Treatment of protein-energy malnutrition in chronic nonmalignant disorders

Gunnar Akner and Tommy Cederholm

ABSTRACT  Protein-energy malnutrition (PEM) is common in connection with chronic disease and is associated with increased morbidity and mortality. Because the risk of PEM is related to the degree of illness, the causal connections between malnutrition and a poorer prognosis are complex. It cannot automatically be inferred that nutritional support will improve the clinical course of patients with wasting disorders. We reviewed studies of the treatment of PEM in cases of chronic obstructive pulmonary disease, chronic heart failure, stroke, dementia, rehabilitation after hip fracture, chronic renal failure, rheumatoid arthritis, and multiple disorders in the elderly. Several methodologic problems are associated with nutrition treatment studies in chronically ill patients. These problems include no generally accepted definition of PEM, uncertain patient compliance with supplementation, and a wide range of outcome variables. Available treatment studies indicate that dietary supplements, either alone or in combination with hormonal treatment, may have positive effects when given to patients with manifest PEM or to patients at risk of developing PEM. In chronic obstructive pulmonary disease, nutritional treatment may improve respiratory function. Nutritional therapy of elderly women after hip fractures may speed up the rehabilitation process. When administered to elderly patients with multiple disorders, diet therapy may improve functional capacity. The data regarding nutritional treatment of the conditions mentioned above is still inconclusive. There is still a great need for randomized controlled long-term studies of the effects of defined nutritional intervention programs in chronically ill and frail elderly with a focus on determining clinically relevant outcomes.

KEY WORDS  Protein-energy malnutrition, chronic obstructive pulmonary disease, chronic heart failure, stroke, dementia, hip fracture, chronic renal failure, rheumatoid arthritis, elderly, nutritional support

INTRODUCTION  Most longstanding, chronic diseases of the organs—particularly of the lungs, heart, nervous system, skeleton, kidneys, and joints—are associated with both general and specific catabolic or hypermetabolic processes, including reduced nutrient intake, that may lead to protein-energy malnutrition (PEM) in some individuals. Extensive documentation exists of the strong relation between PEM in chronic disease and increased morbidity, mortality, and extended hospital stays (1, 2). The causality of these connections is not clear. In addition, reduced food intake and breakdown of body tissues are partly the result of biochemical mechanisms activated by the disease. Accordingly, it is not certain that nutritional supplements can correct disease-related malnutrition or improve a patient's health or prognosis.

The purpose of this review was to summarize studies that evaluated the effect of nutritional treatment in cases of PEM or risk of PEM in connection with certain chronic disorders: chronic obstructive pulmonary disease (COPD), chronic heart failure, poststroke conditions, dementia, rehabilitation after hip fracture, chronic renal failure, rheumatoid arthritis, and multiple disorders in the elderly. We also briefly discuss the prevalence of PEM, the pathogenesis of catabolism, and the consequences of malnutrition in each of the disorders.

METHODOLOGIC ASPECTS  Most patients with chronic catabolic disorders can eat and drink unaided and have a functioning gastrointestinal tract. In most of the treatment studies described here, the treatment consisted of food enrichment or of oral supplements in the form of liquid nutritional drinks. Some studies involved enteral nutrition via a nasogastric tube or percutaneous endoscopic gastrostomy (PEG). We also evaluated studies in which pharmacologic interventions were used, eg, growth hormone or anabolic steroids, either alone or in combination with nutritional supplementation.

MEDLINE (National Library of Medicine, Bethesda, MD) was searched for original articles by using the OVID and PUBMED query programs. Through MEDLINE searches and with access to our own and others' reference files, we found 90 treatment-oriented studies [50 randomized controlled trials (RCTs) and 40 less-well-controlled studies] relevant to the disorders we were studying (Figure 1). For a better overview, the treatment studies are presented in tabular form in chronologic order with RCTs followed by controlled, nonrandomized, and
uncontrolled trials, respectively. In each section, food supplementation studies and studies with other forms of intervention are presented separately.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The prevalence of malnutrition is reported to vary between 20% and 70% for different patient groups with COPD and appears highest in combination with emphysema (3–6). Malnutrition in patients with COPD is associated with an imbalance between energy expenditure and dietary intake (7–12). A study with doubly labeled water showed that although the basal metabolic rate was not higher in COPD patients, their total energy metabolism was 20% higher than in matched control subjects (10). Inflammatory activity probably contributes to catabolic processes (13–16). In a recent study of COPD patients in a stable phase, it was reported that the basal metabolic rate is related to plasma concentrations of tumor necrosis factor α (TNF-α), but not to respiratory function (17). The nutritional deterioration is aggravated during exacerbations of the disease (8, 18).

The loss of lean body mass leads to reduced diaphragm mass (19), poorer respiratory muscle function (20, 21), and reduced peripheral skeletal muscle function (22, 23). Low body weight is an independent predictor of mortality in COPD (24, 25). As early as 30 y ago it was reported that COPD patients with weight loss have a shorter 5-y survival rate (average survival time of 3 y) as 30 y ago it was reported that COPD patients with weight loss are an independent predictor of mortality in COPD (24, 25). As early as 30 y ago it was reported that COPD patients with weight loss have a shorter 5-y survival rate (average survival time of 3 y) as 30 y ago it was reported that COPD patients with weight loss are an independent predictor of mortality in COPD (24, 25). As early as 30 y ago it was reported that COPD patients with weight loss have a shorter 5-y survival rate (average survival time of 3 y). In another study, it was noted that COPD patients with weight loss have a shorter 5-y survival rate (average survival time of 3 y) as 30 y ago it was reported that COPD patients with weight loss are an independent predictor of mortality in COPD (24, 25). As early as 30 y ago it was reported that COPD patients with weight loss have a shorter 5-y survival rate (average survival time of 3 y) as 30 y ago it was reported that COPD patients with weight loss are an independent predictor of mortality in COPD (24, 25). As early as 30 y ago it was reported that COPD patients with weight loss have a shorter 5-y survival rate (average survival time of 3 y).

In Table 1 we summarize 14 studies (5, 27–39), 12 of which were RCTs. All but one (38) included 9–33 patients each, with treatment periods of 2–52 wk. Nine of the studies (8 RCTs: 5, 29, 31–34, 36–38) reported positive effects of nutritional treatment on various anthropometric measures, particularly body weight. Eight studies (7 RCTs: 5, 27–31, 33, 38) noted functional improvements in the skeletal musculature (respiratory or extremity musculature), pulmonary or immune function, or a sense of well-being. Five studies (4 RCTs: 5, 29, 31, 33, 38) found positive effects on both anthropometric and functional measures. Two studies (both RCTs: 35, 39) recorded no effect of nutritional treatment. None of the studies reported effects on mortality. In the 4 studies involving treatment of COPD patients with anabolic steroids or growth hormone, alone or in combination with nutritional supplements (5, 36–38), positive effects were noted for anthropometric measures and in 2 studies (5, 38) for muscular function. In 2 RCTs (27, 34), patients with COPD but without PEM were treated with nutritional supplements; in one of the studies (27), a positive effect on pulmonary function was noted. In a recent meta-analysis that included 277 subjects from 9 RCTs, the authors concluded that energy supplementation for ≥2 wk has no effect on anthropometric measures, lung function, or functional exercise capacity in patients with stable COPD (40). In one study, COPD patients not responding to nutritional supplementation were characterized by increased age, anorexia, and an elevated inflammatory systemic response (41). In summary, nutritional treatment of PEM in connection with COPD may positively affect body composition as well as muscular strength and respiratory function.

CHRONIC HEART FAILURE

The prevalence of PEM in connection with chronic heart failure, ie, cardiac cachexia (42–45), varies between 10% and 25%, depending on the type of heart-failure patients studied (46–50). The effects of increased usage of angiotensin-converting enzyme inhibitors in reducing the risk of developing cardiac cachexia has not been studied.

Examples of pathophysiologic mechanisms, traditionally viewed as leading to cardiac cachexia, are reduced appetite or feeling full sooner, secondary portal hypertension with venous stasis in the hepatic-splanchnic area with dyspepsia, malabsorption of lipids and protein loss in the gut, and abnormalities in catecholamine kinetics (45, 51–55). Cytokine-triggered catabolism, in conjunction with neuroendocrine abnormalities (56, 57), contributes to cardiac cachexia (58–61). Although patients with chronic heart failure have 15–20% higher basal metabolic rates than do matched control subjects (54, 62), total daily energy expenditure as measured by the doubly labeled water technique is lower in these patients (63).

PEM causes a hypotrophy of the cardiac muscle in proportion to the hypotrophy of the skeletal muscles (64). In healthy individuals, this can partially be an adaptive mechanism to reduced metabolic requirements (bradycardia, hypotension, and reduced blood volume), which seldom gives rise to clinical cardiac insufficiency (52). Nutritional therapy in malnourished individuals may provoke cardiac insufficiency, ie, a refeeding syndrome, particularly in connection with parenteral nutrition (45, 52). In patients with chronic heart failure is associated with elevated mortality rates (65–67).

In Table 2 we report the results of 4 studies of oral supplementation in cardiac patients. In one RCT, performed in patients without PEM, 8 wk of liquid dietary supplementation increased subcutaneous fat (49). The other 3 studies comprised a smaller number of patients. Two of the studies (64, 69) noted some improvement of cardiac function after nutritional treatment. In the former study (64), 2 of 5 cachectic patients developed cardiac decompensation after 3 wk of hyperalimentation.

Recently, growth hormone treatment was attempted in patients with various forms of cardiomyopathy. Six of these reports (70–75) are summarized in Table 3. In one study (72), growth hormone treatment worsened the clinical course of 3 patients with severe chronic heart failure, but appeared to be beneficial in 7 patients with more moderate chronic heart failure. Nutritional status was not assessed in any of the reports. Initially promising
<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Nutritional treatment</th>
<th>Anthropometric or biochemical index</th>
<th>Function or mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saudny-Unterberger et al, 1997 (27)</td>
<td>RCT [33]</td>
<td>No</td>
<td>Oral supplement 10 kcal/kg BW → 10 kcal/kg BW</td>
<td>—</td>
<td>Lung function ↑</td>
</tr>
<tr>
<td>Rogers et al, 1992 (29)</td>
<td>RCT [27]</td>
<td>Yes</td>
<td>Diet? 0.3 × REE → 0.3 kcal/kg BW</td>
<td>—</td>
<td>Weight ↑</td>
</tr>
<tr>
<td>Fuenzalida et al, 1990 (30)</td>
<td>RCT [9]</td>
<td>Yes</td>
<td>Oral supplement 1080 kcal/d → 43 kcal/kg BW</td>
<td>—</td>
<td>No effect</td>
</tr>
<tr>
<td>Whittaker et al, 1990 (31)</td>
<td>RCT [10]</td>
<td>Yes</td>
<td>Enteral feeding (NG) 1000 kcal/d → 0 kcal/kg BW</td>
<td>—</td>
<td>Weight ↑</td>
</tr>
<tr>
<td>Otte et al, 1989 (32)</td>
<td>RCT [28]</td>
<td>Yes</td>
<td>Oral supplement 400 kcal/d → 20 kcal/kg BW</td>
<td>—</td>
<td>Weight ↑; subcutaneous fat ↑</td>
</tr>
<tr>
<td>Efthimiou et al, 1988 (33)</td>
<td>RCT [14]</td>
<td>Yes</td>
<td>Oral supplement 690 kcal/d → 29 kcal/kg BW</td>
<td>—</td>
<td>No effect on function</td>
</tr>
<tr>
<td>Lewis et al, 1987 (35)</td>
<td>RCT [21]</td>
<td>Yes</td>
<td>Oral supplement 500–1000 kcal/d → 18 kcal/kg BW</td>
<td>—</td>
<td>No effect on function</td>
</tr>
<tr>
<td>Ferreira et al, 1998 (36)</td>
<td>RCT [23]</td>
<td>Yes</td>
<td>Testosterone —</td>
<td>—</td>
<td>Anthropometry ↑</td>
</tr>
<tr>
<td>Burdet et al, 1997 (37)</td>
<td>RCT [16]</td>
<td>Yes</td>
<td>Diet and growth hormone 40 kcal/kg BW → 40 kcal/kg BW</td>
<td>—</td>
<td>Lean body mass ↑</td>
</tr>
<tr>
<td>Schols et al, 1995 (38)</td>
<td>RCT [217]</td>
<td>Yes</td>
<td>Oral supplement with and without nandrolone 420 kcal/d → 420 kcal/kg BW</td>
<td>—</td>
<td>No effect on function</td>
</tr>
<tr>
<td>Sridhar et al, 1994 (39)</td>
<td>UCT</td>
<td>Yes</td>
<td>Oral supplement 50% → 1.5 g/kg BW</td>
<td>—</td>
<td>No effect</td>
</tr>
<tr>
<td>Pape et al, 1991 (5)</td>
<td>UCT</td>
<td>Yes</td>
<td>Diet and growth hormone 35 kcal/kg BW → 1000 kcal/kg BW</td>
<td>—</td>
<td>Weight ↑; nitrogen balance ↑</td>
</tr>
</tbody>
</table>

1 BW, body weight; NG, nasogastric tube; PEM, protein-energy malnutrition; RCT, randomized controlled trial; REE, resting energy expenditure; UCT, uncontrolled trial.
2 Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.
3 To convert kcal to kJ, multiply by 4.184.
4 Intended supplementation.
5 Estimated total intake.
TABLE 2
Nutritional treatment studies of patients with chronic heart failure

<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Nutritional treatment</th>
<th>Energy ( \text{g/d} )</th>
<th>Protein ( \text{g/d} )</th>
<th>Duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broqvist et al, 1994 (49)</td>
<td>RCT, placebo</td>
<td>19 No</td>
<td>Oral supplement</td>
<td>750 kcal/d ( ^4 )</td>
<td>30 ( ^3 )</td>
<td>8 wk</td>
<td>Subcutaneous fat ↑; no effect on function</td>
</tr>
<tr>
<td>Heymsfield and Casper, 1989 (68)</td>
<td>CT</td>
<td>8 Yes</td>
<td>Enteral feeding</td>
<td>35 kcal/kg BW ( ^5 )</td>
<td>1/kg BW ( ^5 )</td>
<td>2 wk</td>
<td>Weight ↓; lean body mass ↑</td>
</tr>
<tr>
<td>Heymsfield et al, 1978 (64)</td>
<td>UCT</td>
<td>5 Yes</td>
<td>Enteral or parenteral nutrition</td>
<td>3000–4000 kcal/d ( ^5 )</td>
<td>75–135 ( ^5 )</td>
<td>4–6 wk</td>
<td>Weight ↑; left ventricular mass ↑</td>
</tr>
<tr>
<td>Chhetri et al, 1982 (69)</td>
<td>UCT</td>
<td>9 Yes</td>
<td>Oral supplement</td>
<td>1350 kcal/d ( ^4 )</td>
<td>48 ( ^4 )</td>
<td>8 wk</td>
<td>Cardiac function ↑; partially decompensated</td>
</tr>
</tbody>
</table>

1 BW, body weight; CT, controlled trial; PEM, protein-energy malnutrition; RCT, randomized controlled trial; UCT, uncontrolled trial.
2 Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.
3 To convert kcal to kJ, multiply by 4.184.
4 Intended supplementation.
5 Estimated total intake.
6 The study subjects had no cardiac illness.

TABLE 3
Growth hormone (GH) and pentoxifylline (P) treatment studies of patients with dilated cardiomyopathy (DCM) or chronic heart failure (CHF)

<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Duration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osterziel et al, 1998 (70)</td>
<td>RCT, placebo</td>
<td>50 DCM</td>
<td>GH</td>
<td>12 wk</td>
<td>Serum IGF-I ↑; LVM ↑; no effect on NYHA functional class, EF, or walking ability</td>
<td></td>
</tr>
<tr>
<td>Isgaard et al, 1998 (71)</td>
<td>RCT, placebo</td>
<td>20 CHF</td>
<td>GH</td>
<td>3 mo</td>
<td>Serum IGF-I ↑; no effect on cardiac or overall function</td>
<td></td>
</tr>
<tr>
<td>Sliwa et al, 1998 (76)</td>
<td>RCT, placebo</td>
<td>24 DCM</td>
<td>P</td>
<td>6 mo</td>
<td>EF ↑; NYHA functional class ↑; serum TNF ↓</td>
<td></td>
</tr>
<tr>
<td>Spallarossa et al, 1999 (72)</td>
<td>CT</td>
<td>15 CHF</td>
<td>GH</td>
<td>6 mo</td>
<td>Serum IGF-I ↑; exercise capacity and well-being ↑; worse clinical course in patients with severe CHF</td>
<td></td>
</tr>
<tr>
<td>José et al, 1999 (73)</td>
<td>UCT</td>
<td>6 DCM</td>
<td>GH</td>
<td>6 mo</td>
<td>LVM ↑; NYHA functional class ↑</td>
<td></td>
</tr>
<tr>
<td>Genth-Zotz et al, 1999 (74)</td>
<td>UCT</td>
<td>7 CHF</td>
<td>GH</td>
<td>3 mo</td>
<td>Serum IGF-I ↑; LVM ↑; cardiac output ↑; NYHA functional class ↑; effects reversed 3 mo after discontinuation of treatment</td>
<td></td>
</tr>
<tr>
<td>Fazio et al, 1996 (75)</td>
<td>UCT</td>
<td>7 DCM</td>
<td>GH</td>
<td>3 mo</td>
<td>Serum IGF-I ↑; LVM ↑; cardiac output ↑; exercise capacity and life quality ↑; effects partly reversed 3 mo after discontinuation of treatment</td>
<td></td>
</tr>
</tbody>
</table>

1 CT, controlled trial; EF, ejection fraction; IGF-I, insulin-like growth factor I; LVM, left ventricular mass; NYHA, New York Heart Association; RCT, randomized controlled trial; TNF, tumor necrosis factor; UCT, uncontrolled trial.
2 Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.
results on cardiac function and clinical status were not confirmed by 2 RCTs. One RCT evaluated the effect of the TNF-modulating drug pentoxifylline in patients with idiopathic dilated cardiomyopathy. Improved left ventricular systolic function and New York Heart Association functional class were reported (76).

Nutritional support in patients with chronic heart failure is complicated because the patients’ fluid and salt intakes should not exceed 1.5 L and 2 g Na per 24 h, respectively. Therefore, patients with cardiac cachexia should preferably consume high-energy, limited-sodium diets (54, 77). As summarized here, the nutritional treatment of PEM associated with chronic heart failure has been insufficiently studied.

POSTSTROKE CONDITIONS

Eight to sixteen percent of stroke patients show signs of PEM at the time of stroke (78–80). The frequency of malnutrition increases during the hospital stay: in one study from 16% at hospitalization to 22% at discharge (78) and in another study from 16% to 26% after 1 wk (80). More than 80% of patients hospitalized for >21 d because of stroke had difficulty eating (81). About one-half of patients referred to a stroke rehabilitation clinic were malnourished (82).

The effect of a stroke on many aspects of function can contribute to a patient’s nutritional impairment. Dysphagia affects 30–45% of stroke patients (83–84). Within 2 wk most stroke patients (87%) regain the ability to swallow (83, 85). Waiting for spontaneous improvement in the ability to swallow, and the lack of guidelines based on the results of controlled studies, often delays stroke and dysphagia patients’ nutritional supply (86). Other contributing factors to the risk of malnutrition after stroke are paralysis of the dominant side of the body and communication and perception disorders such as aphasia and an altered sense of smell and taste. Davalos et al (80) speculated whether an acute catabolic phase, expressed as increased cortisol concentrations in the urine and plasma, contributes to a negative energy and nutritional balance that may cause a rapid deterioration in the nutritional status of many stroke patients.

Malnutrition in stroke patients is associated with an increased rate of infection, bed sores, extended treatment periods, and increased mortality (80, 87). As with many other conditions, hypoalbuminemia is a strong predictor of an unfavorable progression after stroke (88).

Listed in Table 4 are 7 studies (3 RCTs: 80, 89–94) that represent different types of nutritional treatment, focusing on the prevention of nutritional deterioration after a stroke. In one RCT (89), an increased nutritional intake and less pronounced deterioration of nutritional status were noted as a result of peroral nutritional supplementation. In one uncontrolled short-term study (80), treatment was unable to prevent the deterioration of nutritional status despite a nasogastric nutrient supply. In one RCT (90), PEG was compared with nasogastic tube feeding (NG). Mortality was significantly lower, the hospital-stay shorter, the number of complications (aspiration pneumonia) fewer, and the nutritional status better in the PEG group than in the NG group. A retrospective study of the long-term results of stroke patients who received PEG showed that 25 of 37 consecutive patients died within 3 mo (92). The extent to which these patients’ poor prognoses were due to insufficient nutritional intake before the gastrostomy was unclear. Two studies evaluated the effects of dietary guidance and swallowing exercises in dysphagic stroke patients (91, 94).

In a meta-analysis of interventions against dysphagia in connection with acute stroke, the Cochrane Library (95) concluded that too few studies have been performed. PEG may improve the outcome and nutritional status of stroke patients in comparison with a nasogastric nutrient supply, but more studies of nutritional treatment in patients after stroke are needed. In dysphagia that is considered permanent, PEG inserted ≈2 wk after the onset of a stroke is preferable to a nasogastric tube.

DEMENTIA

Malnutrition occurs in 12–50% of institutionalized patients with dementia disorders (96–98). The frequency is reported to be higher in dementia of Alzheimer type (DAT) than in vascular dementia (99). Within 8 y of the onset of DAT, 50% of patients need help with feeding or require artificial nutrition (100). An annual weight loss of 4% was reported in institutionalized patients with DAT (101).

Dementia leads to a reduced intake of energy, partly because of decreased appetite, hunger, and thirst; dysphagia of eating function, such as chewing and swallowing; altered perception of smell and taste; refusal to eat; and forgetting to eat. Some DAT patients may have hyperactivity-related energy losses, but studies of energy metabolism in connection with dementia, performed with different techniques, produced conflicting results (102–105). Weight loss was retrospectively observed to precede the onset of dementia (106). Inflammatory processes in the brain are suggested to be of etiologic importance in DAT, and patients with DAT show increased concentrations of TNF-α and other proinflammatory cytokines in both plasma and cerebrospinal fluid (107–109). We can speculate as to whether this may contribute to the weight loss. There is also evidence that patients with DAT have a general loss of homeostatic regulatory mechanisms, such as thermoregulation and cardiovascular reflexes, which can reduce the ability to conserve energy (101). A 6-y longitudinal study correlated weight loss with the degree and progress of DAT and with mortality, whereas weight gain was related to a reduced mortality risk (110).

One RCT showed the results of diet therapy for dementia patients with PEM at a British psychiatric hospital (98). Of nearly 300 patients, 80 (27%) were underweight. Of these, 46 were included in a randomized treatment study using liquid dietary supplements of 600 kcal/d (=2500 KJ/d) for 12 wk. The intervention group gained an average of 3.5 kg, whereas the control group maintained a stable weight. No evaluation of functional capacity or mortality was performed. The controversial use of tube feeding in cases of severe dementia was recently reviewed (111). A retrospective study of individuals with severe cognitive disorders in nursing homes found no survival advantages in those who were tube-fed compared with those who were not (112). In conclusion, the nutritional treatment of PEM associated with dementia has been insufficiently studied.

REHABILITATION AFTER HIP FRACTURE

As many as one-half of all elderly patients who suffer hip fractures are malnourished (113–116). Insufficient nutrient intake can contribute to osteoporosis, which is often an important cause of fractures in the elderly. PEM is also associated with muscular weakness and therefore an increased risk of falling (117) and reduced subcutaneous fat to cushion the fall (118). Prospective
<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Nutritional treatment</th>
<th>Energy[^4]</th>
<th>Duration</th>
<th>Anthropometric or biochemical index</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gariballa et al, 1998 (89)</td>
<td>RCT</td>
<td>40 No</td>
<td>Oral supplementation</td>
<td>600 kcal/d[^4]</td>
<td>4 wk</td>
<td>Serum albumin ↓ in control subjects; intake of energy (75%) ↑ and protein (50%) ↑</td>
<td>—</td>
</tr>
<tr>
<td>Norton et al, 1996 (90)</td>
<td>RCT</td>
<td>30 Yes</td>
<td>Enteral feeding via PEG or NG (14 d after onset of stroke)</td>
<td>100 mL/h[^5]</td>
<td>6 wk</td>
<td>Weight ↑ and serum albumin ↑ with PEG; weight ↓ and serum albumin ↓ with NG</td>
<td>Mortality ↓; hospital stay ↓; complications ↓ with PEG</td>
</tr>
<tr>
<td>DePippo et al, 1994 (91)</td>
<td>RCT</td>
<td>114 Yes</td>
<td>Three levels of dysphagia training</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Limited instructions as good as more intense</td>
</tr>
<tr>
<td>Duvalos et al, 1996 (80)</td>
<td>UCT</td>
<td>91 Yes and no Diet or enteral feeding (NG) in case of dysphagia</td>
<td>2000 kcal/d[^4] (diet) or 30 kcal·kg BW[^1]·d[^1] (NG)</td>
<td>1 wk</td>
<td>—</td>
<td>No effect, ie, percentage with low TSF, AMC, or serum albumin ↑, from 17% to 32%, despite nutrition</td>
<td>—</td>
</tr>
<tr>
<td>Wanklyn et al, 1995 (92)</td>
<td>UCT</td>
<td>37 Yes?</td>
<td>PEG 26 d (median) after onset of stroke</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>25 of 37 patients died within 3 mo</td>
</tr>
<tr>
<td>Nyswonger and Helmchen, 1992 (93)</td>
<td>UCT</td>
<td>52 —</td>
<td>Enteral feeding (NG) initiated before or after 72 h of stroke</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Hospital stay ↓: 20 d with early NG or 29 d with late NG</td>
</tr>
<tr>
<td>Elmståhl et al, 1999 (94)</td>
<td>UCT</td>
<td>38 Yes</td>
<td>Training of oral muscles and swallowing technique</td>
<td>—</td>
<td>—</td>
<td>60% improved their swallowing and nutritional status</td>
<td>—</td>
</tr>
</tbody>
</table>

[^1]: Protein-energy malnutrition was not used as a selection criterion in any of the studies. AMC, arm muscle circumference; BW, body weight; NG, nasogastric tube; PEG percutaneous endoscopic gastrostomy; RCT, randomized controlled trial; TSF, triceps skinfold thickness; UCT, uncontrolled trial.
[^2]: Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.
[^3]: To convert kcal to kJ, multiply by 4.184.
[^4]: Estimated total intake.
[^5]: Intended supplementation.
<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>PEM</th>
<th>Nutritional treatment</th>
<th>Energy</th>
<th>Protein</th>
<th>Duration</th>
<th>Anthropometric or biochemical index</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schurch et al, 1998 (120)</td>
<td>RCT, placebo</td>
<td>63</td>
<td>No</td>
<td>Oral supplement</td>
<td>—</td>
<td>20</td>
<td>6 mo</td>
<td>Bone density ↑; serum IGF-I ↑</td>
<td>Hospital stay (in 1 y) ↓: 33 compared with 54 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[82]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6-mo mortality ↓: 0% compared with 50%</td>
<td></td>
</tr>
<tr>
<td>Sullivan et al, 1998 (121)</td>
<td>RCT</td>
<td>15</td>
<td>No</td>
<td>Enteral feeding</td>
<td>1400 mL/d</td>
<td>—</td>
<td>15 d</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Hartgrink et al, 1998 (122)</td>
<td>RCT</td>
<td>116</td>
<td>—</td>
<td>Enteral feeding</td>
<td>≈1500 kcal/d</td>
<td>≈65</td>
<td>1–2 wk</td>
<td>Hemoglobin ↑; serum albumin ↑</td>
<td>No effect on pressure sore risk</td>
</tr>
<tr>
<td>Tkatch et al, 1992 (123)</td>
<td>RCT, placebo</td>
<td>62</td>
<td>No</td>
<td>Oral supplement</td>
<td>—</td>
<td>20</td>
<td>38 d</td>
<td>Complications ↓; hospital stay ↓ in 7 mo: 70 compared with 102 d</td>
<td></td>
</tr>
<tr>
<td>Delmi et al, 1990 (124)</td>
<td>RCT</td>
<td>59</td>
<td>No</td>
<td>Oral supplement</td>
<td>250 kcal/d</td>
<td>20</td>
<td>32 d</td>
<td>Complications ↓; hospital stay ↓: 24 compared with 40 d</td>
<td></td>
</tr>
<tr>
<td>Williams et al, 1989 (125)</td>
<td>RCT?</td>
<td>38</td>
<td>Yes</td>
<td>Oral supplement</td>
<td>400 kcal/d</td>
<td>14</td>
<td>≈3 wk</td>
<td>No effects on mobility or hand grip strength</td>
<td></td>
</tr>
<tr>
<td>Baslow et al, 1983 (126)</td>
<td>RCT</td>
<td>122</td>
<td>Yes</td>
<td>Enteral feeding</td>
<td>1000 kcal/d</td>
<td>28</td>
<td>≈4 wk</td>
<td>AMC ↑</td>
<td>Faster rehabilitation: 10 compared with 12 d and 16 compared with 23 d in “thin” and “very thin,” respectively</td>
</tr>
<tr>
<td>Sloan et al, 1992 (127)</td>
<td>RCT, placebo</td>
<td>29</td>
<td>No</td>
<td>Nandrolone, 2 mg/kg⁶</td>
<td>—</td>
<td>—</td>
<td>4 wk</td>
<td>No positive or negative effects</td>
<td></td>
</tr>
</tbody>
</table>

1AMC, arm muscle circumference; IGF-I, insulin-like growth factor I; PEM, protein-energy malnutrition; RCT, randomized controlled trial; TSF, triceps skinfold thickness.
2Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.
3To convert kcal to kJ, multiply by 4.184.
4Intended supplementation.
5High-risk patients for pressure sore.
6Estimated total intake.
7High rate of tube intolerance.
8Intramuscular dose.
epidemiologic studies showed that maintained weight after menopause is a significant factor in preventing fractures (119). A study evaluating the prognostic importance of PEM in patients with hip fractures noted that the risk of PEM was associated with longer hospitalization and a lower degree of rehabilitation (114).

Eight studies of postoperative nutritional treatment of hip-fracture patients are summarized in Table 5 (120–127). All studies were controlled and randomized, but the randomization procedure was not always clearly described. Two studies described the treatment of established PEM in hip-fracture patients (125, 126), whereas the other studies did not use PEM as an inclusion criterion. Four dietary supplement studies reported a shorter hospitalization period for those who received supplements (120, 123, 124, 126). Two studies from the same researchers showed fewer postoperative complications, such as infections (123, 124). One study indicated beneficial effects on mortality (121). However, the number of deaths was small. In one of the studies, researchers noted that a 4-wk treatment with anabolic steroids (nandrolone) had no effect (127). A meta-analysis of 943 patients aged ≥65 y performed by the Cochrane Library (128) concluded that there was evidence of positive effects of oral protein and energy supplements. In general, however, the quality of the studies was assessed as low and further studies were requested. In conclusion, oral or enteral postoperative treatment with balanced or protein-rich nutritional supplements (protein supplement of ≥20 g/d) for ≥3–4 wk may shorten hospitalization periods in hip-fracture patients.

CHRONIC RENAL FAILURE

The prevalence of PEM in patients with chronic renal failure is reported to vary between 30% and 76% (129–132); PEM is particularly common in elderly patients, especially those with chronic renal failure secondary to diabetes mellitus (133). PEM in connection with chronic renal failure is multifactorial and depends on nutritional, metabolic, hormonal, and inflammatory factors (134–135). The prescription of protein-restricted diets to persons with chronic renal failure may contribute to the risk of PEM (136). Metabolic acidosis can contribute to muscular proteolysis (134) and reduced albumin synthesis (137). However, it is unclear whether the development of PEM can be inhibited by treating the metabolic acidosis (138). Other factors that contribute to PEM in patients with chronic renal failure are insulin resistance, increased glucagon concentrations, secondary hyperparathyroidism, and reduced thyroid hormone concentrations. In addition, comorbidity factors also occur, such as diabetes mellitus, depression, drug-induced side effects, and physical inactivity. It is unclear whether patients with chronic renal failure have an elevated energy metabolism (133, 139–141). The activity of proinflammatory cytokines with anorexic and muscular catabolic effects is elevated in cases of renal failure and is associated with the development of PEM (142). PEM is a strong risk factor for both morbidity and mortality in connection with chronic dialysis (143–145). Data also exist that implicate PEM per se as having a positive effect on renal function (146).

Summarized in Table 6 are 23 studies (7 RCTs: 147–169) reporting the effects of various forms of nutritional treatment: oral supplementation (7 studies), hormonal therapy (9 studies), and intradialytic parenteral nutrition (IDPN; 7 studies). The studies comprised 7–50 patients each and the treatment periods ranged from 7 d to 12 mo. Twenty-one studies (7 RCTs) reported a positive effect of nutritional treatment on anthropometric or biochemical measures. Five studies (3 RCTs) found positive functional effects of nutritional therapy (149, 150, 153, 163, 164), 2 studies (1 RCT) found no functional effect (152, 161), and the other 16 studies (including all oral supplementary studies) did not investigate functional measures.

For patients who do not tolerate oral or enteral nutrition, IDPN [ie, intravenous supplementation of glucose, amino acids, or lipids during the hemodialysis sessions (170)] can provide a high protein-to-energy quotient to compensate for a poor protein intake. Existing studies, including an RCT (153), show small positive effects on weight (153, 161, 162) and biochemical nutritional markers (168), improved immune function (163), and possibly improved survival rates (155, 156, 164). The use of IDPN was recently reviewed (171), and an evidence-based evaluation concluded that the data supporting the use of IDPN are weak and that no clear recommendation can be made (172).

In conclusion, the available nutritional treatment studies of PEM associated with renal failure indicate positive effects on anthropometric and biochemical variables. However, only a few studies, and no oral supplementary study, reported clinical outcome data.

RHEUMATOID ARTHRITIS

The prevalence of malnutrition in cases of rheumatoid arthritis varies between 26% and 71% (173, 174). Rheumatoid arthritis patients seldom have reduced appetites and can suffer from pronounced malnutrition that goes undetected at clinical examination (175). However, young persons with rheumatoid arthritis are rarely malnourished (176).

Rheumatoid arthritis implies a risk of PEM for several reasons. Patients with rheumatoid arthritis lose muscle mass even if they have high protein intakes (177), which is consistent with the catabolism linked to the chronic inflammatory process. This in turn is consistent with findings of increased systemic TNF-α activity being related to the development of PEM in rheumatoid arthritis (175, 177). The activity of the disorder (ie, pronounced radiological changes, extraarticular manifestations, and low functional class) is a strong indicator of risk of PEM (173, 178). Often the patient loses weight during flares (179). New treatment strategies, focused specifically on TNF activity, are being introduced for rheumatoid arthritis (180, 181). The effects that these strategies have on the general disorder-related catabolism are as yet unknown. Other contributing factors to PEM in rheumatoid arthritis can be adaptation to low physical activity, treatment with systemic glucocorticoids (182), and sicca in associated Sjögren syndrome. In addition, repeated periods of fasting or elimination diets to reduce the activity of the rheumatoid arthritis may contribute to the risk of PEM in rheumatoid arthritis patients. No studies have been published on the effect of nutritional treatment of PEM associated with rheumatoid arthritis.

MULTIPLE DISORDERS IN THE ELDERLY

The combination of advanced age, multiple chronic disorders, and polypharmacy leads to an increased risk of PEM. In one study of internal medicine patients (49), the prevalence of malnutrition was twice as high among patients aged ≥74 y (27%) than among those aged 65–74 y (13%). PEM occurs in 20–50%
<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Nutritional treatment</th>
<th>Anthropometric or biochemical index</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tietze et al, 1991 (147)</td>
<td>RCT</td>
<td>HD</td>
<td>Oral supplement (fish proteins)</td>
<td>Weight ↑; muscle mass ↑; AA profile ↑</td>
<td>—</td>
</tr>
<tr>
<td>Allman et al, 1990 (148)</td>
<td>RCT</td>
<td>HD</td>
<td>Glucose polymer Nandrolone</td>
<td>Weight ↑; LBM ↑; fat mass ↑</td>
<td>—</td>
</tr>
<tr>
<td>Johansen et al, 1999 (149)</td>
<td>RCT</td>
<td>HD</td>
<td>GH</td>
<td>Fat free mass ↑; serum IGF-I ↑; serum albumin ↑</td>
<td>Mobility ↑; hand grip strength ↑</td>
</tr>
<tr>
<td>Johannsson et al, 1999 (150)</td>
<td>RCT</td>
<td>HD</td>
<td></td>
<td>LBM ↑; fat mass ↓; serum IGF-I ↑; serum IGFBP-1 ↑; serum IGFBP-3 ↓</td>
<td>—</td>
</tr>
<tr>
<td>Jensen et al, 1999 (151)</td>
<td>RCT</td>
<td>HD</td>
<td>GH</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Iglesias et al, 1998 (152)</td>
<td>RCT</td>
<td>HD, PD</td>
<td>Diet and GH or diet alone</td>
<td>No effect on function</td>
<td>—</td>
</tr>
<tr>
<td>Cano et al, 1990 (153)</td>
<td>RCT</td>
<td>HD</td>
<td>IDPN</td>
<td>Weight ↑; AMC ↑; serum albumin ↑</td>
<td>DCH ↑</td>
</tr>
<tr>
<td>Kuhlmann et al, 1999 (154)</td>
<td>CT</td>
<td>HD</td>
<td>Oral supplement</td>
<td>Weight ↑ in high energy and protein intake group</td>
<td>—</td>
</tr>
<tr>
<td>Chertow et al, 1994 (155)</td>
<td>CT</td>
<td>HD</td>
<td>IDPN</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Capelli et al, 1994 (156)</td>
<td>CT</td>
<td>HD</td>
<td>IDPN</td>
<td>—</td>
<td>Mortality ↓ if serum albumin ≤35 g/L or serum creatinine ≤8 mg/dL; mortality ↑ if serum albumin &gt;35 g/L; immunity ↑</td>
</tr>
<tr>
<td>Acchiardo et al, 1982 (157)</td>
<td>CT</td>
<td>HD</td>
<td>EAA and energy</td>
<td>Serum protein ↑; serum albumin ↑; serum transferrin ↑; TLC ↑; bone density ↑</td>
<td>—</td>
</tr>
<tr>
<td>Hecking et al, 1978 (158)</td>
<td>CT</td>
<td>HD</td>
<td>EAA</td>
<td>No effect</td>
<td>—</td>
</tr>
<tr>
<td>Milano et al, 1998 (159)</td>
<td>UCT</td>
<td>HD</td>
<td>Oral supplement</td>
<td>Anthropometry ↑; fat mass ↑</td>
<td>—</td>
</tr>
<tr>
<td>Elias et al, 1989 (160)</td>
<td>UCT</td>
<td>PD</td>
<td>Oral supplement</td>
<td>Nitrogen balance ↑</td>
<td>—</td>
</tr>
<tr>
<td>Berneis et al, 1999 (161)</td>
<td>UCT</td>
<td>HD</td>
<td>IDPN</td>
<td>Weight ↑; fat mass ↑; LBM ↑</td>
<td>No effect on quality of life</td>
</tr>
<tr>
<td>Mortelmans et al, 1999 (162)</td>
<td>UCT</td>
<td>HD</td>
<td>IDPN</td>
<td>Weight ↑; fat mass ↑</td>
<td>—</td>
</tr>
<tr>
<td>Smolle et al, 1995 (163)</td>
<td>UCT</td>
<td>HD</td>
<td>IDPN</td>
<td>No effect on anthropometry; serum albumin ↑; serum prealbumin ↑; TLC ↑</td>
<td>DCH ↑</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 6 (Continued)

<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Nutritional treatment</th>
<th>Type</th>
<th>Energy $^3$</th>
<th>Protein</th>
<th>Duration</th>
<th>Anthropometric or biochemical index</th>
<th>Function or mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foulks, 1994 (164)</td>
<td>UCT</td>
<td>72 HD</td>
<td>Yes</td>
<td>IDPN</td>
<td>17 kcal·kg $^{2}$, dialysis $^{-1}$·5</td>
<td>—</td>
<td>159–321 d</td>
<td>Weight ↑ and serum albumin ↑</td>
<td>Hospitalizations ↓ and mortality ↓ in responders (74%)</td>
</tr>
<tr>
<td>Foque et al, 2000 (165)</td>
<td>UCT</td>
<td>6 CAPD</td>
<td>Yes</td>
<td>IGF-1</td>
<td>—</td>
<td>—</td>
<td>20 d</td>
<td>Nitrogen balance ↑; no effect on weight</td>
<td>—</td>
</tr>
<tr>
<td>Shinobe et al, 1997 (166)</td>
<td>UCT</td>
<td>30 HD</td>
<td>Yes</td>
<td>GH</td>
<td>—</td>
<td>—</td>
<td>2 wk</td>
<td>Anthropometry ↑; serum IGF-I ↑; serum albumin ↑</td>
<td>—</td>
</tr>
<tr>
<td>Ikizler et al, 1994 (167)</td>
<td>UCT</td>
<td>10 PD</td>
<td>No</td>
<td>GH</td>
<td>—</td>
<td>—</td>
<td>Stable</td>
<td>Serum IGF ↑; serum albumin ↓</td>
<td>—</td>
</tr>
<tr>
<td>Schulman et al, 1993 (168)</td>
<td>UCT</td>
<td>7 HD</td>
<td>Yes</td>
<td>IDPN</td>
<td>18 kcal·kg $^{2}$, dialysis $^{-1}$·5</td>
<td>0.7 g·kg$^{2}$</td>
<td>6 wk</td>
<td>Nitrogen balance ↑; serum —</td>
<td>—</td>
</tr>
<tr>
<td>Ziegler et al, 1991 (169)</td>
<td>UCT</td>
<td>16 HD</td>
<td>Yes</td>
<td>GH</td>
<td>—</td>
<td>—</td>
<td>2 wk</td>
<td>Serum IGF↑; protein catabolism ↓</td>
<td>—</td>
</tr>
</tbody>
</table>

$^1$AA, amino acid; AMC, arm muscle circumference; BW, body weight; CAPD, continuous ambulatory peritoneal dialysis; CT, controlled trial; DCH, delayed cutaneous hypersensitivity; EAA, essential amino acids; GH, growth hormone; HD, hemodialysis; IDPN, intradialytic parenteral nutrition; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein-3; LBM, lean body mass; PEM, protein-energy malnutrition; PD, peritoneal dialysis; RCT, randomized controlled trial; TLC, total lymphocyte count; UCT, uncontrolled trial.

$^2$Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.

$^3$Estimated total intake.

$^4$Intended supplementation.

$^5$Comparison with spontaneous intake.

$^6$Multicenter national database study including 1679 HD patients receiving IDPN and 22517 HD control subjects.

### TABLE 7

Nutritional treatment studies in frail elderly and elderly with multiple chronic disorders.$^7$

<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>Nutritional treatment</th>
<th>Type</th>
<th>Energy $^3$</th>
<th>Protein</th>
<th>Duration</th>
<th>Anthropometric or biochemical index</th>
<th>Function or mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiatarone Singh et al, 2000 (202)</td>
<td>RCT, placebo</td>
<td>50 Y/N $^4$</td>
<td>Oral supplement</td>
<td>360 $^3$</td>
<td>—</td>
<td>10 wk</td>
<td>Weight ↑; fat mass ↑; LBM ↑</td>
<td>No effect on physical activity, cognition, or mood</td>
<td></td>
</tr>
<tr>
<td>Laque et al, 2000 (203)</td>
<td>RCT</td>
<td>78 Y/N</td>
<td>Oral supplement</td>
<td>400 $^3$</td>
<td>~20 $^5$</td>
<td>60 d</td>
<td>Weight ↑ in PEM patients</td>
<td>MNA score in PEM ↑; no effect on grip strength</td>
<td></td>
</tr>
<tr>
<td>Bourdel-Marchasson et al, 2000 (204)</td>
<td>RCT</td>
<td>672 Y/N</td>
<td>Oral supplement</td>
<td>400 $^3$</td>
<td>—</td>
<td>15 d</td>
<td>—</td>
<td>Risk for pressure ulcer ↓</td>
<td></td>
</tr>
<tr>
<td>de Jong et al, 1999 (205)</td>
<td>RCT</td>
<td>145 Y/N</td>
<td>Enriched food and exercise</td>
<td>—</td>
<td>—</td>
<td>17 wk</td>
<td>Vitamins ↑; no effect on weight or serum proteins</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>McWhirter and Pennington, 1996 (206)</td>
<td>RCT</td>
<td>86 Yes</td>
<td>Oral supplement, enteral feeding</td>
<td>590, $^3$</td>
<td>22, $^3$</td>
<td>10 d, 12 d</td>
<td>Weight ↑ after both oral supplement and enteral feeding</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Volkert et al, 1996 (207)</td>
<td>RCT</td>
<td>46 Y/N</td>
<td>Oral supplement</td>
<td>250 $^3$</td>
<td>15 $^3$</td>
<td>6 mo</td>
<td>No effect on weight</td>
<td>ADL ↑; independence ↑</td>
<td></td>
</tr>
<tr>
<td>Hogart et al, 1996 (208)</td>
<td>RCT, placebo</td>
<td>87 No</td>
<td>Glucose and vitamins $^3$</td>
<td>540 $^3$</td>
<td>—</td>
<td>30 d</td>
<td>No effect</td>
<td>No effect on cognition, ADL, or hospital stay</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author, year, and reference</th>
<th>Study design</th>
<th>Patients</th>
<th>PEM</th>
<th>Nutritional treatment</th>
<th>Energy$^1$</th>
<th>Protein</th>
<th>Duration</th>
<th>Anthropometric or biochemical index</th>
<th>Function or mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray-Donald et al, 1995 (209)</td>
<td>RCT 46</td>
<td>No</td>
<td>Oral supplement</td>
<td>150$^1$</td>
<td>5$^1$</td>
<td>12 wk</td>
<td>Weight ↑</td>
<td>Fall accidents ↓</td>
<td></td>
</tr>
<tr>
<td>Woo et al, 1994 (210)</td>
<td>RCT 81</td>
<td>Yes$^7$</td>
<td>Oral supplement</td>
<td>500 (1 mo)$^1$</td>
<td>—</td>
<td>3 mo</td>
<td>Weight ↑; AMC ↑; body fat ↑</td>
<td>ADL ↓ in controls</td>
<td></td>
</tr>
<tr>
<td>Fiatarone et al, 1994 (211)</td>
<td>RCT 94</td>
<td>No</td>
<td>Oral supplement and exercise</td>
<td>360$^1$</td>
<td>15$^1$</td>
<td>10 wk</td>
<td>Weight ↑</td>
<td>No effect on physical function with oral supplement only</td>
<td></td>
</tr>
<tr>
<td>Hankey et al, 1993 (212)</td>
<td>RCT 14</td>
<td>No</td>
<td>Oral supplement</td>
<td>=700$^1$</td>
<td>=24$^1$</td>
<td>8 wk</td>
<td>No effect</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Unosson et al, 1992 (213)</td>
<td>RCT 430</td>
<td>Y/N</td>
<td>Oral supplement</td>
<td>400$^1$</td>
<td>16$^1$</td>
<td>26 wk</td>
<td>—</td>
<td>Activity ↑ in WN after 8 wk</td>
<td></td>
</tr>
<tr>
<td>Larsson et al, 1990 (214)</td>
<td>RCT 435</td>
<td>Y/N</td>
<td>Oral supplement</td>
<td>400$^1$</td>
<td>16$^1$</td>
<td>26 wk</td>
<td>Weight index ↑ and AMC ↑ in WN; serum prealbumin ↑</td>
<td>DCH ↑ in both PEM and WN; mortality ↓ in WN</td>
<td></td>
</tr>
<tr>
<td>McEvoy and James, 1982 (215)</td>
<td>RCT 51</td>
<td>Yes</td>
<td>Oral supplement</td>
<td>644$^1$</td>
<td>36$^1$</td>
<td>4 wk</td>
<td>Weight ↑; TSF ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Banerjee et al, 1978 (216)</td>
<td>RCT 50</td>
<td>No</td>
<td>Oral supplement</td>
<td>265$^1$</td>
<td>18$^1$</td>
<td>14 wk</td>
<td>Skinfold thickness ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Yeh et al, 2000 (217)</td>
<td>RCT, placebo</td>
<td>51</td>
<td>Yes</td>
<td>Megestrol acetate</td>
<td>—</td>
<td>—</td>
<td>25 wk</td>
<td>Weight ↑</td>
<td>Appetite ↑; well-being ↑</td>
</tr>
<tr>
<td>Bos et al, 2000 (218)</td>
<td>CT 23</td>
<td>Yes</td>
<td>Oral supplement</td>
<td>400$^1$</td>
<td>30$^1$</td>
<td>10 d</td>
<td>Protein accretion ↑; fat-free mass ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Olin et al, 1996 (219)</td>
<td>CT 36</td>
<td>Y/N</td>
<td>Energy-enriched diet</td>
<td>450$^1$</td>
<td>17$^1$</td>
<td>6 wk</td>
<td>Weight ↑</td>
<td>Physical activity ↑</td>
<td></td>
</tr>
<tr>
<td>Cederholm and Heléström, 1995 (220)</td>
<td>CT 23</td>
<td>Yes</td>
<td>Oral supplement</td>
<td>400$^1$</td>
<td>40$^1$</td>
<td>12 wk</td>
<td>Weight ↑; AMC ↑; TSF ↑</td>
<td>Grip strength ↑; DCH ↑</td>
<td></td>
</tr>
<tr>
<td>Bunker et al, 1994 (221)</td>
<td>CT 58</td>
<td>Y/N</td>
<td>Oral supplement</td>
<td>—</td>
<td>—</td>
<td>12 wk</td>
<td>Weak effect on DCH</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Johnson et al, 1993 (222)</td>
<td>CT 109</td>
<td>Y/N</td>
<td>Oral supplement</td>
<td>—</td>
<td>—</td>
<td>Retrospective</td>
<td>Weight ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hébuterne et al, 1995 (223)</td>
<td>UCT 46</td>
<td>Yes</td>
<td>Enteral feeding</td>
<td>1300$^1$</td>
<td>68$^1$</td>
<td>2–6 wk</td>
<td>Weight ↑; TSF ↑; AMC ↑; serum prealbumin ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Gray-Donald et al, 1994 (224)</td>
<td>UCT 14</td>
<td>No</td>
<td>Oral supplement</td>
<td>390$^1$</td>
<td>—</td>
<td>12 wk</td>
<td>Weight ↑</td>
<td>Grip strength ↑; well-being ↑</td>
<td></td>
</tr>
<tr>
<td>Elmståhl and Steen, 1987 (225)</td>
<td>UCT 28</td>
<td>No</td>
<td>Oral supplement</td>
<td>240-410$^1$</td>
<td>4-10$^1$</td>
<td>8 wk</td>
<td>Weight ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lipschitz et al, 1985 (226)</td>
<td>UCT 12</td>
<td>Yes</td>
<td>Oral supplement</td>
<td>815$^1$</td>
<td>30$^1$</td>
<td>16 wk</td>
<td>Weight ↑; serum albumin ↑; serum TIBC ↑</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Katakiy et al, 1983 (227)</td>
<td>UCT 12</td>
<td>No</td>
<td>Oral supplement</td>
<td>204$^1$</td>
<td>9$^1$</td>
<td>12 wk</td>
<td>Weight ↑; serum albumin ↑; serum TIBC ↑</td>
<td>Grip strength ↑</td>
<td></td>
</tr>
<tr>
<td>Lipschitz and Mitchell, 1982 (228)</td>
<td>or enteral feeding</td>
<td>9</td>
<td>Yes</td>
<td>Oral supplement</td>
<td>1800-2500$^9$</td>
<td>—</td>
<td>21 d</td>
<td>Weight ↑; serum albumin ↑; serum TIBC ↑</td>
<td>Mobility ↑</td>
</tr>
</tbody>
</table>

$^1$ADL, activity of daily living; AMC, arm muscle circumference; CT, controlled trial; DCH, delayed cutaneous hypersensitivity; LBM, lean body mass; MNA, Mini Nutritional Assessment; PEM, protein-energy malnutrition; RCT, randomized controlled trial; TIBC, total iron binding capacity; TSF, triceps skinfold thickness; UCT, uncontrolled trial; WN, well nourished.

$^2$Number of patients analyzed per protocol; number of subjects randomly assigned in brackets.

$^3$To convert kcal to kJ, multiply by 4.184.

$^4$Denotes that patients were not selected according to nutritional status.

$^5$Intended supplementation.

$^6$Poor compliance with supplementation.

$^7$Mainly lung patients discharged after chest infections.

$^8$Estimated total intake.
of hospitalized patients with multiple disorders (47, 49, 183–185). Similarly, PEM is found in a large percentage of the elderly cared for in nursing homes (186–189).

In elderly patients, it is often difficult to link malnutrition to the course of a specific disorder. The degenerative changes of aging lead to a decreased reserve capacity in many organs. Elderly patients often have concurrent disorders in several organ systems, meaning that different disorder-specific pathophysiologic mechanisms can be combined.

PEM is a strong risk factor for increased mortality in the elderly and chronically ill (66, 190–200). A retrospective study of malnourished elderly nursing home patients showed that patients who increased their body weight by >5% over an average follow-up period of 10–11 mo had significantly lower mortality than did malnourished patients whose weights remained stable or decreased (201).

In Table 7 we summarize the results of 26 nutritional treatment studies (202–228; 15 RCTs) of elderly, multiple-disorder patients with and without concurrent PEM. In nearly all of these studies, liquid, oral nutritional supplements were used. The duration of the studies was from 2 wk up to 6 mo, encompassing 12–435 patients. Twenty of the studies (11 RCTs) noted an improvement in anthropometric or biochemical measures in the intervention groups. Ten of the studies (6 RCTs) found an improvement both in anthropometric or biochemical measures and in function. One RCT described how the nutritional supplement reduced the number of fall-related traumas (209). In one study (213, 214), diet therapy given to nonmalnourished patients was associated with both reduced mortality and increased function in general. One recent study (217) showed promising results when it tested the effect of megestrol acetate, which is often used in patients with HIV (229) or cancer-related wasting (230).

Little evidence supports the often-used routine of providing poor-eating elderly with complementary parenteral nutrition during hospital stays. One randomized study evaluated the effect of total parenteral nutrition in 16 malnourished elderly patients. The results of this study showed that the energy from carbohydrates and fats had to total 200% of the basal metabolic rate to stimulate protein synthesis (231). In conclusion, many studies have shown that nutritional treatment of PEM associated with multiple disorders in the elderly can yield positive effects on body composition, and in some cases on muscular strength, well-being, and immune function.

DISCUSSION

Basal compared with medical nutrition

Although treatment recommendations should be based on the results of RCTs, in some aspects, nutritional treatment is an exception to this scientific truism. We do not need randomized studies to validate the life-sustaining value of a nutrient supply in both healthy and sick individuals. However, how nutritional treatment should be pursued and evaluated in connection with imminent or manifest malnutrition associated with an existing disorder is not clear. Disease-associated malnutrition is caused in part by disease-activated biochemical and physiologic mechanisms, including a systemic inflammatory response and neurohormonal adaptations (232), that affect the individual’s appetite, the body’s tissue composition, and the ability of the metabolic systems to metabolize energy and nutrients. In most cases these pathophysiologic changes are adaptive and homeostatic. Nutritional therapy interacts with the metabolic processes specific to the disorder and under such conditions nutritional therapy must be viewed in a broader medical context.

As this literature review shows, our current knowledge is insufficient to provide a firm scientific basis for recommendations on how nutritional treatment should be formulated in most of the reviewed disease groups. Although many studies were performed, the results were heterogeneous. The definition of PEM varied between studies, which is a logical effect of there being no generally accepted definition of the condition. Several studies were limited by insufficient and widely varying patient data, short treatment periods, and a lack of clinically relevant outcome variables. Moreover, the results are difficult to compare and interpret because of the various nutritional therapies used. There are serious methodologic problems in performing randomized controlled nutritional treatment studies. Examples include uncertain adherence to the treatment and the existence of several other concurrent, interacting treatments. In addition, the results are difficult to monitor because the natural course of the chronic disorder is often the cause of the malnutrition. Positive effects can be difficult to detect because of the complexities that exist in nutritional treatment.

One potential weakness in most treatment studies is that the total energy intake can seldom be specified. Nutritional therapy often corresponds to an energy supplement of 200–500 kcal/d (=840–2000 kJ/d), which does not automatically mean that total intake increases accordingly. Elderly patients’ ability to follow a prescribed nutritional intake varies widely (208, 212, 233). Treatment with nutritional supplements can reduce habitual intake as a result of effects on the appetite or abdominal side effects (24, 35, 202, 211, 225). In contrast, several studies showed that supplementation or enrichment of the diet does improve nutrient intake (89, 203, 206, 207, 210, 219, 234–236). In a retrospective study, the use of supplements in nursing homes was described as a nonspecific intervention for weight loss with no regard to diagnoses and management of underlying problems, amount of supplement consumed, and outcome (237).

Also unclear is the degree to which the quality of the supplemented fat affects health other than being a high energy source. Today, meals are usually energy enriched by adding dairy products, ie, saturated fatty acids. Further evaluation is needed to determine whether this is associated with negative effects, such as increased thrombogenic activity.

Effects on anthropometric and biochemical measures compared with function and mortality

An important consideration is the relevance of treatment-induced increases in anthropometric or biochemical variables. Weight loss and hypoalbuminemia are both strongly correlated with increased mortality in sick persons. However, the causality relations are often unclear, ie, does the patient die from or with reduced weight or low serum albumin? It is not certain that a nutrition-induced increase in anthropometric and biochemical variables improves the patient’s prognosis, or that functional capacity or life quality is amended. A balanced nutritional treatment affects the body composition in a specific time sequence. First, the total body fluid volume rises, then the fat, and finally the lean body mass, ie, muscle and protein mass (238, 239). An important aim of nutritional treatment is to restore the lean body mass. In many of the reviewed studies, however, the nutrition treatment led primarily to increased fat storage. On the other hand, an improvement in
Clinical function does not have to be related to increased weight or size of body compartments because nutritional treatment can affect an organ’s function faster than its size and mass (240).

Several lines of evidence indicate that systemic inflammation is one delineator of nonresponse to nutrition treatment (41, 220, 241). We cannot ignore the possibility that even optimal oral, enteral, or parenteral nutrition may have only a limited potential to improve the health of malnourished chronically ill patients, particularly if the malnutrition is linked to inflammation. Pharmacologic modulation of the inflammatory response, by use of substances such as megestrol acetate, thalidomide, pentoxifylline, and dronabinol, may develop as supplemental methods to promote anabolism and appetite and to achieve growth of lean body mass. Physical exercise (211, 242–245) and anabolic or growth hormone therapy may prove to be further complementary treatments.

Conclusion

We reviewed 90 nutrition treatment studies, 50 of which were RCTs. In 59 studies (66%) oral or enteral nutritional supplements were used. Some of the overall effects are summarized in Table 8. Five studies (6%; 2 RCTs) noted improved mortality, 38 studies (42%; 22 RCTs) found improved functional capacity, and 64 studies (71%; 35 RCTs) reported anthropometric or biochemical improvement. Seventeen studies (19%; 14 RCTs) found no improvement in functional capacity. Some of these studies did not have enough power to answer the question they addressed. Eleven studies (10%; 8 RCTs) noted no effects on anthropometric or biochemical indexes. One small study reported that growth hormone may be deleterious in severely ill heart failure patients (72). This is an important consideration in light of a recent report of increased mortality in critically ill patients treated with growth hormone (246). Otherwise, none of the studies summarized showed any serious side effects.

Even though many factors in the interpretation of the reviewed studies are uncertain, the available treatment data indicate that nutritional supplements, either alone as balanced or protein-rich liquid nutrient drinks or in combination with hormonal administration, can have positive effects when given to chronically ill, nonmalignant patients with manifest PEM or at risk of PEM. In malnourished patients with chronic obstructive pulmonary disease, positive treatment results such as improved respiratory function are seen. However, these results are not homogeneous. In elderly women after hip fractures, liquid oral supplementation (particularly protein-rich formulas) promotes rapid rehabilitation. In elderly persons with multiple disorders, nutrition treatment results in increased functional capacity. The results of several trials including malnourished patients with chronic renal failure imply positive effects on anthropometric and biochemical measures (especially when hormonal treatment is given), whereas few clinical outcome data were provided. The effectiveness of PEM treatment in stroke, dementia, chronic heart failure, and rheumatoid arthritis cannot be measured because of a striking lack of published studies in these areas.

Deductions similar to ours were drawn in a recently published meta-analysis of 32 studies of 2286 randomly assigned patients who received oral or enteral dietary supplements (247). In this meta-analysis, however, there were no indications that the treatment advantages were limited to specific disease categories.

We conclude that there is a great need for randomized controlled (preferably placebo-controlled) long-term studies of the effects of defined nutritional intervention programs for certain PEM conditions associated with both specific and multiple disorders. Along with determining biochemical and anthropometric variables, these studies should focus on determining clinically relevant outcomes such as morbidity, functional capacity, health-related quality of life, hospitalization periods, and mortality. In addition, we require experimental and randomized treatment studies to develop and fine-tune pharmacologic methods to modulate systemic inflammatory responses and to stimulate anabolic processes and appetite.

REFERENCES


Table 8
Number of nutrition intervention trials with positive effects or no effect in patients with chronic obstructive pulmonary disease (COPD), with chronic heart failure, during rehabilitation after hip fracture, or with chronic renal failure, and in elderly patients with multiple disorders

<table>
<thead>
<tr>
<th>COPD</th>
<th>Positive effects</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT</td>
<td>OT</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Function or morbidity</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Anthropometric or biochemical index</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Function or morbidity</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Anthropometric or biochemical index</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Rehabilitation after hip fracture</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Function or morbidity</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Anthropometric or biochemical index</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>

1 OT, observational trial (controlled and uncontrolled studies); RCT, randomized controlled trial.
2 Growth hormone to patients with severe heart failure might be deleterious.
3 Patients treated with pentoxifylline.
4 Small study of 18 patients.
5 Reduced mortality in nonmalignant subjects only.
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