Review

Modular Protein Supplements and Their Application to Long-Term Care

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ABSTRACT: Modular protein supplements are added to either the diet or enteral formula to increase the protein or amino acid intakes of people who are nutritionally compromised. Protein supplements are aggressively marketed to long-term care clinicians because protein energy malnutrition and wounds are a common problem in this care setting. It can be challenging for clinicians to distinguish one product from another and to determine the best product for a specific application or nutrition care goal. Modular protein products can be sorted into 4 categories: (1) protein concentrates derived from a complete protein such as milk, soy, or eggs; (2) protein concentrates derived from collagen, either alone or in combination with a complete protein; (3) doses of 1 or more dispensable (nonessential) amino acids; and (4) hybrids of the complete or collagen-based proteins and amino acid dose. Modular protein supplements are generally provided either as a substrate for protein synthesis or as a source of 1 or more amino acids that may be conditionally indispensable (conditionally essential) under certain disease conditions. This review provides guidelines for the use of modular protein supplements according to their intended physiologic function and the assessment and nutrition care goals of the long-term care resident.

Protein energy malnutrition (PEM) is thought to be a significant problem in the long-term care (LTC) population[1] and is associated with increased morbidity and mortality, including impaired wound healing, pressure ulcers, infections, and mortality.[2] Protein malnutrition has several potential causes, including inadequate intake of both energy and protein and inadequate intake of protein in the presence of adequate energy.[3] These conditions can be reversed with provision of adequate protein and energy. Use of a modular protein supplement is a common intervention strategy for the treatment of PEM in the LTC setting. However, there are no widely accepted clinical guidelines for the use of modular protein supplements in the treatment of PEM.

A multitude of modular protein supplements is currently available on the market for use in LTC residents with PEM. Modular supplements are defined by the Centers for Medicare and Medicaid services as nutritionally incomplete/modular nutrients.[4] In the case of modular protein supplements, the term refers to proteins/amino acids or a combination of protein and other modular nutrients. A tremendous growth in the number and diversity of modular protein products has made it increasingly difficult for clinicians to distinguish one product from another and to determine the best product for a specific application or nutrition care goal.

The amino acid content of various protein supplements can differ dramatically. Most of the modular protein products fall into 1 of 4 categories: (1) protein concentrates derived from a source of complete protein such as milk, soy, or eggs; (2) protein concentrates derived from collagen, either alone or in combination with a complete protein; (3) doses of 1 or more dispensable (nonessential) amino acids; and (4) hybrids of the complete protein and amino acid dose. A given quantity of a supplement from one category (eg, 5 g) is not nutritionally equivalent to the same quantity of protein from a different category. Therefore, it is the responsibility of the practitioner to select a nutritionally appropriate product for a given intervention.

The following paper will discuss issues relevant to the use of modular protein supplements in the LTC setting. It will briefly review the basis of dietary protein and amino acid requirements, with a focus on the needs of older adults and on amino acids that may become conditionally indispensable (condition-

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ally essential) under conditions of physiologic stress common in the LTC setting. A survey of modular protein supplements is included with discussion of proteins intended as a substrate for protein synthesis and purified amino acids intended to meet additional nutrition requirements created by physiologic stress.

The scope of this review has been limited specifically to modular protein supplements intended for use in adults; an assessment of nutritionally complete supplements or enteral formulas that contain all 3 macronutrients and micronutrients has not been included. We have evaluated the protein quality of modular supplements that provide 8 or 9 indispensable (essential) amino acids with the procedure recommended by the Institute of Medicine (IOM)[5] and through a review of the peer-reviewed literature. For products that provide single or combinations of dispensable amino acids (DAAs), published physiologic mechanisms and clinical evidence have been summarized.

The goal of the current review is to provide a framework for the LTC practitioner to use when evaluating a protein supplement for a given dietary application or clinical goal in the LTC setting. To achieve this end, a clinical algorithm has been developed. The algorithm is intended to guide the practitioner to intervention strategies that are appropriate according to the resident's current energy, protein, and fluid intakes and his/her ongoing clinical progress.

Basis of Dietary Protein and Amino Acid Requirements

It is well known that body proteins are composed of amino acids linked together in a polypeptide chain, 9 of which cannot be synthesized by humans and are considered to be indispensable amino acids (IAAs, Table 1). These were formerly known as the essential amino acids. IAAs may also be used for methyl group donation and the synthesis of other essential molecules, such as neurotransmitters, hormones, carnitine, creatine, and niacin.[5] Humans have a dietary "requirement" for each of these amino acids; however, part of the methionine requirement can be met by dietary cysteine and part of the phenylalanine requirement can be met by dietary tyrosine. This ability of these amino acids to "spare" their IAA precursors is reflected whenever the requirements for methionine and phenylalanine are described.

In addition to the 9 IAAs, another 11 amino acids are carried by tRNAs during protein synthesis and incorporated into body proteins. These DAAs (Table 1) will also be used to synthesize other essential compounds, such as nucleic acids, heme, glutathione and nitric oxide.[5] The DAAs were formerly known as the nonessential amino acids. Although the body can make these amino acids, their synthesis requires either a precursor amino acid or nitrogen donation from other amino acids. Therefore, although a healthy person does not have a requirement for any of these specific DAAs, there is a requirement for dietary amino acids to act as substrates for the synthesis of the DAAs. This is known as the *nonspecific nitrogen requirement*.

Table 1
Classification of amino acids

Indispensable*	Dispensable for healthy individuals†	Conditionally indispensable‡
Histidine	Alanine	Arginine
Isoleucine	Aspartic acid	Cysteine
Leucine	Asparagine	Glutamine
Lysine	Arginine	Glycine
Methionine	Cysteine	Proline
Phenylalanine	Glutamic acid	Tyrosine
Threonine	Glutamine	
Tryptophan	Glycine	
Valine	Proline	
	Serine	
	Tyrosine	

*Also known as essential amino acids.
†Also known as nonessential amino acids.
‡Also known as conditionally essential amino acids. Dietary source may be required when endogenous synthesis cannot meet metabolic need (eg, due to a disease process or physiological stress).
Adapted from Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients) with permission from the National Academy of Sciences, courtesy of the National Academies Press, Washington, D.C. © 2005.

A third category of amino acids includes those that may become indispensable under certain conditions. People with various disease states or under physiologic stress may not be able to make enough of certain DAAs. Under these conditions, these amino acids would become "conditionally indispensable." Amino acids in this category were formerly known as conditionally essential. The significance of conditionally IAAs in the LTC setting will be discussed later in this document.

Because we need to consume each of the IAAs in proportion to their use and we need additional amino acids for the synthesis of the DAAs, the "protein requirement" for humans is the sum of the requirement for each of the IAAs plus the nonspecific nitrogen requirement. The 2005 dietary reference intakes (DRIs)[5] state that the average protein requirement for adult men and women of all ages is 0.66 g/kg/day protein and that the recommended dietary allowance (RDA) is 0.8 g/kg/day protein. These values assume "good-quality protein," where protein quality is an expression of a protein's ability to provide the nitrogen and amino acid requirements for growth, maintenance, and repair.[5] This amount of good-quality protein will provide both the necessary variety and proportion of IAAs and the additional amino acids needed for most healthy older adults. However, individuals in various disease states or under physiologic stress may have

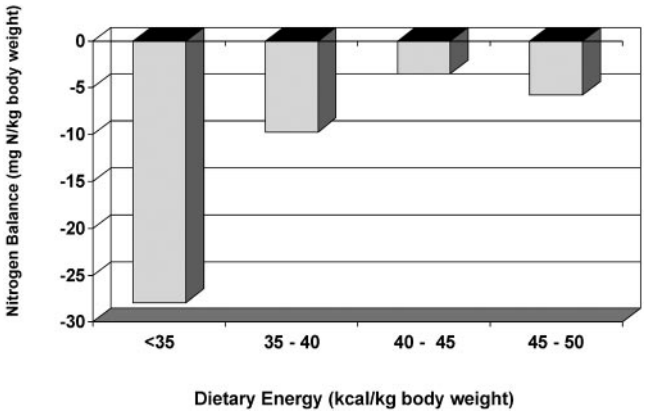

Figure 1. Effect of energy intake on nitrogen balance at protein intakes of 0.58–0.62 g/kg body weight. Data from Pellett and Young.[8]

protein or amino acid requirements that exceed these values.[6]

For the current discussion, it is important to mention that an individual's IAA and protein requirements are affected by the other components or characteristics of the diet (ie, the amounts of other IAAs and DAAs), as well as the overall level of dietary protein and energy.[7] A thorough discussion of this issue is beyond the scope of this paper, but the implications are relevant to the topic at hand. For example, a person who has been habitually consuming a low-protein diet will, to a limited extent, adapt to that protein level and be able to maintain nitrogen balance on a lower level of dietary protein. More important, the protein requirement is significantly increased for an individual who is consuming less than his/her energy needs and is significantly decreased for an individual who is in positive energy balance.[7,8] It is much easier to get someone into nitrogen balance or positive nitrogen balance if nonprotein energy intake is increased (Figure 1). The clinical implications of this are that it may be possible to achieve positive nitrogen balance in an individual with less than optimal protein intake by simply increasing energy consumption. It can also be said that increasing energy intake from any source is likely to improve a resident's protein status.

Relevance of DRIs to Issue of Protein Supplementation

The IOM has published estimated average requirements for each of the IAAs and recommends that these be used as reference values in the determination of protein quality. There are EARs published for both children and adults.[5]

The IOM has also published RDAs for each of the IAAs and for protein.[5] In the LTC setting, modular protein supplements are almost always used to meet the protein needs of individuals. The IOM has stated that the RDA is the appropriate reference value to use when assessing and planning diets for individuals.[9,10]

In their review of the literature to determine an upper tolerable limit (UL), the IOM found that there were insufficient data in humans for determination of the UL for either total protein or any of the amino acids.[5] A lack of studies to assess amino acid toxicity[11] should not be taken to mean that there is no risk associated with the intake of large amounts of either protein or amino acids. Adverse physiologic effects are apparent in animals when most (if not all) amino acids are taken in amounts disproportionate to that normally found in the diet.[12,13] In growing animals, disproportionate amounts of amino acids tend to cause a reduction in growth rate[13]; however, the effect on mature animals is much less consistent. Large quantities of some amino acids are quite toxic (ie, methionine, cysteine, and histidine) and can cause both acute adverse effects and tissue damage with chronic administration.[12] Until we have relevant data in humans, we cannot rule out the possibility that consuming large amounts of amino acids will cause unanticipated adverse consequences,[12] including adverse effects in patients.[14]

Types of Modular Protein Supplements

There are fundamentally 4 types of modular protein supplements currently on the market.

"Complete protein." This type consists of protein concentrates derived from a commodity such as egg white, soy protein, or milk protein (ie, casein or various whey fractions). Most, if not all, of these protein products would be considered "good quality" and "complete" proteins because they provide sufficient amounts of all 9 IAAs relative to the human requirement. Only proteins that contain all 9 IAAs in concentrations sufficient to meet the requirement of humans can be considered to be "complete."[5] Presumably these types of modular supplements are intended to act as both a substrate for protein synthesis and to provide amino acids for the synthesis of other essential compounds. We have also chosen to include supplements that provide sufficient amounts of all of the IAAs except for histidine in the complete protein category. Proteins low only in histidine should be considered "good quality" and should not be differentiated from other complete proteins because the unique metabolism of histidine allows these proteins to be used just as efficiently as if they contained adequate histidine.[15] These proteins will be referred to as "complete except histidine."

"Collagen based." These are protein concentrates derived from hydrolyzed collagen, with some being combinations of collagen and another protein (eg, casein). Eight of 9 IAAs used in protein synthesis are present in collagen; however, the IAA levels are relatively low. Further, collagen is naturally devoid of tryptophan. Collagen-based products are sometimes supplemented with tryptophan or other amino acids to improve the amino acid profile. When collagen is combined with casein or other complete pro-

teins, the resulting combination provides somewhat greater amounts of all of the IAAs. However, collagen-based supplements that provide insufficient amounts of many IAAs when compared with the 2005 DRI reference pattern are not considered to be "complete" proteins.

"Amino acid dose." These modular protein supplements are nutritionally distinct from the protein concentrates discussed above. These products usually provide fairly large doses of 1 or more DAAs, typically arginine or glutamine, but sometimes cysteine or its derivative, N-acetyl cysteine. Presumably, these products are provided to residents as a source of 1 or more amino acid(s) that have become "conditionally indispensable" due to a disease process or physiologic stress. The various amino acids in these products have their own unique metabolic pathways and proposed mechanisms of action, but typically they are provided to promote healing, including healing of wounds. Some of these supplements also provide amino acid precursors or metabolites (eg, β-hydroxy-β-methylbutyrate [HMB] or ornithine α-ketoglutarate [OKG]), intended to promote protein accretion or formation of important amino acids or nitrogenous compounds.

"Protein plus amino acid dose." These are a commodity protein or collagen with an added dose of 1 or more DAAs. Presumably, these products are intended to serve both purposes: to meet overall amino acid and protein synthetic needs and to provide significant amounts of at least 1 conditionally IAA. The protein quality of these products varies, depending on the IAA profile of the source protein(s).

Table 2
The protein quality of source proteins for modular protein supplements

Protein	True digestibility*	NPU†	BV†	PER†	PDCAAS (%)*‡
Milk	95	81.6	84.5	3.1	100
Casein	99	72.1	79.7	2.9	100
Whey	99§	92§	104§	3.0‖	100
Egg white	98	82.5	83.0	3.8#	100
Soy	95–98	61.4	72.8	2.3	100
Collagen	95**	NA	NA	NA	NA
Gelatin	95**	2.5	NA	−1.25	0

BV, biological value; NPU, net protein use; PDCAAS, Protein Digestibility Corrected Amino Acid Score; PER, protein efficiency ratio.
*True digestibility is calculated by subtracting the nitrogen excreted in feces from the amount ingested, with the value being expressed as a percentage of intake.[16] Unless otherwise noted, values from FAO/WHO Expert Consultation.[16]
†Unless otherwise noted, values from Food Policy and Food Science Service, Nutrition Division, FAO.[17]
‡Indispensable amino acid values used in this calculation from US Department of Agriculture, Agricultural Research Service.[21]
§European Dairy Association[20]; the true digestibility of whey is assumed to be equivalent to casein.
‖Schaafsma.[19]
#Schaafsma.[18]
**Oesser et al.[22] This value is not true digestibility; digestibility was determined *via* absorption of ^{14}C-labeled gelatin hydrolysate.
NA indicates that peer-reviewed or government source data were not available.

Evaluation of Proteins Intended as a Substrate for Protein Synthesis

The protein quality of a food has historically been evaluated through an assessment of the protein's chemical composition (chemical methods) and by feeding it to animals to determine its ability to support growth or nitrogen balance (biologic methods).[16] The chemical methods used for the assessment of protein quality include calculation of the crude protein content of the food to estimate the overall proportion of protein in the food and determination of amino acid score (a.k.a. chemical score) to compare the IAA content of the protein to a reference protein or pattern. Sometimes a protein has low digestibility or is not used well by the body for protein synthesis. For these reasons, a common follow-up to the chemical evaluation of a protein is to feed it to research animals to determine the protein's ability to promote nitrogen retention or growth.

The traditional biologic methods used to assess protein quality include net protein utilization (NPU; nitrogen retained in body/nitrogen consumed), biological value (BV; nitrogen retained in body/nitrogen absorbed by gut) and protein efficiency ratio (PER; weight gain/nitrogen consumed).[16] Biologic assessments of proteins are rarely conducted in humans and almost never occur in a clinical setting. They require precise measurements of nutrition intake, and NPU and BV require collection and analysis of body wastes. PER must be conducted on growing animals. All 3 methods also require careful experimental control of energy intake, overall diet composition, and physiologic state. Although it would be ideal to have NPU, BV, or PER data for modular protein supplements, peer-reviewed published data for commercially available modular products are nonexistent. However, numerous biologic assessments of protein quality have been conducted on most of the source proteins (ie, casein, whey, egg white, and soy), and these data can be applied to the current discussion (Table 2).[16–22]

In 1991, the Food and Agriculture Organization/World Health Organization[16] proposed a superior method for the evaluation of protein quality, which has been adopted by the Food and Nutrition Board of the IOM.[5,16] This method is the "protein digestibility corrected amino acid score" (PDCAAS), which tells you how well a particular protein will provide the IAAs required by humans (Table 3). The calculation of the PDCAAS is similar to that of the traditional amino acid score but with 1 additional step: the lowest amino acid ratio is multiplied by the true protein digestibility.[16] Although some manufacturers market their products as having superior digestibility, there are 2 reasons why this is not a

Table 3
Methods and example for calculation of Protein Digestibility Corrected Amino Acid Score (PDCAAS)

Example: Amino acid information provided per 7-g serving of modular supplement: cys 0.03 g; his 0.16 g; ile 0.30 g; leu 0.56 g; lys 0.51 g; met 0.09 g; phe 0.30 g; thr 0.28 g; trp 0.09 g; tyr 0.30 g; val 0.36 g. Label indicates a serving provides 6 g of protein.

	Steps	Example calculation
1	Perform whatever calculations are necessary in order to express the amount of each of the indispensable amino acids (IAAs; also known as essential amino acids) in the test protein in units of mg/g protein. The calculations required will vary, depending on how the information is provided by the manufacturer.	The unit (g) needs to be converted to mg by multiplying values by 1000. Each value is then divided by 6 to arrive at mg/g protein. The IAA values in mg/g protein: cys 5; his 26.7; ile 50; leu 93.3; lys 85; met 15; phe 50; thr 46.7; trp 15; tyr 50; val 60.
2	Create a combined value for methionine + cysteine and phenylalanine + tyrosine.	Met + cys = 20; phe + tyr =100
3	Divide each of the IAAs in test protein by the amount of that IAA in the reference pattern specified in the DRI for protein.[5] This calculation will generate 9 values (ratios) for each protein, one for each IAA. Each value represents how well that specific protein provides that particular IAA relative to the requirement.	Adult reference pattern IAA — mg/g protein His 17 Ile 23 Leu 52 Lys 47 Met + Cys 23 Phe + Tyr 41 Thr 24 Trp 6 Val 29
		His 26.7/17 = 1.57; ile 50/23 = 2.17; leu 93.3/52 = 1.79; lys 85/47 = 1.81; met + cys 20/23 = 0.87; phe + tyr 100/41 = 2.44; thr 46.7/24 = 1.95; trp 15/6 = 2.5; val 60/29 = 2.07
4	The lowest value calculated for that protein, which is the value associated with the limiting amino acid, is the value used to calculate the PDCAAS in the subsequent steps.	In this example, methionine + cysteine is the limiting amino acid. It has the lowest IAA ratio at 0.87.
5	Multiply the lowest amino acid ratio by the true protein digestibility for that protein.	The value associated with the limiting amino acid is 0.87, and this protein's true digestibility happens to be 95%. The PDCAAS is 0.87 × 0.95 = 0.83.
6	Multiply the PDCAAS by 100. Numbers above 100 are rounded off to 100 because the relative efficiency of use cannot be above 100%.[5] Sometimes PDCAAS are expressed as a decimal instead of a percent, in which case values should be rounded off to 1.00.	The PDCAAS for this test protein is 0.83 × 100 = 83.

cys, cysteine; DRI, dietary reference intakes; his, histidine; ile, isoleucine; leu, leucine; lys, lysine; met, methionine; phe, phenylalanine; thr, threonine; trp, tryptophan; tyr, tyrosine; val, valine.

significant issue: (1) all of the commodities used to make modular protein supplements are at least 95% digestible (Table 2); and (2) protein quality is evaluated using the PDCAAS, which corrects for digestibility. The PDCAAS for several protein commodities and a number of modular protein supplements are provided in Tables 2 and 4, respectively.

The PDCAAS is an indication of the overall quality of a protein because it represents the relative adequacy of its most limiting amino acid. For example, if a particular protein is limiting in methionine/cysteine with an amino acid score of 35, then this protein will provide only 35% of the methionine/cysteine requirement. The practical consequences are that, in the absence of another source of methionine/cysteine, only 35% of that protein can be used for protein synthesis. The remainder can be used for synthesis of other nitrogen-containing compounds or can be deaminated and used for energy. To put it another way, to meet the IAA requirements for the day, it will take almost 3 times as much of a protein with a PDCAAS of 35 as it will of a protein with a PDCAAS of 100 (Table 4).

Of course, the diet usually contains many sources of dietary protein, and most will contain some of whatever amino acid is limiting. If a protein contains the limiting amino acid in excess of its other IAA, it could function as a "complementary protein" to the lesser quality protein. Young and Pallett[23] have stated that healthy adults who have protein intakes substantially exceeding the minimum physiologic requirements do not need to consume a balanced IAA profile at every meal but can consume complementary proteins among meals over the course of the day. It is the case, however, that LTC residents with suspected PEM are neither healthy nor eating protein in excess of their physiologic requirements. Therefore, balanced proteins would need to be consumed by LTC residents within the same time frame (eating episode) as the deficient protein to be able to function as a complementary protein. Notable exceptions to the timing requirement for complementary proteins are those proteins limiting in histidine. There is a large pool of free histidine in the body, and this may be used to complement proteins that do not provide enough histidine.[15]

Collagen is naturally low in all 9 IAAs (ie, provides less than the estimated average requirements for each). Simply adding tryptophan, which is completely missing from collagen, improves its protein quality only marginally. Collagen, with or without added tryptophan, would not be considered a good quality protein. Collagen naturally provides <35% of the methionine requirement and only 40%–65% of the requirements for histidine, phenylalanine/tyrosine, isoleucine, and leucine. However, because collagen is composed of large amounts of DAAs that either have a low molecular weight or contain >1 nitrogen (ie, arginine, glycine, proline, hydroxyproline, and hydroxylysine), collagen does contain a high proportion of nitrogen on a gram-for-gram basis. It is possible for someone to consume sufficient quantities of each of the IAAs yet not be consuming enough total nitrogen to achieve nitrogen balance.[24] Under these conditions, collagen may be a good source of amino acids to meet the nonspecific nitrogen requirement. There is also evidence that glycine, proline, and arginine may become conditionally indispensable under some physiologic conditions.[5] However, collagen consumption would likely be of marginal benefit unless there is already a sufficient supply of good-quality protein to meet the requirements for all of the IAAs and enough energy to spare the IAAs for protein synthesis. The same could be said for gelatin, which is produced by the hydrolysis of collagen[22] and so has approximately the same IAA profile as collagen.

No peer-reviewed published data are available relative to the NPU, BV, or PER of any of the brand-name modular protein supplements. However, the source proteins of the milk, egg, and soy-based modular protein supplements have been studied, and published values are available (Table 2).[16–22] It is clear that egg and milk proteins are all of good quality as evidenced by the high NPU, BV, and PER scores. The scores for soy are not as high as for milk and egg but indicate that soy is also a good-quality protein. These biologic tests of protein quality for those proteins are consistent with their PDCAAS of 100. Unfortunately, there are no published reports of the NPU, BV, or PER scores for collagen, although there are NPU and PER values published for gelatin. Gelatin is made from hydrolyzed collagen[22] and so has a similar amino acid profile. The NPU and PER for gelatin are both extremely low, and its PDCAAS is 0, indicating a very poor protein quality.

Because most of the modular protein supplements have a PDCAAS of 100 (or are limiting only in histidine, which can be supplied by the body's histidine pool), it is logical to ask if there are any nutrition benefits of one product over another. Some of the manufacturers claim that their product provides some physiologic benefit beyond the simple provision of amino acid as a substrate for protein synthesis. For example, some of the whey-based (15.5–32.5 mg cysteine/g protein) and egg-based modular proteins (25.9 mg cysteine/g protein) are relatively high in cysteine compared with some other proteins (13.0, 3.7, and 0.7 mg cysteine/g protein in soy, casein, and collagen, respectively). It has been claimed that the cysteine-rich protein whey provides increased amounts of substrate for the synthesis of glutathione, a molecule that is very important in the defense of the organism against oxidative stress and in the processing and elimination of toxic compounds (see section on cysteine below). Unfortunately, only a few studies have explored whether oral supplementation with whey proteins actually affects glutathione levels.[25] In a double-blind clinical trial in patients with HIV,

Table 4
Protein Digestibility Corrected Amino Acid Score (PDCAAS, %) of modular protein supplements

Product	Manufacturer	Form	Protein source	PDCAAS (%)*†	Limiting AA	No. of deficient IAA	Product category
Proteinex Tablet	Llorens Pharmaceutical, Miami, FL	Tablet	Collagen	0	Tryptophan	9	Collagen-based
Additions	Nestle Nutrition, Glendale, CA	Powder	Whey + casein	100	None	0	Complete protein
EggPro	Nutra/Balance Products, Inc, Indianapolis, IN	Powder	Egg white	100	None	0	Complete protein
Enterex Protein Powder	Victus Inc, Miami, FL	Powder	Casein	100	None	0	Complete protein
Immunocal	Immunotec Medical Corporation/NuMedTec, Swanton, VT	Powder	Whey	100	None	0	Complete protein
Imperial High Protein Powder	Sysco, Houston, TX	Powder	Whey	96	Histidine (only)‡	1	Complete protein
Pronutra	Immunotec Medical Corporation/NuMedTec, Swanton, VT	Powder	Whey	100	None	0	Complete protein
ProSource	National Nutrition Inc, Lancaster, PA	Powder	Whey + casein	100	None	0	Complete protein
ReadyCare Protein Plus	Lyons Magnus, Fresno, CA	Powder	Whey	100	None	0	Complete protein
Resource Beneprotein	Novartis Nutrition Corporation, Minneapolis, MN	Powder	Whey	100	None	0	Complete protein
Soy Pro	ND Labs Inc, Great Neck, NY	Powder	Soy	100	None	0	Complete protein
Unjury	ProSynthesis Laboratories LLC, Reston, VA	Powder	Whey	100	None	0	Complete protein
Liquid ProSource	National Nutrition Inc, Lancaster, PA	Liquid	Collagen + casein	46	Histidine	8	Collagen-based
LPS 15/30	ND Labs Inc, Great Neck, NY	Liquid	Collagen + casein	44	Methionine + cysteine	8	Collagen-based
LPS Critical Care	ND Labs Inc, Great Neck, NY	Liquid	Collagen + casein	38	Methionine + cysteine	9	Protein + amino acid dose
Proteinex Liquid	Llorens Pharmaceutical, Miami, FL	Liquid	Collagen	0	Tryptophan	9	Collagen-based
Resource Benecalorie	Novartis Nutrition Corporation, Minneapolis, MN	Liquid	Casein	100	None	0	Complete protein
Resource Arginaid Extra	Novartis Nutrition Corporation, Minneapolis, MN	Beverage	Whey	52	Histidine	2	Protein + amino acid dose
Resource Breeze	Novartis Nutrition Corporation, Minneapolis, MN	Beverage	Whey	93	Histidine (only)‡	1	Complete protein

*Manufacturers of modular protein supplements were invited to provide amino acid information on their products; some declined. This analysis is based on amino acid data provided by the manufacturers between November 15, 2005, and December 31, 2006.
†The PDCAAS was calculated using the adult DRI (dietary reference intakes) reference pattern[5] and digestibility values.[16]
‡Proteins only low in histidine should be considered "good quality" and "complete" proteins because the unique metabolism of histidine allows these proteins to be used just as efficiently as if they contained adequate histidine.

plasma glutathione levels were significantly elevated 2 weeks after a daily dose of 45 g of one modular whey protein supplement but not another.[26] These data indicate that not all whey-based supplements have the same effect on glutathione. The results of this study also demonstrate the need for clinical studies conducted with a specific product whenever a manufacturer claims a unique therapeutic benefit attributable to a particular protein supplement.

There is some evidence that the rate of protein digestion may affect how well a protein is used for protein gain.[27] Whey protein is rapidly digested; it remains soluble in the stomach and is emptied rapidly. Casein is slowly digested; it is converted into a solid clot by the acidic environment of the stomach and is released more slowly into the small intestine.[27] In young adults, slowly digested protein resulted in a better protein gain than rapidly digested protein.[27] However, in a study with 9 healthy older men (mean age 72), the opposite relationship was observed (ie, protein gain was better with the rapidly digested protein [whey protein]).[28] Whether or not there would be any benefit of either rapidly digested or slowly digested proteins in different pathophysiologic conditions is only speculative, and further investigation is required before therapeutic benefit can be assumed.

There is also some evidence that proteins that are not nutritionally complete may be helpful for wound healing if provided in large amounts (ie, enough to increase overall protein intake by 80%), along with additional energy. Significant improvements in Pressure Ulcer Scale for Healing (PUSH) scores were seen in LTC residents provided 15 g of tryptophan-supplemented collagen protein and ~100 kcal 3 times per day, as part of routine medicine distribution.[29] However, the nature of the study design used makes it impossible to determine if the improvements in healing were the result of a general amelioration of the protein and energy deficiency (residents were eating <65% of estimated protein[30] and energy requirements at baseline) or whether there is some property of the collagen-based supplement (ie, conditionally IAA) that provided a benefit. It remains to be investigated whether the same or greater effect on healing could be achieved with consumption of a nutritionally complete protein, perhaps even in smaller amounts because casein, whey, soy, and egg provide at least twice as much IAA as does collagen on a gram-for-gram basis.

It is important to remember that there are also many sources of good-quality protein readily available in existing menus and snacks. Although a complete modular protein supplement may be useful to help a resident with clinical signs of a protein deficiency meet or exceed the RDA of 0.8 g/kg/day good-quality protein, these supplements are fundamentally additional sources of milk, egg, and soy protein. Most modular products provide around 5 or 6 g of protein per serving, and these products generally must be added to some other food to act as a carrier. In comparison, a scrambled egg or 6 oz of yogurt would naturally provide 5 or 6 g of equivalent protein, and a cup of milk would provide 8 g of protein. Meat is, of course, also a source of good-quality protein, and each ounce of lean meat or poultry provides about 8 g.[5] In each clinical situation, it is important to stop and consider whether a modular protein supplement is actually required or whether the resident could consume menu items that are high in good-quality protein along with sufficient energy. Increased feeding assistance or ongoing provision of favorite high-energy foods and beverages may be equally effective at improving the nutrition status of residents with PEM and also may be much more enjoyable for the resident.

It is noteworthy that sometimes the nutrition care goals are to increase dietary protein intake without significantly increasing energy intake or to provide a high-protein low-energy diet (eg, residents for which weight gain is undesirable or residents in the facility for rehabilitation after bariatric surgery). In these situations, use of a modular protein supplement may be helpful to increase dietary protein intake while minimizing intake of energy from nonprotein sources.

Additional Considerations for Use of Modular Protein Supplements to Maximize Effectiveness in the LTC Setting

There are several studies from which we make inferences about the best way to maximize protein synthesis from dietary protein. In general, amino acids are used most effectively for protein synthesis when consumed with carbohydrate or fat. When someone is energy deficient, glucose consumed with protein appears to stimulate protein deposition through the induction of anabolic hormones.[31,32] With energy intakes at or above maintenance levels, most studies show that both fat and carbohydrate will promote positive nitrogen balance.[31]

There also may be benefits to providing the additional protein as a bolus. One study in healthy older women (mean age 68) found that providing 79% of the day's protein at the noon meal improved protein retention compared with a more even distribution of protein across all 3 meals.[33] This effect varied from what had been previously found in younger men and women and was apparently due to higher protein synthesis in older people when large amounts of protein were provided at one time.[33]

The implications of these data for practice are that providing additional protein as part of a mixed meal or high-carbohydrate snack may provide greater benefit to residents than giving it as part of a low-energy snack or a low-energy solution consumed as part of routine medicine distribution. From a quality-of-life point of view, it is generally preferable in LTC to reserve meal times for increasing protein consumption through intake of preferred high-protein foods. If it is also necessary to incorpo-

rate a modular protein into the meal, it should be done in an appealing manner (eg, disguised in food). When a modular protein supplement is provided between meals, it should be consumed as part of high-carbohydrate snack.

It should be noted that residents of LTC facilities who experience severe illness might not benefit from concentrating additional protein at a limited number of meals. According to Soeters et al,[14] empiric and theoretic evidence suggests bolus feeding is ineffective during severe illness. During almost every severe disease state and for patients with compromised gut function, stomach capacity, or liver function, they advise continuous feeding or frequent but small meals.[14]

The kidney function of the LTC resident should also be considered when recommending concentrated protein supplements. There is a linear relationship between protein intake, urea production, renal solute load, and urine production. As protein intake increases, the body produces more urea. More urea in the blood increases the renal solute load. The healthy kidney responds by increasing urine concentration and increasing the volume of urine produced. Several studies have reported that healthy adults are able to tolerate higher protein intakes without changes in hydration status.[34,35] However, LTC residents with compromised kidney or liver function may not be able to process high-protein intakes without changes in hydration status.[36–38]

It is essential to use baseline laboratory test data to assess hydration, kidney, and liver status before recommending concentrated protein supplements for LTC residents with a history of hydration management problems or significantly compromised kidney or liver function. Once the supplements have been incorporated in the diet, routine laboratory monitoring is required to confirm tolerance to the protein levels and to evaluate hydration status.[39] Routine monitoring should be continued for as long as the person is taking the concentrated protein supplements. Abnormal laboratory test results must be addressed promptly.

Finally, it is not uncommon for cachexia to cause PEM-like symptoms.[40] Cachexia is a complex physiologic condition characterized by anorexia, muscle wasting, and a systemic inflammatory response. Although the inflammatory response (ie, cytokines) associated with cachexia reduces appetite,[40] the muscle wasting and drop in circulating hepatic proteins associated with this condition cannot be reversed solely by intake of adequate protein or energy.[3] There are no widely accepted clinical guidelines for the use of modular protein supplements in the treatment of cachexia. Although the strategies of increasing energy and protein intake may be advisable for residents with cachexia, residents are unlikely to show improvements in circulating hepatic proteins (ie, albumin, transthyretin, transferrin) until the underlying inflammatory response is resolved, regardless of protein intake.[3]

Summary of Evaluation of Supplements Intended as a Substrate for Protein Synthesis

The protein quality of a number of modular protein supplements was summarized in Table 4. However, it is likely that the formulations of these products will evolve over time and new products will become available. Thus, instead of focusing our discussion only on the existing products, some guidelines have been developed for selecting a modular protein supplement that has the intended use as a substrate for protein synthesis:

- Before you consider use of a product, know the PDCAAS relative to the reference pattern published in the 2005 DRIs. This is the appropriate standard to evaluate protein quality according to the Food and Nutrition Board of the IOM.[5] This value can be easily calculated by the manufacturer and should be routinely provided on product promotional material. Note: Do not be misled by an amino acid score calculated from a comparison to the 1985 FAO/WHO pattern, which has much lower IAA values than the 2005 IOM pattern.
- A higher PDCAAS means better protein quality. A perfect PDCAAS (%) is 100. Because so many of the products have scores of 100, one should have a specific justification for choosing a protein with a PDCAAS <100. The exceptions to this are proteins limited *only* in histidine, because the unique metabolism of histidine allows these proteins to be used just as efficiently as if they contained adequate histidine.
- The PDCAAS is an indication of the body's ability to use that protein for protein synthesis. For example, a PDCAAS of 50 means that (1) only 50% of that protein can be used for protein synthesis; (2) to meet the IAA requirement, the resident must consume twice as much of a protein with a PDCAAS of 50 than of a protein with a PDCAAS of 100.
- Some proteins are deficient in only 1 IAA, whereas others are deficient in multiple or all IAAs. If the PDCAAS is <100, insist that the manufacturer provide you with the ratio for each of the IAAs relative to the DRI reference pattern. Every value <100 indicates that the supplement is proportionally low in that IAA.
- Manufacturers should be asked to substantiate claims that the amino acid composition of their protein has a unique healing effect or that it provides a physiologic benefit beyond the simple provision of amino acids as a substrate for protein synthesis. This should take the form of clinical trials published in the peer-reviewed scientific literature. Under United States Food and Drug Administration (FDA) regulations, manufacturers of "medical foods" are not required to provide documentation to the FDA before making such claims, but clinicians have not only the right but the responsibility to

demand science-based clinical evidence of benefit before recommending these products for their patients.

Evaluation of Proteins Intended as a Source of Conditionally IAAs

A number of modular protein supplements are designed to provide 1 or more amino acids that may be conditionally indispensable under certain disease conditions, some of which are common in the LTC setting. A smaller number also provide an amino acid precursor or metabolite that is thought to promote an anabolic response. These supplements are proteins in the technical sense (ie, they are composed of one or more amino acids), but they do not contain the full complement of IAAs necessary for protein synthesis.

Historically, amino acids were classified as either essential or nonessential. The distinctions between these 2 categories have become blurred as our understanding of amino acid and protein metabolism has advanced. The 2005 DRIs identified quite a number of amino acids as being indispensable under certain conditions (ie, conditionally indispensable; Table 1).[5,15] Amino acids may be categorized as conditionally indispensable if (1) they are synthesized from other amino acids that may be deficient in the diet; (2) they are synthesized in only a limited number of tissues such that certain pathophysiologic conditions may interfere with their synthesis; or (3) synthesis is limited such that pathophysiologic conditions can cause use to increase beyond the synthetic capacity of the organism.[24] Conditional indispensability means that the synthesis of these amino acids can become limiting for growth and other physiologic functions.[24] It is important to remember that the indispensability of these amino acids represents an increase in the protein requirement beyond that represented by the RDA, which was developed with consideration for healthy people only.

In general, supplements of single amino acids are marketed as having an anabolic or healing effect. There are a number of possible mechanisms whereby an amino acid supplement may promote protein deposition or improve physiologic function. Such supplements may provide an amino acid that is (1) limiting for protein synthesis; (2) a precursor for a DAA that has become limiting for protein synthesis; (3) an energy substrate for certain tissues; or (4) a precursor for an important nitrogen-containing molecule (eg, glutathione, nitric oxide, nucleic acids, or creatine).

It is also possible that an amino acid or amino acid metabolite can have an anabolic effect beyond the functions listed above. There are several potential mechanisms whereby a protein or amino acid supplement may result in positive nitrogen balance. Body protein is metabolically dynamic and is continually being degraded and resynthesized, which together constitutes protein turnover. At nitrogen equilibrium, protein synthesis matches protein degradation. An increase in body protein deposition, or positive nitrogen balance, can be the result of a (1) decrease in protein degradation without a simultaneous decrease in protein synthesis; (2) increase in protein synthesis relative to degradation; or (3) simultaneous decrease in degradation and increase in protein synthesis. Some amino acid or amino acid metabolites can trigger one or more of the physiologic mechanisms (eg, anabolic hormones), which stimulate synthesis or inhibit degradation.

As a precautionary note, scientists are far from consensus regarding the appropriate amino acids and amounts to provide during disease. It appears that during disease, the body prioritizes active metabolism and increased protein synthesis in central organs such as liver, the immune system, and wounds.[14] The amino acid mix used for this process is crucially different from that used in the nondiseased state.[14] As yet, it is unproven which components of the stress response in severe illness should be supported and which should be inhibited to achieve the best clinical outcomes.[14]

The value of amino acid supplementation is even less clear for the LTC population. Almost no long-term studies of amino acid supplementation have been conducted in this cohort. The characteristics of residents in a LTC setting differ dramatically from the populations in which most amino acid supplementation has been studied (ie, critically ill young or middle-aged adults receiving a nutritionally complete enteral formula that is "immuno-enhanced" with various nutrients). People who reside in LTC facilities are often very old and usually have disease conditions that are both chronic and degenerative, as opposed to acute. Further, many residents have inadequate intakes of energy, protein, water, and micronutrients. Thus, multiple nutrient deficiencies and medical comorbidities may be contributing to any delay in wound healing. In the absence of clinical outcomes data, it is unclear if residents benefit from supplementation of 1–3 amino acids under these conditions.

A thorough review of the metabolism of all amino acids considered to be conditionally indispensable is beyond the scope of this paper. Neither is it our intent to complete an exhaustive evaluation of the clinical literature. There are many excellent reviews available, including meta-analyses of the efficacy of immune-enhancing enteral formulas with additional arginine and glutamine.[41,42] Instead, the following discussion focuses on a summary of amino acids being marketed as modular supplements for use in LTC. Included is a brief review of metabolism, with emphasis on the conditions under which an amino acid may become conditionally indispensable and the purported mechanisms for support of healing. For each amino acid, we summarized the clinical applications for which there appears to be con-

sensus, clinical studies that are relevant to the LTC population, and their associated potential hazards.

Arginine

Physiology. In adults, the majority of arginine is produced through a metabolic collaboration between the small intestine and the kidneys. Glutamine, glutamate, and proline can be converted to citrulline by the enterocyte. The intestine-derived citrulline is then released into general circulation and taken up by the kidney for conversion to arginine, which supplies the body's needs. The synthesis of adequate amounts of arginine requires adequate amounts of its natural precursors, glutamate and proline.[24] Intestinal diseases[24] or provision of parenteral nutrition (PN)[43] can interfere with arginine synthesis and make it conditionally indispensable.

Arginine plays many important physiologic roles in addition to being incorporated into body proteins. It functions as an intermediate in the urea cycle, and so its formation is essential for the detoxification of ammonia. Arginine also has important functions as both the sole substrate for nitric oxide production and as a substrate for the synthesis of the amino acids ornithine and proline. Further, it is a secretagogue of hormones like insulin, growth hormone, and insulin-like growth factor-1 (IGF-1).[44]

A review of the complex mechanism by which arginine promotes wound healing is beyond the scope of this manuscript. Readers are referred to Stechmiller et al[44] for an excellent review of this topic. In short, the nitric oxide produced from arginine acts as a host-protective agent by killing pathogens and increasing blood flow to wounds.[44] Among other actions, nitric oxide activates wound macrophages and neutrophils, causes vasodilation, and increases vascular permeability. The ornithine produced from arginine is a substrate for the synthesis of polyamines (putrescine, spermidine, and spermine).[45] Polyamines are important for normal cell and immune cell division, differentiation, and growth and thus are involved in wound healing and regeneration of tissue.[44] At the wound site, some arginine will be converted to ornithine and then to proline, which is a major component of collagen. Also, hormones that are secreted in response to arginine, like growth hormone and IGF-1, stimulate various anabolic pathways that are essential for healing.

Clinical studies of arginine supplements. Arginine has been found to promote healing in healthy adults and elders who are eating sufficient energy and protein. Administering arginine (17 or 24.8 g) to normal middle-aged volunteers for 2 weeks improved collagen synthesis as determined by collagen deposition in a plastic tube implanted in the subcutaneous tissue.[46] In a study of 30 healthy older adults (>65 y of age), 17 g of L-arg for 2 weeks was shown to improve wound bed protein and hydroxyproline accumulation in subcutaneous catheters and to result in greater lymphocyte responses and elevated levels of IGF-1.[47]

Although these studies show the benefit of arginine on artificially induced acute incisional wounds in healthy individuals, it is unknown whether arginine would have the same effect on healing of delayed and chronic wounds (ie, pressure ulcers, diabetic ulcers).[5] Also, there are no data that demonstrate that supplemental arginine actually improves healing of wounds sustained after an injury or operation, thus enhancing clinical outcome in patients.[48] In order to conclude that arginine should be used for patients with wounds, it is necessary to conduct clinical studies in this population.[48] It is critical that studies determine whether supplemental arginine actually improves healing of delayed and chronic wounds.[44] Clinical judgment and close follow-up of clinical outcomes is required when recommending arginine for delayed wound healing because of limited evidence-based support.

One study with arginine was conducted in the LTC setting. Langkamp-Henken et al[49] investigated the role of arginine as an enhancer of the immune system. Either 8.5 g or 17 g of supplemental arginine was provided daily to elderly nursing home residents with pressure ulcers. Markers of immune function (lymphocyte proliferation to phytohemagglutinin and interleukin-2 production) did not improve with either level of supplementation.[49] Additional clinical studies with supplemental arginine need to be conducted specifically in the LTC setting to determine efficacy and safety in this population.

Hazard identification. The Food and Nutrition Board found minimal evidence of adverse effects from arginine supplementation at intakes up to 24.8 g/day of free arginine base.[5] Barbul[50] reached a similar conclusion, finding that large doses (eg, 30 g L-arg/day) have been used without significant adverse effects but that infrequent gastrointestinal symptoms such as bloating and mild diarrhea have been reported at some of the higher intake levels (>20–30 g/day). A 14-day study in which 30 older adults received 17 g of free arginine/day reported no adverse effects.[51]

However, there are potential risks for excessive supplementation of arginine. There has been an unconfirmed finding that 30 g of arginine for 3 days resulted in a stimulation of tumor growth in breast cancer patients.[52] Perhaps more relevant to the LTC population, a recent randomized clinical trial found that arginine supplementation (goal dose of 3 g 3 times a day) was associated with higher rates of postinfarction mortality.[53] Therefore, arginine is not recommended after acute myocardial infarction. There is also evidence that enteral diets containing arginine may be associated with increased mortality in some groups of critically ill patients, perhaps through stimulation of the systemic inflammatory response.[48] Thus, supplementation of arginine in a patient/resident who is septic warrants caution until

further data are published on the potential risks. Use clinical judgment when recommending arginine for patients/residents with end-stage kidney or end-stage liver disease, as urea cycle function is likely to be impaired in these individuals and they will have difficulty catabolizing excess arginine.

Glutamine

Physiology. The body produces large amounts of glutamine daily, especially in muscle and lung.[54] The amount has been estimated at 60–100 g/day for the adult.[55] During catabolic states, the muscle's production of glutamine increases due to the activation of muscle protein breakdown and the enzyme glutamine synthetase. However, these same physiologic stressors also cause use of glutamine to increase dramatically. The overall result is a depletion of muscle glutamine.[56] Because muscle is the source of most body glutamine, the decreased muscle mass found in older individuals may limit the amount of glutamine available during stress conditions.[56] Thus, there may be a beneficial effect of glutamine supplementation in aged individuals who are injured or under some sort of physiologic stress.

Under normal intake levels, glutamine will be catabolized for energy in the intestine, resulting in the production of CO_2, alanine, pyruvate, lactate, and ammonia.[57] Some glutamine will not be used for energy by the gut but will be metabolized in the splanchnic tissues to citrulline, arginine, glutamate, or proline,[57] which will be transported *via* portal blood to the liver.

There are a number of key functions for glutamine beyond its incorporation into body proteins. One central function of glutamine is to serve as a nitrogen transport mechanism in the body, carrying both carbon and nitrogen from peripheral tissue to the kidney and liver, which produce urea and ammonia, respectively. A second critical function of glutamine is as a principal fuel source for enterocytes and immune tissues (lymph nodes, spleen, thymus, Peyer's patches, and leukocytes).[54] A third significant function is as a precursor of the glutamate necessary for the production of glutathione in many cell types, including enterocytes, neural cells, liver cells, and lymphocytes.[54]

Clinical studies. There is considerable evidence that hypercatabolic or hypermetabolic situations are accompanied by a marked depression of muscle intracellular glutamine.[6] It is also clear that glutamine is helpful for patients receiving PN or those who have a disease state or treatment that threatens the intestinal mucosa, and there is evidence that it may reduce pneumonia, bacteremia, and septic events in patients receiving enteral formula.[58] As compelling as these data may be, it is much less clear whether a glutamine supplement improves outcomes in an LTC resident that consumes a regular diet and is not critically ill.

It is generally accepted as logical to supplement glutamine during chronic disease states or in situations where the organism cannot produce them due to depletion.[14] Fürst and Stehle[6] have suggested a tentative glutamine requirement of ~0.15–0.2 g/kg/day after uncomplicated major operations, major injury, gastrointestinal malfunctions, and during cachexia, and a requirement of ~0.3–0.5 g/kg/day for critical illness. The former value is somewhat contradictory to Ziegler et al,[59] who concluded that doses lower than 0.285 g/kg/day had no benefit over standard feeding. Although the pathophysiologic states common to LTC are likely to cause the glutamine requirement to increase, there are no studies that have specifically looked at the glutamine requirement in this population. It has been suggested[60] that glutamine doses are best divided throughout the day in order to reduce the potential for adverse effects and to optimize use.

Hazard identification. There appears to be a consensus that very few, if any, adverse effects have been reported despite the substantial number of published investigations in which glutamine has been administered to humans.[5,14] Zeigler et al[59] reported that doses of up to 0.57 g/kg/day (eg, 40 g per day for a 70-kg man) have been given without any adverse effect being reported. However, the Food and Nutrition Board points out that the published studies of toxicity have not fully taken account of a number of important factors, including the chronic consumption of glutamine.[5] There has been some concern that glutamine supplementation may promote tumor growth by acting as fuel source, although evidence points to the contrary and studies have not confirmed this suspicion.[5]

Glutamine supplementation is contraindicated in patients/residents with hepatic failure and chronic renal failure. Blood ammonia levels are of concern if the patient/resident has liver disease. Patients/residents with chronic renal insufficiency may have an altered metabolism of glutamine. Glutamine may also be contraindicated for patients/residents taking methotrexate because supplementation may inhibit renal clearance of the drug resulting in increased serum levels of the medication. Use clinical judgment when recommending glutamine for patients/residents with liver or kidney disease.

Cysteine/Cystine/N-Acetyl Cysteine

Physiology. Cysteine is a DAA that is formed metabolically from methionine and serine. Two cysteines can bond together to make cystine. Traditionally, cysteine is considered conditionally indispensable because its synthesis depends upon adequate amounts of dietary methionine[15] and a healthy liver.[6] However, the recent interest in cysteine (or N-acetyl-cysteine) as a component of modular protein supplements is related to its role as a precursor for glutathione.

Glutathione plays important roles in antioxidant defense, nutrient metabolism, and regulation of cellular events, including gene expression, DNA and protein synthesis, cell proliferation and apoptosis, signal transduction, cytokine production, immune response, and protein glutathionylation.[61] A deficiency of glutathione contributes to oxidative stress, which plays a key role in both aging and the pathogenesis of many diseases, including kwashiorkor, seizure, Alzheimer's disease, Parkinson's disease, liver disease, cancer, heart attack, stroke, and diabetes.[61]

Animal and human studies demonstrate that adequate protein nutrition is crucial for the maintenance of glutathione homeostasis.[61] The supply of dietary protein and cysteine can measurably alter the ability of the organism to maintain glutathione synthesis.[62]

There are convincing data to support the view that cysteine is generally the limiting amino acid for glutathione synthesis in humans.[63] However, there are other aspects of dietary amino acid balance that have an important effect on glutathione homeostasis. The adequate provision of glutamate (glutamine or branched-chain amino acids [BCAAs]) and glycine (or serine) is also critical for the maximization of glutathione synthesis.[61] In fact, the commercial amino acid supplements that provide N-acetyl cysteine usually also provide glutamine. However, these supplements do not contain glycine, which can become limiting in the synthesis of glutathione.[64]

Clinical studies. Studies have shown that enteral cysteine, cystine, or N-acetyl-cysteine are all effective precursors of cysteine for tissue glutathione synthesis under various nutrition and pathologic conditions, including protein malnutrition, adult respiratory syndrome, HIV, and AIDS.[65,66] Replenishment of glutathione is associated with improved survival in patients with HIV[67]; however, there are no published human data regarding the effects of supplemental dietary cysteine, cystine, or N-acetyl-cysteine on wound healing or nitrogen balance.

Hazard identification. The 2005 DRIs reported insufficient data regarding adverse effects of L-cysteine or L-cystine from supplements to conduct a dose-response assessment. As mentioned previously, in animal studies, high doses of cysteine are associated with adverse effects, including reduced food intake, weight gain, high mortality in growing animals, histopathologic changes in kidney and liver of adult animals, and brain and retina damage in newborn animals.[12] In healthy humans, an FDA report indicated no adverse effects with single doses up to 7 g/day, with higher doses producing nausea and bad feeling.[68] Carlson et al[69] reported that single oral doses of 5 and 10 g of L-cysteine produced nausea, lightheadedness, and disassociation. Reports of chronic administration of L-cysteine to humans were not found.[5] Several clinical trials have provided daily supplementation of N-acetyl-cysteine up to 440 mg/kg/day, with no reports of adverse events.[66] Cysteine or its derivatives may be contraindicated in patients/residents with liver disease because the metabolism of sulfur amino acids may be altered.[66]

Other

OKG. OKG is a salt formed of 2 molecules of ornithine and 1 of α-ketoglutarate.[70] When ornithine and α-ketoglutarate are provided together, they induce the generation of key metabolites, such as glutamine, proline, arginine, and polyamines.[71] OKG can also induce the secretion of anabolic hormones, such as insulin, growth hormone, and IGF-1/Sm-C.[70]

In general, OKG has been reported to have both anabolic and anticatabolic actions, depending on the tissue type and the nature of the injury (ie, burn, trauma and sepsis, surgery, and cancer).[72] For example, OKG may reduce catabolism after burns by stimulating the release of human growth hormone and arginine.[73] Burn patients had significantly improved wound healing when OKG was provided as a bolus,[73,74] although total nitrogen retention was not different than control.[74]

A review by Blonde-Cynober et al[71] summarizes 5 clinical studies of OKG supplementation in older people. Unfortunately, these studies are limited by either lack of a placebo control or a placebo that was not matched with OKG according to both calorie and nitrogen content.[71] With that caveat, 3 studies reported that 10 g/day OKG resulted in an increase in appetite (self-reported), and 1 study reported observed increases in protein and energy intake at 15 and 30 days of treatment. Three of those studies reported statistically significant increases in body weight after 60 days, and 2 studies reported improvements in circulating hepatic proteins (eg, albumin) by 30 or 60 days. Lack of appropriate controls in these studies precludes the conclusion that OKG supplementation results in improved clinical outcomes in LTC residents.

Amino acid combinations with HMB. HMB is a metabolite of leucine that has been demonstrated to reduce the rate of proteolysis in animals and humans.[75] It has been hypothesized that HMB may increase collagen deposition, inhibit muscle proteolysis, and modulate protein turnover.[76]

The effect of a mixture of HMB, arginine, and glutamine has been evaluated in several clinical situations. The mixture of HMB (3 g), arginine (14 g) and glutamine (14 g) was shown to be effective in increasing fat-free mass of middle-aged and older patients with advanced-stage cancer[77] and in younger subjects with AIDS-associated wasting.[78] A mixture of HMB (2 g), arginine (5 g), and lysine (1.5 g) has also been shown to improve functionality, strength, and whole-body protein synthesis in older women (mean age, 76.7 years).[79] There did not seem to be any adverse effects of this mixture in the

treatment of muscle wasting associated with AIDS or cancer.[80]

To study wound healing, the same mixture was administered to healthy older adults (mean age, 75.4 years) in a blinded study.[76] After 7 and 14 days, there was a significant increase in collagen deposition in subcutaneous catheters, as reflected by hydroxy-proline content. Because arginine and glutamine were administered with HMB in all of these studies, it is not possible to determine which of the components in the mixture was active or inactive. Further, because this study was not conducted in individuals with delayed and chronic wounds (ie, pressure ulcers, diabetic ulcers), it is unknown whether a mixture of arginine, glutamine, and HMB would have the same effect on healing in these patients.

Additional Considerations for Use of Amino Acid Supplements in LTC

Because the DRIs are based on the nutrition needs of healthy individuals, the increased use of an amino acid due to disease or physiologic stress would represent a protein need above the estimated average requirements and RDA values provided in the DRIs. The Agency for Health Research and Quality (AHRQ) recommends 1.25–1.5 g/kg/day protein to achieve positive nitrogen balance in patients with pressure ulcers.[30] These recommendations are based on studies conducted with high-nitrogen enteral formulas.[30] With amino acid supplements, the nitrogen is being provided by only a few DAAs; they contain none of the IAAs needed for protein synthesis and would not be considered a source of good-quality protein. Thus, the provision of 1.25–1.5 g/kg/day protein for individuals with wounds should, in large part, be achieved through the provision of proteins with a complete IAA profile. Supplements containing only 1 or more DAAs would most appropriately be provided in addition to good-quality protein. Also, keep in mind that without provision of adequate calories, the protein will be used as an energy source and not as protein.

It is also important to remember that intakes of large amounts of any individual amino acid are not without risk. Unfortunately, not enough data exist on any of the amino acids for the Food and Nutrition Board to set a UL. It should be noted that the toxic effect of amino acids depends on overall protein levels. In animal studies, the greatest adverse effects were seen when excess amino acids were given with a low-protein diet,[81] so it is critical that amino acid therapy not be used unless the minimum protein requirements are already being met.

The particular amino acids used in modular protein supplements have been associated with potential side effects (eg, nausea, bloating, mild diarrhea, and lightheadedness). The safety of long-term use in frail older adults has not been thoroughly evaluated. Thus, in practice it is important to look for adverse effects that may decrease food intake or reduce quality of life. Because toxicity has not been studied relative to chronic consumption, clinicians should consider limiting amino acid provision to a relatively short course, and assessing both clinical progress and side effects at regular intervals. Amino acid supplements should be discontinued if a resident does not seem to be demonstrating expected medical outcomes such as wound healing (for guidance on the physical assessment of a wound, see Thompson and Fuhrman[82]).

Finally, use of amino acids for the synthesis of proteins or important nitrogenous compounds is often dependent upon the availability of other dietary nutrients. When an amino acid supplement is being provided, the clinician should consider what other nutrients are necessary for full efficacy of the amino acid. For example, in order for cysteine (or N-acetyl cysteine) and glutamine to make glutathione, there must be adequate amounts of dietary glycine from food proteins. Also, many amino acid pathways require cofactors synthesized from vitamins such as B_6, folate, and B_{12}. A resident with poor dietary intake is likely to have poor B-vitamin and trace mineral status unless he/she is receiving a multivitamin and mineral supplement.

Implications for Practice

Overall Supplement Summary

Before a clinician can decide the "who, what, when, and how" regarding use of a modular protein supplement, he or she must be clear about the nature of the various supplements and their intended physiologic effect. It may be possible to categorize the existing products a number of ways, but according to their composition and physiologic function, we have categorized them into 4 different types (Tables 4 and 5), with some notable variations.

1. "Complete Protein": Supplements provide all 9 IAAs in a nutritionally complete protein derived from milk, egg, or soy. These proteins contain sufficient amounts of both IAAs and DAAs necessary for the synthesis of protein and essential compounds. They are appropriate to meet the RDA for healthy individuals of 0.8 g/kg/day good-quality protein.
    a. A subcategory of the "Complete Protein" type is supplements derived from whey fractions or egg, which are particularly rich in cysteine, an amino acid that is conditionally indispensable under some types of physiologic stress.
2. "Collagen-based": Supplements are derived primarily from collagen. They provide at least some of 8 or 9 IAAs but are not complete proteins. However, collagen is a rich source of glycine and proline and a relatively good source of arginine. Thus, although collagen is a relatively poor source of IAAs, it may be a good source of amino

Table 5
Conditionally indispensable amino acid content of modular protein supplements

Product	Arginine, mg/g pro	Glutamine, mg/g pro	N-Acetyl cysteine/ cysteine, mg/g pro	Protein source	Product category
ArgiMent*	429	571	0	Amino acids	Amino acid dose
Glutapak 10†	0	1000	0	Amino acids	Amino acid dose
Juven‡	500	500	0	Amino acids	Amino acid dose
LPS Critical Care§	188	94	1	Collagen + casein + amino acids	Protein + amino acid dose
Resource Arginaid‖	1000	0	0	Amino acids	Amino acid dose
Resource Arginaid Extra‖	441	50	26	Whey + amino acids	Protein + amino acid dose
Resource Glutasolve‖	0	1000	0	Amino acids	Amino acid dose
Restore-X#	13	931	56	Amino acids	Amino acid dose
Sympt-X/Sympt-X GI#	0	1000	0	Amino acids	Amino acid dose
Syst-Amune#	0	943	57	Amino acids	Amino acid dose

*National Nutrition Inc, Lancaster, PA.
†Victus Inc, Miami, FL.
‡Also contains calcium β-hydroxy-β-methylbutyrate; Abbott Laboratories, Columbus, OH.
§Contains cysteine/cystine; ND Labs Inc, Great Neck, NY.
‖Novartis Nutrition Corporation, Minneapolis, MN; Resource Arginaid Extra contains cysteine/cystine.
#Baxter International Inc, Deerfield, IL; Restor-X and Syst-Amune contain n-acetyl cysteine.

acids to meet the nonspecific nitrogen requirement and increase intakes of some amino acids that may have become indispensable due to a pathophysiological state. Refer to manufacturer's nutrient analysis to determine if the collagen-based products are fortified with additional amino acids.

3. "Amino Acid Dose": Supplements provide 1–3 amino acids (eg, glutamine, arginine, and cysteine) that may be conditionally indispensable under some conditions of physiologic stress common in the LTC setting. These products are most appropriate for individuals who are already meeting their estimated protein requirements but are not demonstrating expected medical outcomes such as wound healing. Keep in mind that these supplements contain none of the IAAs needed for protein synthesis and so should not be counted toward the RDA for healthy people of 0.8 g/kg/day good-quality protein. Further, the goal of providing 1.25–1.5 g/kg/day protein for individuals with wounds should be met largely through the provision of proteins with a complete IAA profile.
    a. A subcategory of the "Amino Acid Dose" type is a supplement that also contains metabolites or amino acid precursors (OKG or HMB). These metabolites are thought to be precursors of some conditionally IAAs or to have an anabolic effect.
4. "Protein Plus Amino Acid Dose": Supplements provide a protein, which varies in quality, depending upon the source protein, combined with large amounts of a conditionally IAA (eg, arginine). Thus, this type of protein supplement provides at least some of the IAAs and DAAs necessary to meet the RDA for healthy adults while also providing greater amounts of an amino acid that may be essential under certain pathophysiological conditions.

Framework for Clinical Decision Making

Which type of modular protein supplement is clinically appropriate and for whom? What modular protein products should be available to residents in our facility, and which are unnecessary? With the dizzying array of protein supplements currently available, these are common questions for both clinicians and providers. It is probably necessary to think through the first question in order to arrive at a logical answer to the second. Unfortunately, the answer to the first question is not a simple one. For an individual resident, the appropriateness of a modular protein supplement can only be determined after a thorough assessment, followed by reassessments to evaluate clinical progress and quality-of-life issues.

The framework for clinical decision making must also accommodate the heterogeneous LTC settings that provide care to residents with an ever-widening range of health conditions, ages, and acuity level. Many residents have the potential to recover from an acute illness or injury and can look forward to returning to a good quality of life, either in the facility or at home. The resident admitted for rehabilitation after bariatric surgery is one example. For this subgroup, the potential for a good clinical outcome may justify consumption of unappealing supplements or the risk of mild side effects. However, many other residents have a degenerative condition for which there is no cure, and their days in the LTC

facility represent the best days of the end of their lives. For these residents, particularly, it is a priority to optimize quality of life on a day-to-day basis.

With the wide range of modular protein supplements available, it is important to choose a product that (1) has a mechanism of action appropriate to meet the physiologic/nutrition needs of that resident and (2) is likely to yield the best results, given the current intake patterns and overall nutrition status of that resident. To achieve this goal, the clinician must be clear in his/her thinking about the purported mechanism for each type of supplement and the prioritization of the clinical/nutrition goals for that resident.[82] The assessment process should provide a good understanding of each resident's food intake patterns, current nutrition status, and nutrition care goals.

The following is a clinical decision-making framework based on resident intake patterns and nutrition status (Figure 2). In general, modular protein supplements should only be considered in the LTC setting after (1) adequate intakes of both energy and water are achieved, and (2) provision of favorite foods that are high in good-quality protein have failed to achieve desired outcomes.

Resident is not eating enough food, neither enough energy to maintain weight and spare dietary protein nor enough protein to meet estimated needs.

- Focus intervention first on increasing overall energy intake and intake of foods that are high in good-quality protein. Provide adequate feeding assistance, including socialization and encouragement, and offer favorite foods. Provide food items that are energy and protein dense (eg, enhanced or "super foods").
- If satisfactory clinical progress is not achieved though increased intake of energy and high-protein foods, or if increased energy intake is not desirable, consider the addition of a "complete protein" supplement.

Resident is eating enough energy to maintain body weight. Resident appears to eat a variety of foods, including some foods that are high in good-quality protein, but is not eating enough protein to meet estimated needs.

- If not already doing so, focus intervention first on provision of feeding assistance, favorite foods, and nutrient-dense foods. If follow-up reassessment indicates unmet protein needs, consider the addition of one of the "complete protein" modular protein supplements.
- If inadequate fluid intake is also an issue, provide feeding assistance and encouragement regarding fluid intake. Also consider one of the "complete protein" supplements that are administered as a beverage.

Resident is not healing well despite consumption of enough energy to maintain body weight, sufficient fluids to meet water needs, and frequent intake of foods that are high in good-quality protein.

- Consider addition of a "complete protein." It may be helpful to try a product that also provides more of a conditionally IAA (ie, either a high-cysteine "complete protein" or a "protein plus amino acid dose" supplement, provided that the PDCAAS is also high).
- If the resident has been previously provided with a supplement of "complete protein" and reassessment indicates unsatisfactory clinical progress, consider the addition of:
  - "collagen-based" protein as a source of nonspecific nitrogen and some conditionally IAAs. This may be most appropriate for the tube-fed resident who should be getting adequate energy and IAAs from the enteral formula (although a high-N enteral formula is an equally appropriate option and may be more convenient).
  - "amino acid dose" supplement to provide 1–3 conditionally IAAs, either with or without amino acid metabolites.

After careful consideration of the facility's resident population, it may be possible to choose a limited number of modular protein products for the formulary that will still meet the wide range of resident needs. A facility may want to have available at least 1 product from the "complete protein" category and one or more from the "amino acid dose" category. These would cover the range of needs for complete protein and conditionally IAAs. Depending on the resident population in that facility and whether or not high-N enteral formulas are available, there may be particular applications for which a "collagen-based" modular supplement is appropriate. A product from the "protein plus amino acid dose" category may be convenient and may be something that you want to have available, but the same nutrient intake can also be achieved by combining the products from the other categories.

Additional considerations. There are a number of issues that are of significant practical, but not nutritional, importance when choosing a modular protein product. These include product taste, ease of incorporation into food or drink, ease of administration by tube feeding, ease of giving as part of routine medicine distribution, and cost. These topics have not been addressed because objective evidence is scarce and because the practitioner must weigh the relative importance of these issues on a case-by-case or facility-by-facility basis.

Once the appropriate category of modular protein supplement has been identified according to the supplement's mechanism of action and the nutrition status and care goals of the resident, other characteristics of the proteins can be considered in choosing a specific product to use. For example, in choosing a "complete protein" supplement, it may be most important to consider palatability and ease of incorporation into food or fluid. For other applications, like the "amino acid dose" supplements, the various amino acid combinations and cost may be the big-

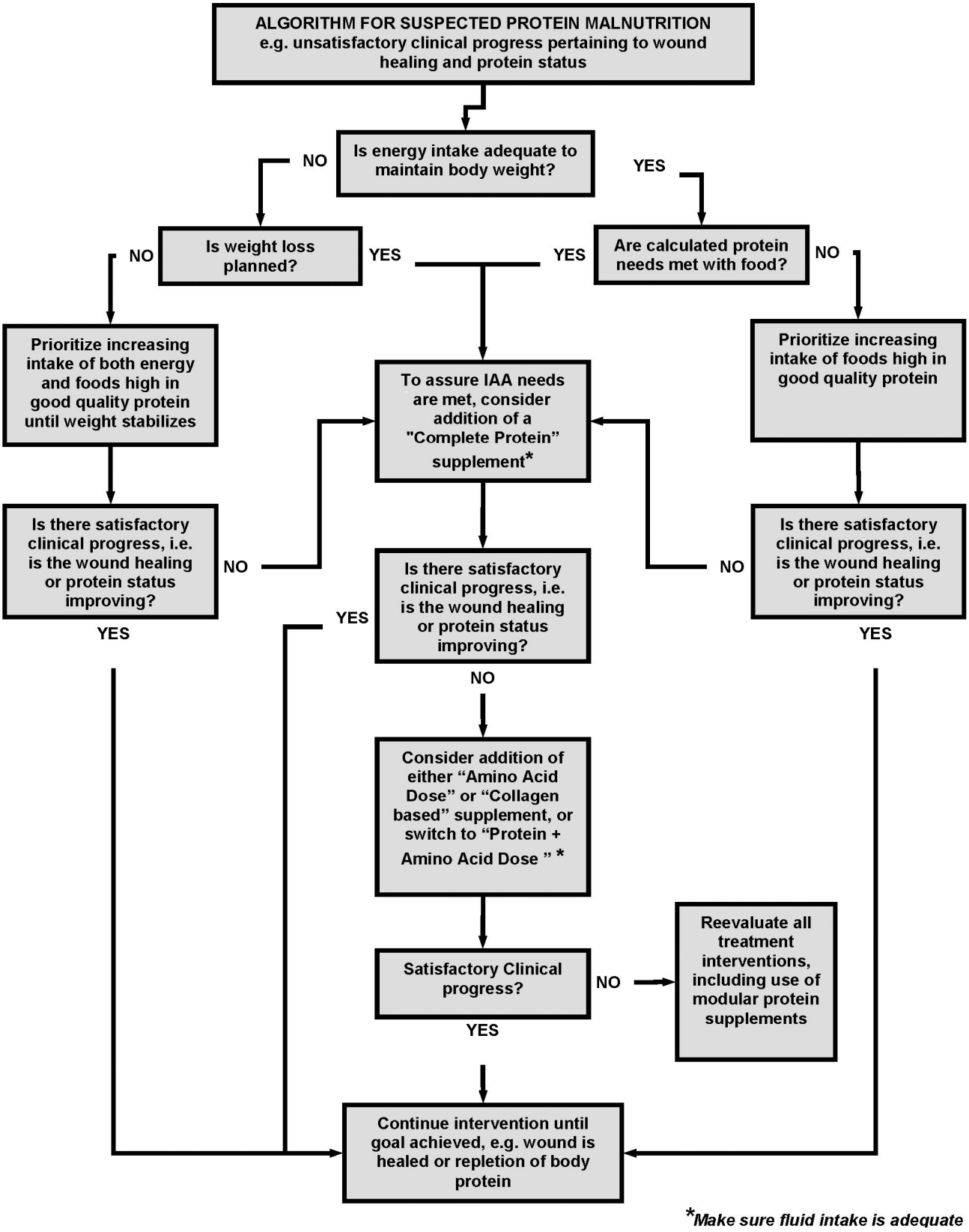

Figure 2. Clinical algorithm for the use of modular protein supplements to treat suspected protein malnutrition in the long-term care setting.

gest issues. The PDCAAS may be the most important thing to look at when choosing a "collagen-based" supplement because the total protein content and solubility are similar across products. However, it is important to keep in mind that the "complete protein," "collagen-based" and "amino acid dose" categories of supplements provide significantly different nutrition. Thus, the products from the 3 categories are *not* interchangeable. It is incumbent upon the clinician to select a product that is within the appropriate category for a particular application.

Future Research Needs and Challenges to Industry

Although we have outlined a framework to help the clinician arrive at the best type of modular protein supplement to provide under various nutrition states, it is clear that there are insufficient data to determine if protein or amino acid supplementation will actually result in desired outcomes in the LTC setting. At the current time, we must rely on our general understanding of amino acid and protein metabolism and data from healthier[5] populations and critically ill patients (ie, studies of immune-enhancing enteral therapy). However, for a number of physiologic reasons, it may not be valid to extrapolate from these existing data to the frail chronically ill older adults that are the majority of LTC residents.

From a basic research point of view, we need to apply modern research methods to the problem of determining the amino acid requirements in various disease conditions,[6] including disease conditions that are common in the LTC setting and in older people in general (eg, wounds, infection, diabetes, cachexia, immobility). This research will provide the basis for reasoned decisions about the provision of complete proteins, nonspecific nitrogen, and supplements that provide 1 or more of the conditionally IAAs.

In the realm of applied research, it is critical that the safety and efficacy of specific products, particularly amino acids and metabolites, be evaluated in the LTC population. Clearly, it would not be responsible or ethical to give a medication to frail older adults without proof of safety and efficacy. Further, manufacturers should not be making unsupported claims of therapeutic benefits attributed to particular modular protein supplements. These claims should be substantiated with relevant clinical data in the LTC population.

Last, it is important that clinicians challenge manufacturers to provide complete and accurate information on their products. For all modular supplements, except from those in the "amino acid dose" category, manufacturers should readily provide information on PDCAAS for each of their products. For all categories of products, they should also provide metabolically sound and evidence-based guidance as to when and how their product should be used in the LTC setting.

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