 12 subjects: SVLPD 0.3 g protein/kg/day, vegetable origin. Energy: 30–35 kcal/kg/day. Follow-up: 4 mo. Monthly interval: clinical and biochemical evaluation.	BIA (single frequency) Anthropometry (TSF, MAMC, BW) Baseline and 2-month interval: complete nutritional assessment.	Percent body fat remained constant in both groups throughout study. Mean standard % of TSF and MAMC did not change and was within normal range throughout study. TSF ↑ from baseline to 4 mo in LPD group ( <i>P</i> < .05). LBM did not change during follow-up. No results on BW presented, but no change in BMI in either group during follow-up.	Dietary assessment: 3-day food diary and 24-h UUN excretion. Adherence to diet: DPI according to diary followed prescription, but was approximately 28% higher when measured as UUN. Energy intake lower than prescribed: 23–24 kcal/kg). Patients in clinically stable condition during survey period.
Rayner et al., 1993: <sup>21</sup> Changes in nutritional status of patients with chronic renal failure in a low-protein diet.	Prospective, nonrandomized, clinical trial. Outcome measure: change in nutritional status during treatment with LPD from January 1985 until dialysis or until September 1990.	n = 142, 85 ♂ and 57 ♀. Age: 50.3 ± 18.3 y, range unclear. GFR: serum creatinine 555 ± 152 μmol/L. Exclusion: malignant disease.	0.6 g/kg ideal body weight/day. 35 kcal/kg ideal body weight/day. Calorie supplementation 600 kcal to subjects with kcal intake <35 kcal/kg or decline in anthropometric values. Body composition measurement monthly.	Anthropometry (TSF, AMC, BW)	No clear trend in mean rate of change in AMC or TSF. BW ↓ on diet by 0.64%/year ( <i>P</i> < .001).	Adherence to diet not discussed. Mean diet therapy duration = 16 mo (range, 5–8.6 y).

<p>Lucas et al., 1985:<sup>22</sup> The risks and benefits of a low protein-essential amino acid-keto diet.</p>	<p>Prospective, nonrandomized, clinical trial. Outcome measure: change in nutritional status during <math>\geq 6</math> mo with SVLPD.</p>	<p>n = 12, 6 ♀ and 6 ♂. Age: 45.6 y; range, 28–61 y. GFR: P-creatinine 899 <math>\mu\text{mol/L}</math>; range, 594–1,432 <math>\mu\text{mol/L}</math>. No specific exclusion criteria presented, no diabetics participated in study.</p>	<p>SVLPD 0.25 g/kg/d, principally of vegetable origin. 50 kcal/kg/d. Diet therapy duration in mean 12.25 mo; range, 6–24 mo. Monthly visits to physician and dietitian. Monthly evaluation of body composition.</p>	<p>Anthropometry (TSF, MAC, MAMC, total muscle mass kg, BW)</p>	<p>Significant TSF and MAMC <math>\downarrow</math> during initial 3 and 6 mo, although several patients did not show any changes. BW <math>\downarrow</math> during initial 3 mo (<math>P &lt; .01</math>). Thereafter stable weight. <math>\downarrow</math> muscle mass in 2 patients presented in detail due to association with fall in plasma creatinine. Other than this, no more information on change in muscle mass. LPD not recommended in CRF.</p>	<p>Dietary assessment: discussion with dietitian, and reductions in blood and urinary urea excretion, were used as indicators of dietary compliance. Energy intake: <math>&gt;36</math> kcal/kg/d in 9, 30–35 kcal/kg/d in 2, <math>&lt;30</math> kcal/kg/d in 1 patient. 5 patients had followed a protein-restricted diet before the study. 4 patients were overweight and given dietary advice based on desired weight.</p>
<p>Kopple et al., 1997:<sup>2</sup> Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study.</p>	<p>Prospective, randomized, controlled clinical trial. Outcome measure: effect of treatment with LPD and SVLPD on nutritional status during mean follow-up of 2.2 y.</p>	<p>Baseline screening: n = 2507. Inclusion criteria: 18–70 y with CRF. Exclusion: IDDM or previously transplanted. Relative BW <math>&lt;80\%</math> or <math>&gt;160\%</math> of standard BW, s-albumin <math>\leq 30</math> g/L, urine protein loss <math>\geq 10</math> g/day. Baseline period (3 mo): n = 1785. GFR: <math>^{125}\text{I}</math>-iothalamate. If GFR <math>\geq 25</math> mL/min <math>\rightarrow &gt;1</math> g</p>	<p>LPD: 0.58 g/kg/day. SVLPD: 0.28 g/kg/day. Energy: <math>\geq 30</math> kcal/kg standard body weight/day. Overweight patients, 25–30 kcal/kg/day. For each gram <math>U_{\text{protein}}</math> loss, 1 g HBV dietary protein was added up to 8 g/day. Follow-up: mean.</p>	<p>Anthropometry (skinfolds: triceps, biceps, and subscapular; MAC, AMA, %BF, BW)</p>	<p>During follow-up: anthropometric indices generally well within normal limits in both groups. Relative BW averaged <math>&gt;100\%</math> in both groups. Changes from baseline to follow-up: LPD group: significant <math>\downarrow</math> in mean BW, %BF, and AMA. SVLPD group: significant <math>\downarrow</math> in mean BW and</p>	<p>Dietary assessment: monthly UUN excretion. Dietary diaries with interviews every 3rd mo. Low adherence to diet prescription: total protein intake in LPD group, 0.72 g/kg/day; in SVLPD group, 0.66 g/kg/day from UUN. Energy intake <math>\approx 23</math> kcal/kg/day during</p>

(continued)

**Table 1.** Data Extraction (Continued)

Authors, Year, Reference Number	Design	Study Group	Prescribed Diet and Intervention	BCA	Results	Comments
		protein/kg/day. If GFR $\leq 24$ mL/min $\rightarrow \geq 0.6$ g/kg/day. Reassessment after 3 mo: GFR, blood pressure, and protein intake. 255 subjects with GFR 13–24 mL/min entered study B, randomized to either LPD or SVLPD. Results include 219 patients with $\geq 1$ y of follow-up. No. of $\delta$ and $\eta$ is unclear. Age baseline: LPD $51.1 \pm 12.8$ y, SVLPD $50.5 \pm 12.9$ y. Mean GFR in both groups $\approx 18.5 \pm 3.4$ mL/min.	2.2 y (range, 0–44 mo). Body composition assessment at 2nd mo of baseline period and every 6 mo thereafter. Average rates of change in nutritional status were estimated by regressing measurements beginning at 4 mo of follow-up. BW monthly.		AMA. Declines in BW occurred abruptly in both groups after randomization and stabilized after ca 4 mo. %BF $\downarrow$ significantly more in LPD group than in SVLPD group during first 6 mo with diet. Changes in nutritional-status variables from 4 mo to end of follow-up were not associated with mean level of protein intake during follow-up. LPD and SVLPD are safe despite small but significant declines in indices of nutritional status.	follow-up in both groups. Decline in nutritional indices can be explained by low energy intake, due in part to desire of 50% of participants to lose weight.
Tom et al., 1995: <sup>23</sup> Long-term adaptive responses to dietary protein restriction in chronic renal failure.	Prospective, nonrandomized clinical trial. Outcome measure: change in nutritional status during 1-y treatment with SVLPD.	n = 6, 4 $\eta$ and 2 $\delta$ . Age: $49 \pm 3$ y; range, 39–60 y. GFR at baseline measured with iothalamate clearance: $18 \pm 2$ mL/min. No diabetic, obese, or malnourished patients included.	SVLPD 0.28 g/kg/day. 35 kcal/kg standard body weight. Diet therapy duration: at least 1 year (mean, $16 \pm 2$ mo). Body composition measurement at baseline and quarterly.	Anthropometry (SSSF, AMC, BW)	No significant overall change in body weight or anthropometrics during study. SVLPD can maintain nutritional status during long-term therapy.	Metabolic acidosis corrected before starting diet. Dietary assessment from 3-day diaries and 24-h UUN excretion monitored quarterly. Protein intake $125\% \pm 7\%$ of prescribed diet.

<p>Vendrey et al., 2003:<sup>24</sup> Nutrition in hemodialysis patients previously on a supplemented very low-protein diet.</p>	<p>Prospective case-control study. Outcome measure: nutritional status in patients starting dialysis with either predialysis SVLPD or age- and gender-matched patients with standard prescription.</p>	<p>n = 15, 9 ♂ and 6 ♀. Age: 57.6 ± 12.6 y, range unclear. GFR: <sup>51</sup>Cr-EDTA 6.3 ± 1.6 mL/min; Cockcroft and Gault formula, 8.7 ± 2.1 mL/min. Controls: n = 15, 10♂ and 5 ♀. Age: 59.5 ± 12.4 GFR: Cockcroft and Gault formula. 8.2 ± 2.4 mL/min. All diagnoses accepted.</p>	<p>Diet group: SVLPD 0.3 g protein/kg/day, vegetable origin. Proteinuria &gt;2 g/24h: supplemented with 1.25 g HBV protein for each lost g. 35 kcal/kg/day. Monthly visits to physician and dietitian. Control group: ≤1 g protein/kg/day. Energy: 30–35 kcal/kg/day. Follow-up ≥6 mo before dialysis treatment. Dietetic counseling when needed.</p>	<p>DEXA (whole-body scan) BW</p>	<p>No difference in LBM, BF, or %BF between groups starting dialysis. No difference in BW between two groups starting dialysis. Treatment with SVLPD before hemodialysis initiation is nutritionally safe.</p>	<p>Energy intake 69% ± 2% of prescribed intake. DPI estimated quarterly from 3-day food records. DPI in SVLPD group: 0.33 ± 0.09 g/kg/day, and in control group: 0.89 ± 0.21 g/kg/day (<i>P</i> &lt; .001). Energy intake in SVLPD group: 31.5 ± 6.8 vs. 28.5 ± 6.5 kcal/kg/day in controls, NS. No information available on duration of SVLPD, but subjects were part of a larger study<sup>25</sup> as well, with inclusion criteria &gt;3 mo of diet treatment and a mean duration of 29.6 ± 25.1 mo on SVLPD. 3 subjects with DM in control group, none in diet group.</p>
<p>Woodrow et al., 1996:<sup>12</sup> Whole body and regional body composition in patients with chronic renal failure.</p>	<p>Cross-sectional study of body composition in LPD patients compared with healthy subjects.</p>	<p>n = 23, 12 ♂ and 11 ♀. Age: ♂ = 57.4 ± 12.4, ♀ = 52.2 ± 17.0, range unclear. GFR: advanced renal failure: s-urea &gt;30 mmol/L or s-creatinine &gt;500 μmol/L. Mean creatinine clearance was 7.3 ± 3.6 mL/min. Free of significant acute illness within previous</p>	<p>0.6–0.8 g/ideal body weight/day. LPD started in later stages of predialysis period. 70% HBV.</p>	<p>DEXA, regional analysis of arm, leg, and trunk regions BIA Anthropometry (TSF: triceps, biceps, subscapular, and suprailiac, MAC, %BF, BW)</p>	<p>DEXA: NS differences in total lean tissue, limb lean tissue, or arm lean tissue between LPD group and controls, except significantly ↓ arm lean tissue in females compared to controls. TBF significantly lower in ♂ compared with controls. Limb/trunk</p>	<p>Dietary assessment and evaluation of adherence to diet not investigated in predialysis group. Unclear when or if LPD diet was introduced and what different levels of protein and energy intake the LPD group and</p>

(continued)

**Table 1.** Data Extraction (Continued)

Authors, Year, Reference Number	Design	Study Group	Prescribed Diet and Intervention	BCA	Results	Comments
		3 mo. Only Caucasians included. Diabetics excluded. Controls: n = 33, 17 ♂ and 16 ♀. Age: ♂ = 59.1 ± 8.8, ♀ = 57.2 ± 8.9. Recruitment unclear.			lean tissue ratios reduced ( $P < .05$ ). BIA: NS differences in mean values of FFM. Significant ↓ of TBF in ♂ compared to controls. Anthropometry: 26% of patients below lower centiles for TSF (controls, 3%) and 43% of patients below lower centiles for MAC (controls, 6%). %BF significantly lower in ♂ compared with controls. NS difference in BW or BMI between groups.	controls actually had. Small group sizes and large SD in measurements of total body fat by DEXA. Results influenced by patient-selection criteria: the study patients are expected to represent optimal nutritional state of patients treated at the unit.

AMA, arm muscle area; AMC, arm muscle circumference; BCA, body composition assessment method; BF, body fat; BIA, bioelectrical impedance analysis; BMI, body mass index; BW, body weight; <sup>51</sup>Cr-EDTA, chromium-51 labelled ethylene diamine tetraacetic acid; CRF, chronic renal failure; DEXA, dual-energy X-ray absorptiometry; DM, diabetes mellitus; DPI, daily protein intake; FFM, fat-free mass; GFR, glomerular filtration rate; HBV, high biological value; IDDM, insulin-dependent diabetes mellitus; LBM, lean body mass; LPD, low-protein diet; MAC, mid-arm circumference; MAMC, middle arm muscle circumference; N, nitrogen; NS, nonsignificant; SD, standard deviation; SSSF, subscapular skinfold; SVLPD, supplemented very low protein diet; TBF, total body fat; TBK, total body potassium; TBW, total body water; TSF, triceps skinfold; UUN, urine urea nitrogen; y, year.

**Table 2.** Grading of Methods for Assessing Skeletal Muscle Mass and Evidence

Authors, Years	Precision of BCA Method*	Accuracy of BCA Method*	Level of Evidence According to Rating of Study Methodology†	Comments
Attman et al., 1980, 1986	TBK = 4	TBK = 2	Strong evidence	Strength: large group, target population, estimates change in body composition, BCA method with high precision. Weakness: nonrandomized, low accuracy of BCA method.
Chauveau et al., 1999	DEXA = 5 Anthropometry = 3	DEXA = 4 Anthropometry = ?	Strong evidence	Strength: target population, estimates change in body composition, BCA method with high precision and accuracy. Weakness: small study group, anthropometry measurements have low precision.
Chauveau et al., 2003	DEXA = 5	DEXA = 4	Strong evidence	Strength: target population, estimates change in body composition, BCA method with high precision and accuracy. Weakness: small study group.
Cupisti et al., 2004‡	BIA = 4 Anthropometry = 3	BIA = ? Anthropometry = ?	Moderate evidence	Strength: large group, target population, BIA good precision. Weakness: does not look at change of body composition, anthropometry measurements have low precision.
Cupisti et al., 2004§	BIA = 4 Anthropometry = 3	BIA = ? Anthropometry = ?	Moderate evidence	Strength: target population, BIA good precision. Weakness: small study group, does not look at change of body composition, anthropometry measurements have low precision.
Cupisti et al., 1990	Anthropometry = 3	Anthropometry = ?	Weak evidence	Strength: target population, large group, estimates change in body composition. Weakness: follow-up during diet not described, cases had been treated with LPD before starting study, control group not clearly presented, anthropometry measurements have low precision.
Feiten et al., 2005	BIA = 4 Anthropometry = 3	BIA = ? Anthropometry = ?	Moderate evidence	Strength: target population, estimates change in body composition. Weakness: small study group, short follow-up, anthropometry measurements have low precision.
Rayner et al., 1993	Anthropometry = 3	Anthropometry = ?	Moderate evidence	Strength: large group, target population, estimates change in body composition. Weakness: adherence to diet not discussed, anthropometry measurements have low precision.
Kopple et al., 1997	Anthropometry = 3	Anthropometry = ?	Strong evidence	Strength: RCT, multicenter, large group, target population, estimates change in body composition. Weakness: low adherence to diet, anthropometry measurements have low precision.

(continued)

**Table 2.** Grading of Methods for Assessing Skeletal Muscle Mass and Evidence (Continued)

Authors, Years	Precision of BCA Method*	Accuracy of BCA Method*	Level of Evidence According to Rating of Study Methodology†	Comments
Lucas et al., 1986	Anthropometry = 3	Anthropometry = ?	Weak evidence	Strength: target group, estimates change in body composition. Weakness: small study group, one-third of patients were given hypocaloric advice, nearly half of cases had been treated with LPD before study, anthropometry measurements have low precision.
Tom et al., 1995	Anthropometry = 3	Anthropometry = ?	Moderate evidence	Strength: target population, estimates change in body composition. Weakness: small study group, anthropometry measurements have low precision.
Vendrely et al., 2003	DEXA = 5	DEXA = 4	Moderate evidence	Strength: target population, BCA method with high precision and accuracy. Weakness: small study group, does not look at change of body composition.
Woodrow et al., 1996	DEXA = 5 BIA = 4 Anthropometry = 3	DEXA = 4 BIA = ? Anthropometry = ?	Weak evidence	Strength: three different BCA methods evaluated. Weakness: small study group, does not look at change of body composition, diet prescription and management not well-described, and adherence to diet not assessed.

BCA, body composition assessment method; BIA, bioelectrical impedance analysis; RCT, randomized, controlled trial; TBK, total body potassium; DEXA, dual-energy X-ray absorptiometry.

\*From Heymsfield et al.<sup>7</sup> Ranking system for precision and accuracy of BCA: ascending scale: 1 = least, and 5 = greatest.

†From Levey et al.<sup>6</sup> Levels of evidence: Strong evidence = evidence includes results from well-designed, well-conducted studies in the target population that directly assess effects on net health outcome (in this case, effect on body composition). Moderate evidence = Evidence meets any of the following criteria: (1) is sufficient to determine effects on net health outcome (in this case, effect on body composition) in target population, but the strength of the evidence is limited by the number, quality, or consistency of individual studies; or (2) is from a population other than the target population, but is from well-designed, well-conducted studies; or (3) is from studies with some problems in design or analysis; or (4) is from well-designed, well-conducted studies on surrogate endpoints for efficacy or safety in the target population. Weak evidence = Evidence meets any of the following criteria: (1) is insufficient to determine the effects on net health outcome (in this case, effect on body composition) because it is from studies with some problems in design or analysis on surrogate endpoints for efficacy or safety in the target population; or (2) is only for surrogate measures in a population other than the target population; or (3) is from studies that are poorly designed or analyzed.

‡From Cupisti et al., 2004.<sup>14</sup>

§From Cupisti et al., 2004.<sup>18</sup>

Question marks denote insufficient accuracy according to Lukaski.<sup>7</sup>

with respect to the validity of the equation used for the calculation of body composition. Recently, Macdonald et al.<sup>26</sup> introduced an equation which specifically predicts appendicular lean mass (ALM) in predialysis patients with chronic renal disease stages 1 to 5 according to the KDOQI. The ALM is interesting in that it provides a clinically obtainable and a potentially valid method to predict muscle mass.<sup>26</sup>

Five studies used  $\geq 2$  techniques to evaluate body composition.<sup>12,14,16,18,20</sup> Neither Cupisti et al.<sup>14,18</sup> nor Feiten et al.<sup>20</sup> found any differences in the evaluation of body composition between LPD patients and healthy controls using both BIA and anthropometry. Chauveau et al. found significant changes in lean body mass (LBM) using DEXA, whereas the values for anthropometry remained unchanged.<sup>16</sup> In the study by Woodrow et al., three methods were used to investigate body composition: DEXA, BIA, and anthropometry. All three methods showed lower values of TBF or %BF in men with LPD compared with healthy controls. Bioelectrical impedance analysis showed no differences in FFM, whereas DEXA found significantly lower limb:trunk ratios in LPD patients. When protein depletion occurs, protein stores in the visceral organs tend to be relatively well-preserved, with a predominant loss of muscle mass. This was demonstrated by Woodrow et al. using DEXA, where measurements showed lean tissue depletion due to a loss of limb lean tissue (especially the arm), with preservation of trunk tissue.<sup>12</sup> Chauveau et al. similarly found a more pronounced reduction of regional lean-tissue composition in their study.<sup>16</sup> Measurement of limb lean tissue may therefore be a more sensitive way of detecting lean-tissue loss in CRF patients than measurement of whole-body FFM,<sup>12</sup> and DEXA appears to detect changes in LBM earlier than do BIA and anthropometry.

### Methodological Considerations: Diet Prescription and Management

The progression of renal failure is associated with a spontaneous decrease in daily protein intake, when CrCl is reduced to 25 mL/min.<sup>27</sup> This motivated the chosen value of GFR for inclusion in this review. Ikizler et al. found that the mean daily protein intake in patients with a CrCl of 10 to 24 mL/min was 0.7 g/kg/day,<sup>27</sup> i.e., slightly below the daily protein requirement of

0.75 g/kg/day.<sup>28</sup> These changes presumably reflect uremic anorexia. Critics of LPD question the safety of further restricting protein intake in this condition, and advocate the initiation of dialysis instead, a so-called "timely initiation of dialysis."<sup>29</sup> The patients studied by Chauveau et al. had no dietary protein restriction before the study, but their spontaneous dietary protein and caloric intake was low at time of inclusion.<sup>16</sup> In Lucas et al., nearly half of the included subjects had followed a LPD before inclusion, and several were anorexic.<sup>22</sup> Attman et al. found that nearly half of their patients exhibited a moderate decrease in TBK before treatment, presumably associated with the catabolic effects of untreated uremia and anorexia.<sup>3</sup> This highlights the importance of considering the bias of pre-LPD-induced change of body composition because of a spontaneous decrease in protein intake when evaluating the results from both longitudinal and cross-sectional studies in patients with CRF. Kopple et al. reduced this bias somewhat by excluding patients with <80% of standard body weight from their study.<sup>2</sup>

All studies except two<sup>12,21</sup> included an evaluation of protein and energy intake of their subjects. Most of the studies used 24-h urine urea nitrogen excretion as a validation of adherence to protein prescription, complemented by food diaries. The results showed that protein intake was reduced, if not always to the prescribed level.<sup>2,14,16-20,23</sup> Only two studies described a level of protein with high biological value in the prescription, and none evaluated the adherence to this prescription.<sup>17,20</sup>

Nitrogen balance studies in patients with CRF not undergoing dialysis and eating 0.6 g protein/kg/day indicate that energy intake should be ~30 to 35 kcal/kg/day for optimal utilization of dietary protein.<sup>30</sup> In addition, there is an increased energy expenditure per body cell mass in progressive renal failure.<sup>31</sup> The average energy intake was very low (<25 kcal/kg/day) in four studies,<sup>2,20,23,24</sup> and low (<30 kcal/kg/day) in three studies.<sup>16,17,24</sup> If the low-energy intakes in the MDRD study<sup>2</sup> are correct, this could contribute to the decline in anthropometric values. However, the evaluation of energy intake from food diaries is unreliable, and is often affected by underestimations of intake.<sup>32</sup>

The differences in patient baseline status and spontaneous nutrient intake, as well as differences

in adherence, tend to obscure the evaluation of the impact of LPD on body composition.

### Considerations Regarding Grading of Level of Evidence

The studies included here investigated body composition in a group of patients with LPD compared with healthy controls, within-group changes in body composition over time, or changes in body composition in groups of patients with different levels of protein restriction. Only one study investigated body composition in patients treated with LPD in comparison to patients with equivalent kidney function but no LPD prescription.<sup>24</sup> That study used a body-composition method with high precision and accuracy, and its design was best fit to investigate whether treatment with LPD in renal disease stages 4 and 5 is detrimental to nutritional status compared with normal protein intake. Although the results from this study did not show any difference in LBM,

BF, %BF, or BW between the two groups starting dialysis, the evidence was graded as moderate because of its small study group and method of evaluating adherence to diet prescription (quarterly 3-day food records).

All patients included in the reviewed studies were either selected and motivated patients or patients with regular monitoring, and may in these aspects differ from the overall predialysis population. This is one of the main points of criticism stated by LPD opponents. The majority of studies included in this review would most likely be described as a per-protocol (PP) analysis. Conversely, the use of an intention-to-treat (ITT) analysis would by many be considered the valid method for answering the clinical question of whether the prescription of LPD affects body composition. However, it is not obvious which method should be preferred. The American Food and Drug Administration requires both types of analysis in studies regarding approval of a new drug or treatment. The study of Kopple et al. was clearly an

**Table 3.** Data to Consider When Evaluating Body Composition in Renal Disease

Patient Features	Disease Features
Age	Renal function
Gender	Nephropathy and comorbidity (e.g., diabetes mellitus)
Weight	Intercurrent illnesses
Nutritional status (e.g., wasting, obesity)	Metabolic acidosis
Physical activity	Proteinuria
	Steroid or immunosuppressive therapy
	Secondary hyperparathyroidism and vitamin D deficiency
	Edema
Intervention with LPDs	
Protein prescription (g/kg/day)	
Supplements with essential amino acids or keto-analogues	
Percentage of protein with high biological value	
Energy prescription (kcal or kJ/kg/day)	
Supplements with carbohydrates and fat	
Has LPD been followed before starting follow-up of body composition?	
Does the subject have a spontaneous reduced protein intake before starting LPD?	
Patient dietary knowledge	
Adherence to diet	
How are diet instructions given?	
How is follow-up implemented?	
How is protein intake evaluated?	
Compliance with amino-acid/keto-acid supplements?	
How is energy intake evaluated?	
Variables to consider regarding evaluation of body-composition measurement methods	
Type of method: What does it measure?	
How to interpret results in patients with renal disease?	
Has the patient consciously strived to attain weight reduction?	
Time of follow-up?	
Existence of any other comorbidity affecting body composition?	

LPD, low-protein diet.

ITT, and showed declines in several nutritional markers.<sup>2</sup> On the other hand, a majority of studies with a PP analysis showed preserved body composition.<sup>3,14,16–18,20,23,24</sup> Hence, our conclusion is that LPD prescriptions can be unfavorable in patients with complicating comorbidities, an inability to adhere to the diet, or inadequate follow-up. Nevertheless, a prescribed LPD for a compliant patient is nutritionally safe and of considerable value because it reduces uremic symptoms, postpones the need for dialysis, and slows renal progression rate. Based on the results from the MDRD study, it can be estimated that 25% to 45% of predialysis patients could comply with and benefit from a carefully supervised treatment with LPD.<sup>33</sup>

### Suggestions for Future Research

More studies are needed to investigate this topic. Table 3 offers an overview of variables to consider for the evaluation of body composition. If patients with DM are included in the evaluation, the consideration of type of diabetes (Type I or Type II), duration of DM, duration of DM-nephropathy, proteinuria, and control of blood-glucose levels should be included as well.

Neutron activation analysis is a direct method of assessing protein via total body nitrogen. This parameter provides data on metabolically active tissue that will identify malnutrition earlier than conventional methods.<sup>7</sup> Hence, it would be of great interest if a study were to be conducted using this method of assessing body composition, combined with the variables presented in Table 3. It would also be of value to apply the equation for BIA measurements developed by Macdonald et al. to evaluate changes in body composition in patients with LPDs.<sup>26</sup>

### Conclusion

There is no strong evidence that LPDs (0.6 g/kg/day or 0.3 g/kg/day + supplements) impair body composition in patients with a GFR  $\leq$ 20 mL/min, and that their use should be discouraged. However, LPDs should not be introduced in patients with a complicating disease, e.g., acidosis, septicemia, or surgical treatment, and they should not be continued in patients who are unable to adhere to their diet prescription. The LPD should be introduced with great caution in patients with an expected time to dialysis of  $\leq$ 4

months. Systematic and regular clinical monitoring of treatment with LPDs must be emphasized, including body-composition measurements and evaluations of protein intake and energy intake. These conclusions do not apply to patients with DM, because this diagnosis was excluded in a majority of the reviewed studies.

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### References

1. Campistol JM: Uremic myopathy. *Kidney Int* 62:1901–1913, 2002
2. Kopple JD, Levey AS, Greene T, et al: Effect of dietary protein restriction on nutritional status in the Modification of Diet in Renal Disease Study. *Kidney Int* 52:778–791, 1997
3. Attman PO, Ewald J, Isaksson B: Body composition during long-term treatment of uremia with amino acid supplemented low-protein diet. *Am J Clin Nutr* 33:801–810, 1980
4. Johnson DW: Dietary protein restriction as a treatment for slowing chronic kidney disease progression: the case against. *Nephrology* 11:58–62, 2006
5. Blumenkrantz MJ, Kopple JD, Gutman RA, et al: Methods for assessing nutritional status of patients with renal failure. *Am J Clin Nutr* 33:1567–1585, 1980
6. Levey AS, Coresh J, Balk E, et al: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 139:137–147, 2003
7. Lukaski HC: Assessing muscle mass. In: Heymsfield SB, Lohman TG, Wang Z, Going SB (eds): *Human Body Composition*. Leeds, UK, Human Kinetics, pp 203–218, 2005
8. Wang Z, St-Onge MP, Lecumberri B, et al: Body cell mass: model development and validation at the cellular level of body composition. *Am J Physiol Endocrinol Metab* 286:E123–E128, 2004
9. Bergström J, Alvestrand A, Furst P, et al: Muscle intracellular electrolytes in patients with chronic uremia. *Kidney Int* 16(Suppl): S153–S160, 1983
10. Patrick J: Assessment of body potassium stores. *Kidney Int* 11:476–490, 1977
11. Chumlea WC: Anthropometric and body composition assessment in dialysis patients. *Semin Dial* 17:466–470, 2004
12. Woodrow G, Oldroyd B, Turney JH, et al: Whole body and regional body composition in patients with chronic renal failure. *Nephrol Dial Transplant* 11:1613–1618, 1996
13. Foster KR, Lukaski HC: Whole-body impedance—what does it measure? *Am J Clin Nutr* 64(Suppl):388S–396S, 1996
14. Cupisti A, D'Alessandro C, Morelli E, et al: Nutritional status and dietary manipulation in predialysis chronic renal failure patients. *J Ren Nutr* 14:127–133, 2004
15. Attman PO: Long-term treatment with low protein diet in uremia. *Contrib Nephrol* 53:128–136, 1986

16. Chauveau P, Barthe N, Rigalleau V, et al: Outcome of nutritional status and body composition of uremic patients on a very low protein diet. *Am J Kidney Dis* 34:500-507, 1999
17. Chauveau P, Vendrely B, El Haggan W, et al: Body composition of patients on a very low-protein diet: a two-year survey with DEXA. *J Ren Nutr* 13:282-287, 2003
18. Cupisti A, Licitra R, Chisari C, et al: Skeletal muscle and nutritional assessment in chronic renal failure patients on a protein-restricted diet. *J Intern Med* 255:115-124, 2004
19. Cupisti A, Guidi A, Giovannetti S: Nutritional state of severe chronic renal failure patients on a low-protein supplemented diet. *Contrib Nephrol* 81:161-168, 1990
20. Feiten SF, Draibe SA, Watanabe R, et al: Short-term effects of a very-low-protein diet supplemented with ketoacids in nondialyzed chronic kidney disease patients. *Eur J Clin Nutr* 59:129-136, 2005
21. Rayner HC, Burton PR, Bennett S, et al: Changes in nutritional status of patients with chronic renal failure on a low protein diet. *Nephron* 64:154, 1993
22. Lucas PA, Meadows JH, Roberts DE, et al: The risks and benefits of a low protein-essential amino acid-keto acid diet. *Kidney Int* 29:995-1003, 1986
23. Tom K, Young VR, Chapman T, et al: Long-term adaptive responses to dietary protein restriction in chronic renal failure. *Am J Physiol* 268:E668-E677, 1995
24. Vendrely B, Chauveau P, Barthe N, et al: Nutrition in hemodialysis patients previously on a supplemented very low protein diet. *Kidney Int* 63:1491-1498, 2003
25. Aparicio M, Chauveau P, De Prectigout V, Bouchet JL, Lasseur C, Combe C: Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. *J Am Soc Nephrol* 11:708-716, 2000
26. Macdonald JH, Marcora SM, Jibani M, et al: Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transplant* 21:3481-3487, 2006
27. Ikizler TA, Greene JH, Wingard RL, et al: Spontaneous dietary protein intake during progression of chronic renal failure. *J Am Soc Nephrol* 6:1386-1391, 1995
28. Food and Agriculture Organization/World Health Organization/United Nations University: Energy and protein requirements. Geneva, World Health Organization 1985
29. Mehrotra R, Nolph KD: Treatment of advanced renal failure: low-protein diets or timely initiation of dialysis? *Kidney Int* 58:1381-1388, 2000
30. Mitch WE: Mechanisms causing loss of lean body mass in kidney disease. *Am J Clin Nutr* 67:359-366, 1998
31. Kuhlmann U, Schwickardi M, Trebst R, et al: Resting metabolic rate in chronic renal failure. *J Ren Nutr* 11:202-206, 2001
32. Avesani CM, Kamimura MA, Draibe SA, et al: Is energy intake underestimated in nondialyzed chronic kidney disease patients? *J Ren Nutr* 15:159-165, 2005
33. Levey AS, Adler S, Caggiula AW, et al: Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 27:652-663, 1996