Improving Outcomes in

CHRONIC DISEASES WITH SPECIALIZED NUTRITION INTERVENTION

• Abbott Nutrition •

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Introduction

Proper nutrition plays a key role in both the prevention and treatment of many chronic diseases. An ever-growing body of research demonstrates that in treating common chronic diseases, timely, adequate, and appropriate nutrition intervention can improve patients' clinical outcomes, improve their quality of life, and reduce health care costs.

However, despite the recognized link between good nutrition and good health, traditional medical treatment and health care coverage in the United States have not addressed adequate nutrition care. *This must change.* As consumer-driven health care models demand easy and low-cost solutions, nutrition is a critical piece that can no longer be overlooked. Appropriate medical nutrition therapy can be patient administered under medical supervision, help keep patients out of the hospital, and reduce the need for invasive and expensive treatments. Thus, in health care reform models, medical nutrition therapy should be positioned as a *first* treatment of choice, and nutrition care and specialized nutrition products should be routinely reimbursed.

This document summarizes recent research demonstrating the clinical and health care cost benefits of specialized nutrition intervention. It provides an important and critical resource for policy makers and health care professionals as they move forward to define new models for effective health care. Specifically, the document details five common disease states/conditions that have a strong nutritional component:

- Cancer, especially solid tumors
- Diabetes
- Kidney disease
- Sarcopenia (age-related loss of muscle mass)
- Wounds, including pressure ulcers

Costs of Malnutrition and Benefits of Nutrition Intervention: An Overview

In developed nations such as the United States, inadequate or unbalanced nutrition—ie, malnutrition—is not a routine clinical concern. Yet undernutrition and overnutrition frequently contribute to poor health outcomes and rising health care costs. Undernutrition is particularly prevalent in certain US populations, such as hospitalized patients and older adults. As many as half of hospitalized patients[1–5] and 35% to 85% of older long-term care residents[6,7] are undernourished.

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MALNUTRITION IS LINKED TO POOR OUTCOMES

A multitude of studies have verified that undernourished patients and older adults, compared to those who are adequately nourished, are at increased risk for poor outcomes:

- Increased complications and excess morbidity[8–17]
- Increased mortality[18–30]
- Decreased quality of life[6,31–33] (In frail older adults, protein-energy malnutrition can have devastating effects on physical and mental functioning.)

Increased care costs | Because poorly nourished patients experience more complications and increased morbidity compared to adequately nourished patients, their health care costs are significantly higher.[2,4,22] Among hospitalized undernourished patients, a longer length of hospital stay (LOS) contributes to increased total care costs.[3–5,34–42] In some studies, the LOS of undernourished patients was at least twice as long as that of adequately nourished patients.[33,39,41]

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NUTRITION INTERVENTION IMPROVES OUTCOMES

Decreased health risks | Just as a wealth of research reveals the negative outcomes and high costs of malnutrition, many studies confirm the benefits of nutrition intervention for poorly nourished patients:

- Decreased complications and morbidity[43–49]
- Decreased mortality[44,50–54]
- Improved quality of life (QOL)[55–61]

Initiating standardized nutritional guidelines in 11 community and 3 teaching hospitals resulted in significantly shorter LOS (P=0.003) and a trend toward lower mortality rates.[62]

"Literature demonstrates that nutrition services improve modifiable health risks that increase likelihood of developing a chronic condition, lead to adverse events, and raise cost."[67]

Decreased care costs | Routine nutrition screening and assessment for patients identified as malnourished or at risk for malnutrition and appropriate nutrition intervention are key components of good health care. These steps are *cost-effective* measures that help improve clinical outcomes and thus reduce health care costs.[43,63–66] An important measure of improved outcomes with nutrition intervention is hospital LOS. Several studies have shown that hospitalized patients who receive nutritional supplements spend significantly fewer days in the hospital than those who do not.[46,53,68,69]

Nutrition Intervention in Cancer

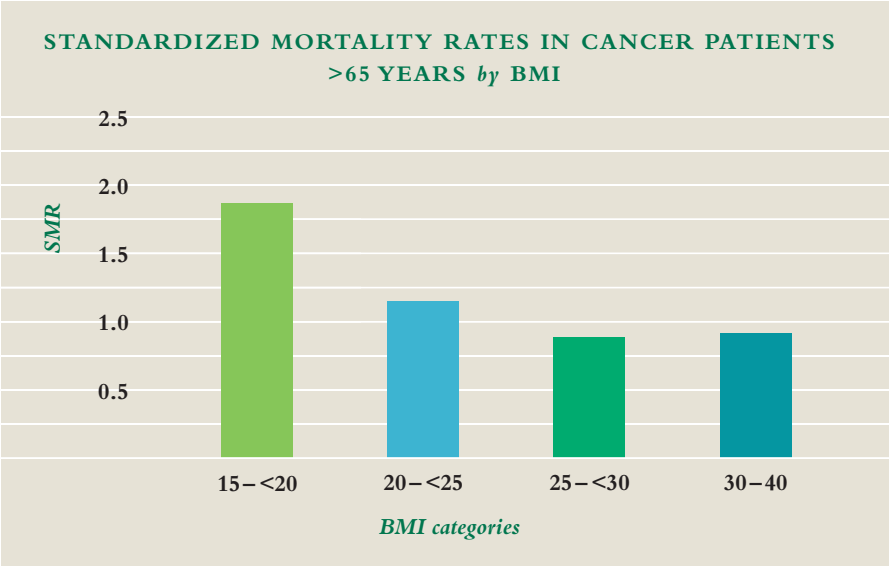
Approximately 1.5 million new cases of cancer are diagnosed annually in the United States, excluding basal and squamous cell skin cancers.[70] Nearly 600,000 of these cases result in death.[70] In addition to the toll this disease takes on patients and their families, the direct and indirect costs to the country and its health care system exceed $104 billion a year.[71]

NUTRITIONAL CHALLENGES IN CANCER

Malnutrition is highly prevalent among people with certain types of cancers and contributes to the human and economic costs of the disease. Prevalence can range from 9% in patients with urological cancer, to 46% in those with lung cancer, to 85% in patients with pancreatic cancer.[72]

Involuntary weight loss is often the presenting symptom in patients with cancer,[73] and it also can develop as the disease and treatment progress. Weight loss in cancer patients is associated with several serious complications:[21,31,74–76]

- Increased toxicity of chemotherapy, which may require a reduction in dose, limiting its effectiveness
- Decreased response to therapy
- Increased morbidity, including infection
- Increased hospital LOS
- Decreased quality of life
- Increased mortality



(Edington et al. *Proc Nutr Soc* 1999;58:655–661. Used with permission.)

In one large prospective study,[21] researchers followed 10,317 patients aged 18 years and older who had either cancer or cardiovascular disease to determine whether nutritional status as indicated by body mass index (BMI) affected rates of health care usage and mortality. Results showed that among cancer patients, a low BMI (<20) was associated with higher rates of consultation with a general practitioner, higher rates of medication use, and higher death rates during follow-up compared to a higher BMI. The figure above shows the standardized mortality rates (SMR, vertical axis) in a sub-group of cancer patients aged 65 years and older according to BMI categories (horizontal axis).

Weight loss from reduced dietary intake can arise from mechanical obstruction due to the tumor, as well as from anorexia caused by pain, cancer treatment, or psychological factors such as depression. Weight loss due to these factors can be reversed with increased dietary intake once the primary issues are addressed.[76]

Even in the absence of obstruction and anorexia caused by treatment and psychological issues, many patients with cancer lose weight. This type of cancer-induced weight loss (cachexia) is a complex syndrome in which altered metabolism of protein, carbohydrate, and lipids produce anorexia, weight loss, and muscle loss.[77] The rate of whole-body protein turnover increases and synthesis of muscle protein decreases.

These metabolic alterations are produced by ongoing inflammation and catabolism caused by compounds such as proinflammatory cytokines

and hormones produced by the tumor itself, as well as by the response of the "host" to the tumor. Thus, cancer-induced weight loss can not be reversed by simply increasing energy intake.[76]

BENEFITS OF SPECIALIZED NUTRITION INTERVENTION IN CANCER-INDUCED WEIGHT LOSS

Eicosapentaenoic acid (EPA) | Research suggests that providing calories and protein along with the omega-3 fatty acid EPA can help modulate the metabolic changes responsible for cancer-induced weight loss. Among other actions, EPA downregulates the release of proinflammatory cytokines and inhibits the catabolism of lean tissue.

Nutrition support with an energy- and protein-dense nutritional supplement that includes EPA, as a part of overall care, has been shown in several studies to promote weight gain, help build lean body mass, improve quality of life, and increase strength and physical activity level in those who gained weight.[57,78,79] Other research has demonstrated that EPA supplementation improves immune function,[80] reduces complications such as infection,[81] and improves survival.[80]

- In a multicenter randomized double-blind clinical trial, 200 patients were randomized to consume either an energy- and protein-dense supplement containing EPA or a control supplement. Post hoc analysis of data found that patients in the experimental group who complied with the recommended daily intake of supplement (48 of 91 patients) experienced significant improvements in weight gain, lean body mass, and quality of life.[78,79]

A meta-analysis of nutrition support in cancer found that EPA supplementation significantly reduced mortality and complications and improved immune function in some patient groups, such as those receiving bone marrow transplantation.[81]

- In a study of 24 patients with advanced pancreatic cancer, those receiving an energy- and protein-dense supplement containing EPA experienced increased physical activity. This change was not seen in the group receiving a similar supplement that did not contain EPA.[57]

- Sixty patients with solid-tumor cancer were randomized to receive either a fish oil supplement containing EPA or placebo for 40 days or until death. The supplement had a significant positive effect on measures of immune function and on length of survival.[80]

- Cancer patients randomized to receive an enteral formula containing fish oil with EPA soon after surgery had fewer total infections than those who received a standard formula.[82]

Arginine, glutamine, and HMB | Arginine and glutamine are both conditionally essential amino acids. Although the body can synthesize them, endogenous synthesis may be inadequate to meet needs during serious illness. HMB (beta-hydroxy-beta-methylbutyrate) is a metabolite of another amino acid, leucine. All three of these compounds have been shown to modulate protein turnover. Supplementation with arginine, glutamine, and HMB enhances protein synthesis, and HMB supplementation also reduces protein breakdown.[83] Thus, these nutrients may benefit patients with wasting diseases, including cancer, sarcopenia, and AIDS.

- Patients with solid tumors who had lost at least 5% of their body weight were randomized to receive either a supplement containing arginine, glutamine, and HMB or an isonitrogenous mixture of nonessential amino acids. The patients who consumed the HMB mixture gained body weight and lean tissue over a four-week period, while those who consumed the control mixture lost weight and lean tissue.[83]

Arginine supplementation also enhances wound healing, and both arginine and glutamine have positive effects on immune function. For that reason, medical nutritional formulas that contain these nutrients are called immunonutritionals. (These formulas may also contain omega-3 fatty acids and nucleotides. Nucleotides are structural components of DNA and RNA that play a significant role in energy production and metabolism.)

- Ninety patients undergoing surgery for head and neck cancer were randomized to receive either an arginine-enhanced formula with fiber or a similar formula without arginine. Those who received the arginine-enhanced formula had significantly fewer wound complications and a significantly shorter LOS than those who received the standard formula.[84]

- In a study of 305 well-nourished patients with gastrointestinal cancer, those who received nutrition support with an immunonutritional product either before surgery or before and after surgery had (1) significantly fewer infectious complications, (2) significantly fewer days of antibiotic therapy, and (3) significantly shorter LOS than those who did not receive this support.[46]

- A series of clinical trials using an immunonutritional formula or a control formula for surgical patients with cancer had varied results, but most found fewer complications—especially infectious

A meta-analysis was conducted of studies in which cancer patients were supplemented with "key nutrients" such as arginine, glutamine, omega-3 fatty acids, and nucleotides. Supplemented nutrition support was associated with a significant decrease in infectious complications and hospital LOS.[87]

complications—and a shorter LOS with the immunonutritional intervention.[85] In one of the trials, care costs were also reduced with the immunonutritional intervention.[86]

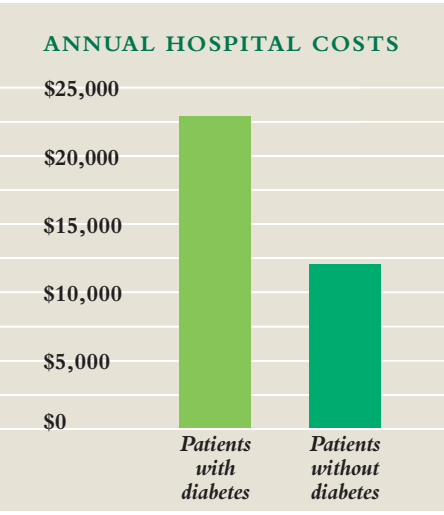
Many randomized, controlled clinical trials have verified that providing specialized nutrition support to cancer patients can reduce complications, reduce the length of their hospital stay, and likely produce health care cost savings.

Nutrition Intervention in Diabetes

Diabetes is a group of diseases characterized by higher-than-normal levels of blood glucose (hyperglycemia) that result when the body does not produce enough insulin or does not use insulin effectively, or both. More than 20 million people in the United States have diabetes, and another 41 million have pre-diabetes and are at high risk of developing the disease. More than 1.5 million new cases of diabetes are diagnosed each year,[88] most of them type 2 diabetes. Two primary defects are linked to this type of diabetes:

- Insulin resistance, in which tissues become less sensitive and less responsive to insulin over time.
- Impaired beta-cell function, in which insulin production is delayed or inadequate.

Obesity is a major risk factor for type 2 diabetes. Typically, this type of diabetes is diagnosed in people aged 40 years or older. Increasingly, however, it is being diagnosed in younger patients as well, as a consequence of the growing incidence of childhood obesity.[88]



The costs of diabetes to the United States and to the US health care system are tremendous—direct health care expenditures total more than $92 billion, and indirect costs from such outcomes as lost productivity total approximately $41 billion more. One of every

10 health care dollars spent in the United States is spent on diabetes and complications of the disease.[88] One publication reported that 1998 hospitalization costs for patients with diabetes were $23,500, nearly twice the $12,000 for patients without diabetes.[89] The increased costs were due to consequences of hyperglycemia.

Costs related to diabetes are high because, over time, chronically elevated blood glucose levels damage multiple organs and cause serious complications:

- Heart disease and stroke
- Hypertension
- Peripheral vascular disease that can result in amputation of a foot or leg
- Retinopathy that can result in blindness
- Kidney disease
- Neuropathy

Furthermore, diabetes increases mortality and decreases quality of life.[88]

NUTRITIONAL CHALLENGES IN DIABETES

Even small improvements in glycemic control help reduce risk for diabetes complications.[90,91] One study showed that every 1% reduction in the mean level of hemoglobin A1C (a measure of glucose control over the previous two to three months) was associated with a 21% reduction in risk for death from diabetes, a 14% reduction in risk for myocardial infarction, and a 37% reduction in microvascular disease.[92]

In a four-year study of 4,744 patients with type 2 diabetes, those whose A1C levels were reduced by at least 1% had fewer primary care and hospital visits than those without a reduction in levels. Mean health care costs among the former were reduced by $686 to $950.[93]

Many people with diabetes must take medications and/or insulin to attain glycemic control, but others are able to manage their condition with appropriate nutrition and exercise. The table at the left shows glycemic control goals established by the American Diabetes Association.[94]

GLYCEMIC GOALS

Hemoglobin A1C	*<7.0%*
Preprandial (fasting) blood glucose	*90–130 mg/dL*
Peak postprandial blood glucose	*<180 mg/dL*

The overall goal of nutrition intervention in diabetes is to achieve and maintain optimal

metabolic outcomes with respect to glucose and lipid levels. Moderating the postprandial (after-meal) glycemic response in people with diabetes is integral to meeting these objectives, as is achieving and maintaining a healthy weight.

Postprandial hyperglycemia is associated with increased risk of mortality.

Postprandial glucose levels correlate with mean blood glucose levels, which are considered a key predictor of overall glycemic control. Several studies have found that postprandial hyperglycemia is associated with increased risk of mortality, especially from heart disease.[95–98] Thus, managing postprandial hyperglycemia is both a management goal and a treatment target in diabetes.

Dietary recommendations for people with diabetes do not differ significantly from those for the general population. However, carbohydrate intake is a dietary focus because it has a greater impact on postprandial glucose levels than protein and fat intake. The postprandial glycemic response to carbohydrate is affected by both the amount and the type of carbohydrate consumed. Whole-grain carbohydrates, for instance, produce a lower and slower glycemic response than processed carbohydrates.

Postprandial glycemic response to various foods can be compared using the glycemic index (GI). The GI ranks carbohydrate foods on a scale of 0 to 100 based on the blood glucose response they evoke compared to a reference food—either white bread or glucose. The higher the GI, the faster a food is digested into glucose and absorbed and the greater the postprandial blood glucose response. There is evidence that glycemic control as measured by A1C levels is better in patients consuming a low-GI diet than in those consuming a high-GI diet.[99]

Some diabetes experts recommend that, together, carbohydrate and MUFAs should provide 60%–70% of energy intake.[101]

In addition to consuming slowly digested carbohydrate, patients with diabetes can help improve glycemic and lipid control by replacing some dietary carbohydrate and saturated fats with fat sources high in monounsaturated fatty acids (MUFAs).[100] MUFAs are derived from plant sources such as olives, canola, nuts, avocados, and sesame seeds. High-MUFA diets do not promote weight gain and are more acceptable than low-fat diets for weight loss by obese patients.[101]

BENEFITS OF SPECIALIZED NUTRITION INTERVENTION IN DIABETES

Glycemic control | Nutritional formulas designed specifically for people with diabetes typically offer reduced amounts of carbohydrate and increased amounts of MUFAs compared to standard formulas. The carbohydrate blends contain slowly digested starch, prebiotics, and

soluble and insoluble fibers for bowel health and other carbohydrate sources, such as fructose and the sugar alcohol maltitol, which also help moderate the glycemic response.

- One hundred sixty-eight subjects with type 2 diabetes were randomized to receive one serving of a formula containing a blend of slowly digested carbohydrate, a commercial diabetes formula, a standard nutritional formula, or a standard weight-control formula in a meal glucose-tolerance test. The formula with the slowly digested carbohydrate blend and the commercial diabetes formula produced a significantly lower glycemic response than the standard formula. The former two formulas also produced a lower glycemic response at 30 minutes than the weight-control formula and trended to a lower glycemic response as measured by area under the curve.[102]

- Thirty enterally fed long-term care patients with diabetes were randomized to a reduced-carbohydrate, high-MUFA formula, or a standard, high-carbohydrate formula. After 3 months, A1C levels were lower in the group receiving the experimental formula (the difference did not reach statistical significance). In addition, the group receiving the experimental formula had 10% fewer complications. The amount of insulin administered was decreased in the experimental-formula group and increased in the standard-formula group.[103]

- Thirty-two patients with type 2 diabetes were randomized to receive either a standard medical nutritional formula (30% fat) or a high-MUFA diabetes formula (50% fat) for 28 days. The postprandial rise in blood glucose levels was significantly lower in the group that consumed the diabetes formula.[104]

- Fifty-two patients with type 2 diabetes were randomly assigned to receive either a formula high in complex carbohydrates (HCF) or a formula with a reduced carbohydrate content and increased MUFAs (RCF). The glycemic response of patients to the HCF was significantly greater than to the RCF.[106]

- A total of 150 obese patients with type 2 diabetes were randomized to either a treatment group or control group. Patients in the treatment group replaced one meal a day with the diabetes-specific meal replacement product and monitored their blood glucose levels. After six months, both groups had lost a significant amount of weight, but fasting blood glucose and A1C levels improved significantly from baseline in the treatment group—not in the control group.[107]

A meta-analysis of studies of nutrition support with diabetes-specific formulas vs standard formulas found that the diabetes-specific formulas resulted in significantly lower postprandial response and peak blood glucose levels.[105]

According to the American Diabetes Association, meal replacements, as part of a weight-loss plan for people with diabetes, can help produce significant weight loss. People who continue to use these products after losing weight may find they are helpful in maintaining that loss.[110]

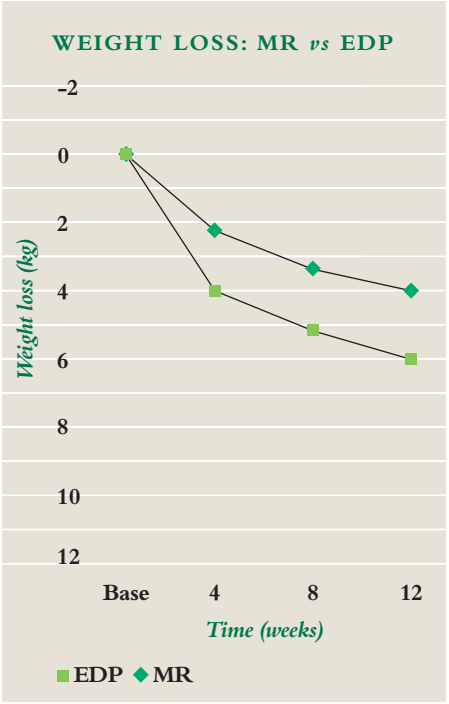
Weight loss | Risk for diabetes complications is increased in patients who are overweight—and more than 85% of people with type 2 diabetes are overweight or obese. Thus, weight management is an important goal for the long-term health outcomes of many patients. Clinical research has shown that a modest weight loss of 5% to 10% of body weight can improve glycemic control, as well as reduce blood pressure and improve lipid profile.[108] Furthermore, 12-year follow-up data for 4,970 overweight people with diabetes showed that intentional weight loss was associated with a 25% reduction in total mortality and a 28% reduction in cardiovascular disease and diabetes mortality.[109]

Overweight people with diabetes can lose weight by following a program of decreased energy intake and increased physical activity. However, compliance to such programs is frequently poor.

Research shows that the success of weight-loss diets can be improved by use of commercial meal replacement (MR) formulas and bars.[111] Whatever diet strategies patients use—food exchanges, low-energy diets, and/or carbohydrate counting—these products offer convenient and healthy alternatives to meals that provide a lot of energy without much nutrient value. They also provide structure and help take the guesswork out of meal planning. Diabetes-specific MRs are especially helpful for overweight people with diabetes because they promote both weight loss and glycemic control.

- Seventy-five obese patients with type 2 diabetes were randomized to one of three groups in a 12-week clinical study. Two groups used MR products (a different formulation for each group). The third group followed a food exchange diet plan (EDP). By week 12, mean weight loss in the pooled MR groups was significantly greater than in the EDP group.[112] (See figure at right.)

- In a one-year prospective study,[104] obese patients with type 2 diabetes were



(Yip et al. *Obes Res* 2001;9 (suppl 4):341S–347S. Used with permission.)

randomized to one of two interventions—either an MR plan or an individualized diet plan (IDP). The percentage of weight loss was significantly greater in the MR group than in the IDP group, and metabolic parameters improved more in the former group as well.[113]

- In a one-year study of two weight-loss strategies, 61 overweight or obese people with type 2 diabetes were assigned to receive either standardized (educational) intervention or a combination intervention that also included 10 mg–15 mg of sibutramine (a weight loss medication that induces feelings of satiety) daily and use of MR products. Compared to the standardized intervention, the combination intervention resulted in significantly greater weight loss, as well as a significant reduction in A1C values.[114]

- A total of 147 people with type 2 diabetes received diet and lifestyle counseling and consumed two diabetes-specific MRs and snack bars daily for 24 weeks. The patients experienced significant decreases in fat mass, fasting blood glucose levels, and A1C values, as well as significant improvements in insulin sensitivity, risk factors such as blood pressure, and quality of life. Thirty percent required a reduction in oral diabetes medication.[116]

A total of 965 obese patients were followed for six years and their medication use and costs recorded. The average annual cost for diabetes and cardiovascular disease medications increased by 96% among patients with a weight loss <5%, while the costs decreased by 8% among those with a weight loss >15%.[115]

A large body of research reveals that consuming appropriate, specialized nutrition can help patients with diabetes control blood glucose levels and lose weight—two measures that help reduce risk for serious and costly complications.

Nutrition Intervention in Kidney Disease

Approximately one in nine Americans—about 20 million people—have chronic kidney disease (CKD), and another 20 million are at risk.[117] Their disease severity ranges from mild to end-stage renal disease (ESRD). The prevalence of CKD is growing in the United States, largely due to the increase in obesity and diabetes.[117]

The table at right shows the classification stages of chronic kidney disease based on patients' glomerular filtration rate (GFR).[118] Glomeruli are small structural units in kidney nephrons that filter wastes from circulating blood. Thus, GFR is an estimate of the filtering capacity of the kidneys. It is usually expressed as milliliters (mL) per minute (min) and adjusted to a standard body size with a surface area of 1.73 meters^2.

STAGES *of* CHRONIC KIDNEY DISEASE

Stage 1	**Kidney damage, normal GFR**	**≥90 GFR**
Stage 2	**Kidney damage, mild GFR**	**60–89 GFR**
Stage 3	**Moderate GFR**	**30–59 GFR**
Stage 4	**Severe GFR**	**15–29 GFR**
Stage 5	**Kidney failure**	***<15 or dialysis***

GFR = mL/min/1.73m^2

Healthy kidneys not only filter excess water and wastes such as urea from protein degradation from the blood, but they also play a role in control of blood pressure, maintenance of electrolyte balance, production of red blood cells, and metabolism of bone.[119] Diseased kidneys are no longer able to perform their functions to full capacity, resulting in the accumulation of wastes in the blood.

Over time, CKD reduces the number of functioning nephrons, thus overloading those that remain.[119] The consequences of declining kidney function include hypertension, anemia, malnutrition, bone disease, neuropathy, decreased functioning and well-being, and, eventually, kidney failure (ESRD). CKD also is associated with increased risk for mortality, especially from cardiovascular disease.[120]

It is estimated that Medicare saves $250,000 for every patient with CKD who does not progress to dialysis.[121]

Approximately 450,000 people in the United States with CKD have declined to stage 5—kidney failure.[121] At this stage, patients require dialysis or kidney transplantation to survive. Health care costs for patients with ESRD are significant. Medicare alone spends nearly $20 billion for their care, which is 6% of total Medicare expenditures.[121]

Up to 40% of patients with CKD are malnourished, and risk for malnutrition increases as CKD progresses.[122] In fact, as many as 70% of patients on dialysis may be malnourished.[117]

NUTRITIONAL CHALLENGES IN CKD

Malnutrition, which is common among people with CKD, further increases their risk for negative outcomes.

- Undernourished patients with ESRD have significantly increased morbidity compared to adequately nourished patients, including a 27% to 43% increased risk for stroke.[13,16]
- In CKD patients, several indicators of nutrition status are independently associated with increased mortality.[123–125]
- The increased morbidity of malnourished CKD patients results in more and longer hospitalizations and higher health care costs.[4,41,42,126,127]
- Malnutrition in CKD patients negatively affects functioning and quality of life.[128,129]

Because poor nutritional status in CKD is caused by metabolic disturbances and not just by insufficient dietary intake, it is sometimes called uremic malnutrition.[130]

Malnutrition results, in part, from reduced dietary intake related to anorexia, nausea and vomiting, changes in taste and smell, and dietary restrictions.[128] Also implicated are heightened catabolism and metabolism, which increase as the disease progresses. Inflammation is linked to the increased energy expenditure seen in CKD.[129]

Issues other than malnutrition must be considered in planning nutrition intervention for CKD patients. Because kidney function is inadequate, metabolic abnormalities appear, including anemia, acidemia, high blood levels of potassium, and disruption of the calcium-vitamin D metabolic pathway. Vitamin D is activated in the kidneys, and as the kidneys fail, this activity decreases, contributing to decreased calcium absorption from the gastrointestinal tract. The resulting hypocalcemia stimulates the parathyroid gland to excrete parathyroid hormone, producing hyperparathyroidism. Metabolic abnormalities such as acidemia and hyperparathyroidism can exacerbate malnutrition by increasing protein catabolism.[119]

As indicated previously, as urine output decreases, waste products in the blood are not filtered out and can build to dangerous levels. High blood phosphorus levels promote calcium loss from bone. High blood potassium levels can cause irregular heartbeat and even death. Too much sodium can cause fluid retention and worsen hypertension.[117,119] Fat-soluble vitamins A and E also may accumulate under these conditions.[119] Finally, failing kidneys are increasingly unable to handle the function of protein degradation and excretion of urea nitrogen.[119]

Failing kidneys are increasingly unable to handle the function of protein degradation and excretion of urea nitrogen.

Dialysis presents another set of nutritional challenges. In hemodialysis, blood is filtered through a semi-permeable membrane outside the body, along with a solution (dialysate) that helps remove wastes and excess fluid. However, hemodialysis can stimulate protein catabolism,[130] and some vitamins and minerals may be lost in the filtering process. In peritoneal dialysis, the body's peritoneal membrane inside the abdomen is used as the filter. A solution that removes wastes is infused into and remains in the abdomen for a time, and then is drained out. Since this solution contains electrolytes and glucose, patients on peritoneal dialysis can absorb significant calories each day. These calories must be considered in dietary planning. However, the resulting "over-nourished" appearance of these patients can mask protein malnutrition.[119] Thus, nutrition intervention for patients with CKD must consider their disease stage, nutritional status, metabolic abnormalities, and for patients with ESRD, type of dialysis.

BENEFITS OF SPECIALIZED NUTRITION INTERVENTION IN KIDNEY DISEASE

Although kidney disease cannot be cured, the rate of decline may be slowed by clinical interventions, such as careful glucose control in diabetes, strict blood pressure control, use of angiotensin-converting enzyme inhibitors and receptor blockers, and dietary modifications.

Several systematic reviews and meta-analyses have shown a significant reduction in risk for ESRD (31%–40%) with reduced-protein diets.[131–134] A large clinical trial found that blood pressure control along with reduced protein intake helped delay disease progression by 41%.[135] Another clinical trial with a supplemented very-low-protein intake found dialysis was delayed, with a beneficial effect on mortality.[137]

Dietary modifications | Following is a summary of some dietary modifications recommended for predialysis and dialysis CKD patients:

- **Protein.** Reduced protein intake is typically advised for predialysis patients to reduce the workload of the kidneys.[131–135] The National Kidney Foundation recommends an intake of 0.6 g to 0.75 g/kg body weight/day, although a protein intake as low as 0.3 g/kg/day supplemented with amino acids and/or keto acids has been shown to be safe and effective.[136] To avoid malnutrition, energy levels must be maintained. An increased protein intake of 1.2 g–1.3 g/kg/day is recommended for dialysis patients because some protein may be lost in the dialysate. For both categories of patients, at least 50% of the protein should be of high biological value.[119]

- **Sodium, potassium, phosphorus, and calcium.** Restricted intake of sodium, potassium, and phosphorus throughout the progression of CKD can help reduce risks associated with accumulation of these minerals in the body. (Potassium restriction is not always necessary in peritoneal-dialysis patients.) Foods that are rich in phosphorus, such as dairy products, nuts, and legumes, are also good sources of calcium. Thus, balancing the intake of phosphorus and calcium is important in nutrition intervention. Patients may need to take phosphate binders and calcium and/or vitamin D supplements.[117]

- **Vitamins and minerals.** Of the fat-soluble vitamins A, D, E, and K, only vitamin D supplementation is typically recommended for CKD patients. Vitamins A and E may accumulate in the body as kidney failure progresses, and excessive amounts of vitamin K can have harmful effects. However, water-soluble vitamins such as B-complex vitamins may need to be supplemented because of dialysate losses.[117] Intravenous iron is typically given during hemodialysis to replace iron lost in blood and decreased kidney production of erythropoietin.

As urine output decreases with disease progression, fluid intake must be restricted.

- **Fluids.** The volume of fluid intake must match volume of urine output in patients who are in CKD stages 1 through 4. As urine output decreases with disease progression, fluid intake must be restricted (typically not until stage 4). In stage 5, fluid intake must match the volume removed during dialysis in addition to fluid losses from evaporation and any remaining urine output.[117]

Predialysis patients who adhere to these dietary modifications may be able to slow the progression of their disease. Dialysis patients may reduce their risk for malnutrition, and thus their risk for morbidity and mortality.

Nutritional supplementation | Some CKD experts have found oral and/or tube fed nutritional supplementation to benefit CKD patients.[122,128,130,138,139] Supplementation improves dietary intake[128] and thus can help minimize risk for malnutrition in patients with dietary restrictions. Patients with ESRD may be supplemented during dialysis, and commercial standard formulas and CKD-specific formulas also are available.

A systematic review and meta-analysis of oral supplementation and tube feeding in dialysis patients concluded that such interventions can increase serum albumin concentrations and improve total dietary intake. As a result, clinical outcomes may improve.[128]

Commercial CKD-specific formulas vary by brand, and different products are available for predialysis and dialysis patients. One formula for patients in predialysis stages of CKD, for instance, offers a reduced level of protein—10.6 g per serving—while its counterpart for dialysis patients offers 19.1 g of protein. Both these formulas have reduced levels of potassium compared to standard formulas. Furthermore, both are energy-dense formulas that offer twice the calories as a standard formula in the same volume. Thus, these formula features can help CKD patients follow the dietary recommendations that are appropriate for them. In one study of 79 normally nourished hemodialysis patients, those randomized to consume one of two CKD-specific formulas as their sole source of nutrition for two weeks had better serum phosphorus values and calcium-phosphorus balance than those who consumed a standard formula.[140]

CKD-specific formulas have features that can help patients follow recommendations for protein, potassium, and fluid intake.

Several studies show the benefits of oral supplementation in CKD patients:

- Eighty-five hemodialysis patients with protein-energy malnutrition were provided with a CKD-specific oral supplement for six months. With this intervention, several indicators of nutritional status improved significantly.[139]

- In a four-week nonrandomized pilot study, 20 hemodialysis patients with low serum albumin values (a marker of malnutrition-inflammation complex syndrome) were given two nutritional formulas during dialysis. One product was a CKD-specific formula, the other contained anti-inflammatory components. Serum albumin levels increased significantly in the treatment group, but not in untreated controls.[141]

- Twenty-six patients on hemodialysis who were determined to be at high risk for hospitalization using the hemodialysis prognostic nutrition index (HD-PNI) score were supplemented orally with calories and protein for three months. At that point, the HD-PNI scores indicated significant reduction of risk.[142]

- Seventeen hemodialysis patients with a low normalized protein catabolic rate (nPCR, an estimate of protein intake) and low protein intake as indicated in a food diary were given dietary supplements for two months. Low nPCR values are associated with increased risk for morbidity and mortality. At two months, the supplements had significantly increased both nPCR and protein intake.[143]

Research shows that following dietary recommendations for protein, micronutrients, and fluid intake may help predialysis CKD patients delay the initiation of dialysis. In people with ESRD, appropriate nutrition intervention can reduce risk for malnutrition and the increased morbidity and mortality associated with it.

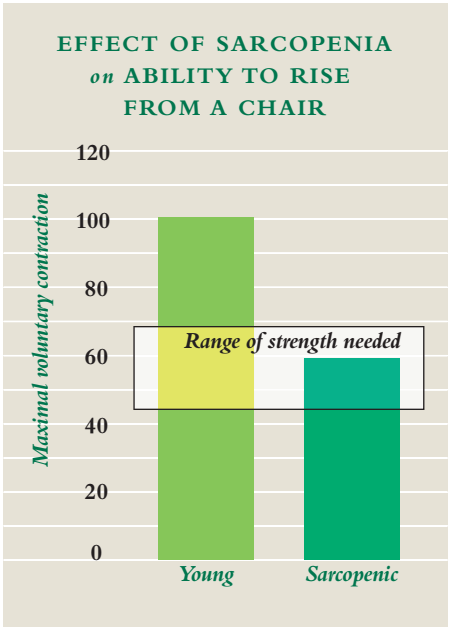
Nutrition Intervention in Sarcopenia

In middle age, people begin to lose skeletal muscle mass at the rate of about 8% a decade.[144–146] After the age of 75 years, this process accelerates to about 15% a year.[146] This unintentional age-related loss of muscle mass is called sarcopenia. Experts do not agree on how much muscle loss constitutes sarcopenia, how to measure muscle loss, or whether, since it is a normal part of aging, it should be considered a disease.[147]

In one study of 4,504 adults 60 years of age and older, those with severe sarcopenia had a two to three times greater likelihood of functional impairment and disability than those without sarcopenia.[150]

Moderate or severe sarcopenia may affect as many as 30% of people over 60 years of age.[148] In one study, more than half of women older than 80 years were sarcopenic.[149] This high prevalence of sarcopenia is cause for concern because the condition is linked to several negative outcomes:[150–152]

- Reduced muscle strength
- Impaired functioning
- Increased physical disability and frailty
- Increased dependency
- Decreased quality of life
- Increased morbidity and mortality



Roubenoff R: Sarcopenia: Inevitable, But Treatable. Available at http://www.unsystem.org/scn/archives/scnnews19/ch12.htm. Accessed September 22, 2006.

As sarcopenia progresses, mobility is increasingly impaired and risk for falls and fractures increases.[151] People with the condition may become increasingly sedentary, which in turn causes further loss of muscle mass. Lack of physical activity may result in an increase in body fat, which masks the loss of lean muscle.

The figure on page 18 shows how loss of muscle strength affects the ability to perform an action, such as rising from a chair. The bar on the left represents young healthy adults and that on the right represents older people with sarcopenia. The figure shows that the latter lack the strength to perform the action. (MVC is maximal voluntary contraction. Actions that exceed one's MVC cannot be performed.)[152]

Health care costs of people with sarcopenia increase as they become increasingly disabled. In the United States in 2000, the estimated direct health care costs related to sarcopenia totaled $18.5 billion—about 1.5% of the total health care expenditures that year. Excess annual health care expenditures were $860 and $933 for every man and woman with sarcopenia, respectively.[153]

A 10% reduction in the prevalence of sarcopenia would save $1.1 billion a year in US health care costs.[153]

The causes of sarcopenia are not well understood, but several factors have been proposed:[148,151,154–156]

- Loss of motor neurons and skeletal muscle fibers
- Decreased production of and muscle response to hormones that help maintain and increase muscle mass, such as testosterone and growth hormone
- Decline in muscle anabolic response to nutrient intake (decreased protein synthesis resulting in a chronic imbalance of protein anabolism and catabolism)
- Increased production of inflammatory mediators, such as cytokines
- Oxidative damage
- Decreased physical activity
- Anorexia and decreased energy and protein intake

Several of these factors, such as loss of muscle fibers and decreased protein synthesis, are age-related changes, and effective intervention is not

currently available. Others, such as decreased physical activity and dietary intake, may be changed by simple and relatively inexpensive interventions.

One review of studies of protein-energy supplementation in people with sarcopenia found greater gains in muscle mass and strength compared to placebo.[159]

NUTRITIONAL CHALLENGES IN SARCOPENIA

Because sarcopenia is caused by multiple factors, studies of interventions with dietary supplementation have not always produced positive results. Some research using a standard oral nutritional supplement with a program of resistance training showed a positive effect of the training on muscle mass, strength, and functioning, but not an effect from the supplement.[157–159] Other studies, however, have found a positive impact of supplementation on those outcomes.[160,161]

One issue in nutritional intervention in sarcopenia is determining appropriate protein intake.

One issue in nutritional intervention in sarcopenia is determining appropriate protein intake. The current recommended intake is 0.8 g/kg/day, or 56 g for a 154-lb male. However, some clinicians and researchers are challenging this recommendation. They propose that a higher protein intake of 1.0 g to 1.6 g/kg/day may help offset the increasing inefficiency of protein synthesis that accompanies aging.[151,160,162] One study of healthy older people found that a protein intake of 1.6 g/kg/day for three months enhanced the effect of a resistance training program more than an intake of 0.8 g/kg/day.[163]

BENEFITS OF SPECIALIZED NUTRITION INTERVENTION IN SARCOPENIA

Amino acids | While studies have not uniformly shown a positive effect of protein-energy supplementation in sarcopenia, studies of supplementation with essential amino acids (EAA) have.[151,164] EAAs are amino acids that the body cannot synthesize; thus, they must be provided in dietary intake. EAAs, and especially branched-chain amino acids such as leucine, stimulate the synthesis of muscle protein in both younger and older people.[151,165–167]

- In a study of amino acid infusion in healthy older adults, significantly increased amino acid transport and delivery to the legs, as well as increased muscle protein synthesis, were seen. The researchers concluded that increased intake of protein or amino acids can help maintain muscle mass in older people.[165]
- Amino acids given by bolus to younger and older subjects stimulated muscle protein synthesis in both groups.[166]
- In a study of 14 older subjects given amino acids either orally or intravenously, researchers found that increased availability of amino

acids stimulates the rate of muscle protein synthesis independent of the route of administration.[167]

Beta-hydroxy-beta-methylbutyrate (HMB) | HMB, a product of leucine metabolism, has been used by young people in resistance training to decrease muscle damage and degradation and increase lean body mass.[168] Recently, studies have shown that HMB supplementation can benefit older people as well.[168,169]

Thirty-one older men and women were randomly assigned to receive capsules containing either HMB or placebo for eight weeks. During that period, the subjects also participated in a strength training program. HMB supplementation tended to increase lean body mass and decrease body fat in the treatment group.[168]

In another study, 57 women ages 62 to 90 years of age were randomized to receive either a drink containing HMB and the amino acids arginine and lysine or one of two placebo drinks. After 12 weeks, there was a 17% improvement in a "get-up-and-go" functionality test in the treatment group (no change in the control group), as well as significant improvement in leg and hand-grip strength.[169]

Supplementation with HMB, arginine, and lysine produced a 17% improvement in a "get-up-and-go" functionality test.

Research shows that in older people, nutrition intervention with protein-energy supplements containing increased levels of protein or amino acids and HMB may increase muscle mass and strength and improve functionality.

Nutrition Intervention in Wound Healing

Discussion of the benefits of nutrition intervention in wound healing is complicated by the variety of wounds—eg, surgical wounds, burns and other trauma wounds, and pressure ulcers—described in the medical literature. It is also difficult to determine the total number of people who develop wounds that require medical treatment each year in the United States. However, some data are available:

- Approximately 1.1 million burn injuries require medical attention, and about 50,000 of these require hospitalization annually.[170]
- The incidence of pressure ulcers is estimated to be up to 38% in general acute care, up to 24% in long-term care, and up to 17% in home care patients.[171] Older immobilized adults are at increased risk for pressure ulcers.

In a 12-week study of 2,420 long-term care residents with or at risk for pressure ulcers, 28% had an existing ulcer and 19% developed a new ulcer.[172]

Much of the literature on wound healing relates to pressure ulcers. A pressure ulcer is an area of skin that breaks down when a person is immobilized for too long, as is common with bedridden older adults. Pressure against the skin over bony areas, such as elbows and heels, reduces the blood supply to that area, and the affected tissues die. A pressure ulcer starts as reddened skin (stage 1), but without treatment gets progressively worse, forming a blister (stage 2), then an open sore (stage 3), and finally a crater (stage 4).

The estimated annual cost of treating pressure ulcers in the United States is $3 billion.[48]

Pressure ulcers are associated with increased risk for morbidity, such as septic infection and a four- to six-fold increased risk for mortality.[173,174] Thus, pressure ulcers increase health care costs for older adults, especially when hospitalization is necessary. In a 1996 year-long study of 30 long-term care residents, the subjects developed 45 ulcers. The mean cost of treatment per patient was $4,647 (including hospitalization). Eighty percent of the total cost of treatment was generated by the 4% who required hospitalization.[175] (Rate of healing of other kinds of wounds, such as burns, also affects length of hospital stay and, thus, health care costs.[176,177])

Additional costs are borne by long-term care facilities that are sued because a resident develops pressure ulcers.[178]

NUTRITIONAL CHALLENGES IN WOUND HEALING

The wound healing process is a complex series of events that begins at the moment of injury and can continue for months or even years as collagen, the main protein in connective tissue, is produced and matures. Nutrition, wound risk, and wound healing are linked in multiple ways, including the following:[15,19,179,180]

- Protein-energy malnutrition increases risk for pressure ulcers, in part due to loss of the "cushioning" effect of body mass when body mass is lost, and to compromised skin integrity.
- Wounds, especially serious wounds such as burns, increase energy needs.
- Nutrients, such as protein, are lost in wound fluid (exudates).
- Physiologic stress caused by wounds can increase need for dietary sources of conditionally essential amino acids.
- Nutritional supplementation can reduce risk for pressure ulcers and promote wound healing.

In one study, burn patients who consumed less than 30 Cal/kg/day were significantly more likely to have complications and to die than those who consumed more than 30 Cal/kg/day.[181]

To enhance wound healing, patients need adequate energy and protein, and they may benefit from supplementation with amino acids and several micronutrients as well.[179,180]

Energy | Adequate energy is essential for collagen synthesis and other wound-healing processes. For people with pressure ulcers, 30 to 35 Cal/kg/day are recommended, but recommendations may differ for people with other kinds of wounds, such as severe burns.

Protein | Adequate protein intake is essential in all stages of wound healing. The intake recommended for pressure ulcer healing is 1.25 g to 1.5 g/kg/day, although some people might require more. Some studies have shown a positive healing effect from intakes at least 1.5 g/kg/day.[179] (Protein intakes greater than 1.5 g/kg/day may cause dehydration. Also, the amount of protein patients can tolerate depends on their liver and kidney function. Thus, patients receiving higher protein intakes should be monitored carefully.)[182]

Amino acids | Arginine and glutamine—especially arginine—promote wound healing. Under conditions of stress, such as wounding, the body cannot synthesize sufficient amounts of these amino acids to meet metabolic needs, so supplementation is recommended.

- Arginine enhances collagen deposition and supports the immune system, which in turn promotes restoration of injured tissues.[179,180]

- Glutamine stimulates collagen production, serves as a fuel source for some of the rapidly dividing cells that are part of the healing process (eg, fibroblasts and macrophages), and enhances the immune system.[179,183]

- The leucine metabolite HMB also increases collagen deposition and appears to have other positive effects on wound healing.[179]

Vitamins and minerals | Vitamins A and C and zinc play a role in collagen synthesis and strengthening of the healing wound. These micronutrients also enhance immune function.[179,180]

Patients also need adequate fluid to ensure good skin turgor and blood flow to the wound. Fluid intake must compensate for fluids lost in exudate and from evaporation at the wound site.[179] Furthermore, patients in air-fluidized beds require an additional 10 mL to 15 mL of fluid/kg body weight to prevent dehydration caused by the beds' drying effect.[182]

A meta-analysis of five randomized controlled trials that included a total of 1,224 older adult patients showed that oral nutritional supplementation can significantly reduce the risk of developing pressure ulcers in that population (by 25%).[48]

BENEFITS OF SPECIALIZED NUTRITION INTERVENTION IN WOUND HEALING

Studies have shown that, compared to routine care, any nutritional intervention (ie, with either a standard or a specialized formula) can reduce risk for pressure ulcers and may help wound healing.[48,184] On the other hand, some studies have shown that specialized nutrition intervention with extra protein and energy, as well as with some combination of arginine, glutamine, HMB, vitamin C, and/or zinc, has a greater effect on wound healing than standard intervention.[48]

Protein/energy | Since wounding increases protein and energy needs, supplementation with formulas containing extra protein and calories promotes wound healing.[49,181,185–187]

- A study of 50 home-dwelling older adults referred to a nursing service for wound management found that provision of energy- and protein-dense oral supplements significantly improved some indices of wound healing.[49]

- In a small (12 patients) randomized controlled trial, supplementation with a high-protein formula resulted in healed pressure ulcers in four of six patients. In contrast, none of the wounds in the group given a standard formula healed.[185]

High-protein formulas are associated with improved pressure ulcer healing compared to standard formulas.

- A controlled clinical trial of patients with pressure ulcers demonstrated that the surface area of the wounds in those who received a high-protein formula for eight weeks were significantly reduced compared to those in patients who received a standard formula.[186]

- Eighty-nine long-term-care residents with pressure ulcers were randomized to receive standard care plus a fortified collagen protein hydrolysate supplement or standard care plus placebo. After eight weeks, the rate of pressure ulcer healing in the treatment group was approximately twice that of the rate in the control group.[187]

- In a prospective study of 103 burn patients, those who consumed more than 30 Cal/k/day of protein had significantly reduced morbidity, mortality, and hospital LOS compared to those with a lower protein intake.[181]

Amino acids and micronutrients | Several studies have shown that formulas with increased amounts of these substances help promote wound healing.[176,177,188–191]

- Sixteen hospitalized patients with pressure ulcers were randomized to receive a standard hospital diet, a standard diet plus high-protein and energy supplements, or a standard diet plus high-protein and energy supplements containing additional arginine, vitamin C, and zinc. Only patients receiving the supplements with the extra arginine and micronutrients demonstrated clinically significant improvement in pressure ulcer healing.[188]

- Thirty-nine patients with pressure ulcers received a high-protein supplement that contained additional arginine, vitamin C, and zinc. After three weeks, wound area was reduced significantly compared to baseline, and wound condition was improved.[189]

- Sixty-six patients undergoing surgery for gastric cancer were randomized to receive postoperative nutrition support with either a formula supplemented with arginine, omega-3 fatty acids, and RNA or an unsupplemented formula. Patients who received the supplemented formula demonstrated significantly better surgical wound healing and fewer wound complications than those receiving the standard formula.[190]

- In a controlled clinical trial, 48 patients with severe burns were randomized to receive or not receive glutamine supplementation with their enteral nutrition. Wound healing was faster and hospital LOS significantly shorter in the glutamine-supplemented group than in the control group.[176]

- Forty patients with severe burns were randomized to receive or not receive glutamine-supplemented enteral nutrition. On post-burn day 30, the wounds of glutamine-supplemented patients showed significantly greater healing than those of the control, and their hospital LOS and care costs were significantly less.[177]

- Researchers created wounds in 35 healthy older adults and randomly assigned them to receive either a supplement containing a specialized amino acid mixture (arginine, glutamine, and HMB) or a supplement without that mixture. Those who received the specialized supplement demonstrated a significant increase in collagen deposition.[191]

In two studies of burn patients, glutamine supplementation of enteral nutrition was associated with a significantly decreased hospital LOS.[176,177] One of the studies found that this reduced LOS translated into a significant reduction in hospital costs.[177]

Research shows that in people with wounds, nutrition intervention with high-protein formulas and those containing arginine, glutamine, HMB, vitamins A and C, and zinc may promote wound healing, shorten LOS, and reduce health care costs.

Conclusion

Research demonstrates that in cancer, diabetes, chronic kidney disease, sarcopenia, and wounds—diseases and conditions with a strong nutrition component—timely, adequate, and appropriate nutrition intervention can improve patients' clinical outcomes, improve their quality of life, and reduce health care costs.

Nutritional needs are complex and vary by individual and disease state. Care is most effective when nutrition is tailored by the health care professional to meet specific patient needs. Nutritional products and treatments are highly differentiated; therefore, effective treatment of acute and chronic disease requires disease-specific nutrition.

Because of its proven efficacy and cost-effectiveness, appropriate nutritional care should be considered standard practice in the treatment of chronic diseases.

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