SARCOPENIA, WEIGHT LOSS, AND NUTRITIONAL FRAILTY IN THE ELDERLY[*]

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Key Words malnutrition, underweight, body composition, cytokines, geriatrics

■ **Abstract** The progression of the aging process leads to a decreased margin of homeostatic reserve and a reduced ability to accommodate metabolic challenges, including nutritional stress. Nutritional frailty refers to the disability that occurs in old age owing to rapid, unintentional loss of body weight and loss of lean body mass (sarcopenia). Sarcopenia, a loss of muscle mass and strength, contributes to functional impairment. Weight loss is commonly due to a reduction in food intake; its possible etiology includes a host of physiological and nonphysiological causes. The release of cytokines during chronic disease may also be an important determinant of frailty. In addition to being anorectic, cytokines also contribute to lipolysis, muscle protein breakdown, and nitrogen loss. Whereas the multiple causes of nutritional frailty are not completely understood, clinical interventions for weight loss, sarcopenia, and cytokine alterations have been used with modest success.

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NUTRITIONAL FRAILTY: NATURAL COURSE OF THE PROBLEM

Interaction of Aging, Food Intake, and Body Composition

Aging is a highly variable process, affected by numerous factors including genetic predisposition, disease, and a host of environmental factors. Older adults comprise a heterogeneous group, with some very robust and some very frail individuals. Several characteristics that are common to this diverse group, however, include a decreasing margin of homeostatic reserve and an increasing likelihood of experiencing numerous assaults to homeostatic balance. A variety of problems contribute to the development of frailty, including but not limited to reduced food intake, loss of lean body mass (sarcopenia), illness and its cachexic effects, and subsequent functional impairments that limit mobility. In fact, frailty usually results from a combination of problems, rather than one distinct cause, and it is eventually expressed as overall functional decline. This review focuses on the nutritional aspects of the rapid, unintentional loss of body weight and accompanying disability that often signals the beginning of a terminal decline in an elderly individual and that we term "nutritional frailty."

Sarcopenia, weight loss, and nutritional frailty can all occur independently of each other among older adults. The health impact of each can only be fully understood in the context of both the phenotypic variability in aging processes and the general tenuousness of homeostasis in the face of some perturbation. Sarcopenia appears to be an age-related phenomenon, exacerbated by a sedentary lifestyle, nutritional factors, and chronic disease. Weight loss, especially if involuntary, is not a normal part of aging and usually represents some underlying disease process. Functional decline may occur separately from sarcopenia and weight loss (as in a hip fracture or stroke) but often occurs together with these two factors, especially when functional decline develops in a more insidious way. Because sarcopenia and weight loss are both nutritional entities that can lead to major functional impairment, morbidity, and mortality, we discuss them together in this review.

Prevalence of the Problem

The anticipated dramatic rise in the numbers of older adults worldwide is expected to have far-reaching effects on health patterns in the future (17). Exponential increases in the number of elderly in the population are expected to continue well into the first half of the twenty-first century. The fastest growing segment of the elderly population is the "oldest old," individuals who are 85 years and older. Those in the oldest-old group report the greatest number of disabilities, have poorer health status, and utilize more health care services than do those 65–84 years of age

(18, 31). Nutritional frailty is also most common in the oldest old. Thus, if current trends continue, its incidence will show substantial growth in the coming years. Along with the rapid increase in the number of older and oldest adults comes a growing concern about their future quality of life and the staggering medical costs that may result if current rates of nutritional frailty continue.

The exact incidence of nutritional frailty is difficult to quantify and has been mainly studied in the long-term care setting, where data are most easily gathered. Estimates of malnutrition rates in nursing homes range from 30 to over 50% (1, 76). Although less well documented, nutritional frailty also occurs in hospitalized elderly and in homebound elders in the community. A recent study by Sullivan et al. (72) of 497 hospitalized patients ≥65 years of age found that 21% were consuming less than 50% of required calories and that this under-nutrition was associated with increased in-hospital and 90-day mortality. Community-based studies also show the age-related progression toward frailty. In a follow-up study to the National Health and Nutrition Examination Survey, 50% of subjects aged 65–74 had lost at least 5% of their body weight, and 26% of women and 14% of men had lost at least 15% (85).

CAUSES OF FRAILTY AND FUNCTIONAL DECLINE

Unintentional Weight Loss

In elderly individuals the loss of body weight, apart from intentional weight reduction in the case of being overweight, almost inevitably leads to poor health outcomes (82). Low body mass index (BMI) is well recognized to be associated with an increased risk of morbidity and mortality; a BMI <23.5 in males and <22 in females is associated with an increased mortality risk (7). Weight loss is independently associated with mortality even when the data are adjusted for baseline health status (49, 82); thus, weight loss is not merely a marker for ongoing chronic illness. A low BMI also increases risks for other health problems, including disability (29). Thus unintentional weight loss in the elderly contributes to loss of functional status, increased risk of illness, and increased mortality.

A predominant cause of the weight loss occurring with old age is a reduction in food intake (43, 55). Morley (42, 43) has delineated physiological and non-physiological causes of this reduced consumption of food (and thus calories) with aging. Physiological changes that influence food intake include loss of appetite, alterations in taste and smell (44, 64, 70), poor oral health (26, 67), gastrointestinal changes (10, 35), dementia (84), and a reduced ability to regulate appetite in response to acute weight changes (55–57). Nonphysiological causes include social factors (12), psychological causes (22), economic limitations, and a variety of pathologic factors including illness and medication effects (42).

One of the most important physiological causes of reduced food intake with aging is a loss of appetite. Although the reduction in taste/smell sensitivity and changes in a number of peripheral and systemic factors that regulate food

intake/satiety are suspected to influence this phenomenon (see 20a), the problem is multi-factorial and not completely understood. In fact, the decline in food intake is influenced by age-related alterations in a number of complex and redundant mechanisms (including hedonic factors and gastrointestinal and neuroendocrine controls) and it varies over time in terms of severity and its impact on body weight and health outcomes.

Food intake gradually declines throughout adult life. Between ages 20 and 80, mean energy intake is reduced by up to 1200 kcal in men and 800 kcal in women (81). This age-related reduction in food intake has been documented in virtually every large-scale study of healthy, community-dwelling elderly (79, 81). The causes of this relative reduction in food intake are thought to be reduced physical activity, decreases in resting energy expenditure, and loss of lean body mass, which produce a decrease in demand for calories and thus for food intake (21, 25).

Whereas the reduction in calorie intake begins fairly early in adulthood, body weight does not decrease until much later. Body weight peaks about the fifth to sixth decade of life and remains stable until around age 65–70 (82). The efficiency of fat accretion increases during this time, and the ability to oxidize fat may also be compromised (39). A slow decrease in body weight begins around age 70 and continues for the remainder of life.

A very different type of food intake reduction can (but does not always) take place in later old age. The onset of this type of decline is characterized by an acute, dramatic reduction in appetite as well as food consumption and is termed nutritional frailty—the subject of the remainder of this chapter. It is distinguished from the earlier type of reduction in food intake by a precipitous drop in body weight and negative changes in other health parameters (82, 83). This deterioration takes place over a period of weeks to months and is well recognized as a hallmark of terminal physical decline. It may be called by a variety of other names in clinical settings, including failure to thrive (80), wasting away, taking to bed, or "the dwindles." The weight loss, depressed appetite, poor nutrition, and inactivity may be accompanied by dehydration, depressive symptoms, impaired immune function, and low cholesterol. These symptoms are commonly observed in the last year of life for many elderly patients.

Although nutritional frailty is known to be accompanied by a number of important metabolic changes, the originating cause or causes remain a subject of active scientific investigation. Change in body composition, primarily loss of lean body mass or sarcopenia, can be one important piece of the frailty puzzle.

Sarcopenia

Sarcopenia has been defined as the loss of muscle mass and strength that occurs with aging (59, 60). Along with diseases, neuroendocrine dysregulation and chronic inflammation, it contributes significantly to the development of frailty and functional impairment in older age. Baumgartner and co-workers (4) defined sarcopenia as values of 2 standard deviations or more below the mean for appendicular muscle mass of young healthy adults. Sarcopenic individuals in this study were further differentiated into being sarcopenic-lean and sarcopenic-obese.

Sarcopenic-obese individuals were characterized as those with percent body fat greater than sex-specific cutoff values, approximately equal to a BMI of 27 kg/m^2. Using these definitions, 13.5% of men under age 70 and 29% of men over age 80 were sarcopenic-lean. Sarcopenic obesity ranged from 13.5% in the younger male group to 17.5% in those over 80 years. In women sarcopenic-lean included 8.8% of those less than 70 and 16% of those older than 80. Sarcopenic obesity ranged from 5.3% in those under 70 years of age to 8.4% in those over 80 (5). Both types of sarcopenia were associated with functional impairment, disabilities, and falls independent of age, ethnicity, smoking, and comorbidity, but the relationships were strongest with sarcopenic obesity (5).

Although sarcopenia has been defined for epidemiologic purposes to be a loss in muscle mass, changes in muscle with aging also include a decrease in muscle strength, a decrease in muscle efficiency (muscle strength/unit of muscle mass), and a decrease in muscle protein synthesis (33, 45, 68).

Sarcopenia, like many other geriatric phenomena, involves a number of underlying mechanisms including intrinsic changes in the muscle and central nervous system and humoral and lifestyle factors. Intrinsic changes in muscle include a reduction in the proportion of fast myosin heavy-chain isoforms and type II fibers, and muscle mitochondrial DNA damage (28, 58). A central feature of sarcopenia is loss of alpha motor units from the spinal cord. Motor unit remodeling appears to be related to selective denervation of muscle fibers with re-innervation by axonal sprouting from juxtaposed innervated units (6). Many hormones and cytokines affect muscle mass and function (see Figure 1). Reductions in testosterone and estrogen that accompany aging appear to accelerate loss of muscle mass (5, 52). Although growth hormone has been hypothesized to contribute to loss of lean body mass, the relationship between growth hormone and lean mass is confounded by fat mass, and recent studies have not borne out this association (61). Activation of pro-inflammatory cytokines (interleukin-1, tumor necrosis factor, and interleukin-6) commonly occurs among older adults after acute illness or with chronic inflammatory conditions such as rheumatoid arthritis. These cytokines can cause amino acid export from muscle and accelerated protein breakdown (63). Although sarcopenia is not completely reversed with exercise, physical inactivity leads to accelerated muscle loss. Even in very old individuals, exercise can increase muscle mass and strength (14).

Cytokine Activation in Chronic Disease

Cytokines are intercellular messengers that are released in response to chronic inflammation, infection, injury, and cancer. Pro-inflammatory cytokines commonly involved in cachexia include interleukin-1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α). IL-1 and TNF-α cause significant anorexia. Both of these cytokines increase IL-6. They also increase leptin and corticotropin releasing hormone levels, both potent anorexigenic agents (48, 78). In addition to being anorectic, these cytokines also contribute to lipolysis, muscle protein breakdown and nitrogen loss. They augment the acute phase response, upregulating the production of C-reactive protein and downregulating the transcription of albumin (2).
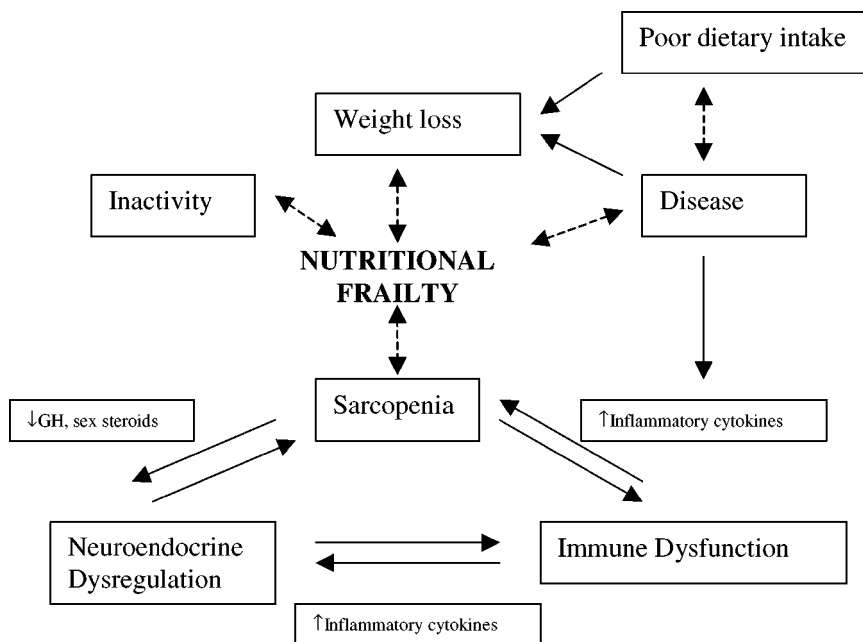
Figure 1 Dimensions of nutritional frailty. GH = growth hormone.

TNF-α concentrations are often elevated in chronic congestive heart failure and in rheumatoid arthritis, especially when these conditions are accompanied by cachexia (3, 63). Elevated IL-6 levels are also seen in inflammatory diseases, infections, and trauma. In a study of older Framing Heart Study participants, IL-6 levels were elevated in older subjects and correlated well with C-reactive protein concentrations (62). IL-1 reduces food intake in laboratory animals. In humans, increased IL-1 levels occur in patients with cachexia, even when infection and cancer are not present (32). In summary, elevated pro-inflammatory cytokines (especially IL-1, IL-6, and TNF-α) are commonly seen in older adults, especially those with cachexia, suggesting that targeting these cytokines may be an effective method to counter cachexia and nutritional frailty in older adults.

INTERVENTIONS

Interventions for Increasing Food Intake

Because of the previously noted relationship of nutritional frailty to increased morbidity and mortality, elderly individuals with pronounced unintentional weight loss and/or chronically low BMI have a condition that requires urgent intervention.

Although it seems obvious that providing more food/energy should increase consumption and thus body weight, in actuality this rarely accomplishes the goal.

This is because most of the factors responsible for producing the nutritional frailty are not related to food access. The success of the intervention is affected by an array of determining factors including available social support, affective status, economic concerns, functional status, and living situation. These factors may or may not have caused the malnutrition, but they will strongly affect efforts to correct it.

A variety of approaches have been attempted in an effort to slow or reverse the development of nutritional frailty (Table 1). The enteral route of feeding is the preferred choice for providing additional calories and protein. The provision of extra calories in the form of an oral protein/calorie (liquid) supplement is a common strategy, but it does not produce consistent benefit. In some (30, 77), but

TABLE 1 Interventions to increase food intake and body weight in nutritional frailty

Type of intervention	Reported effectiveness[a]	Type of subjects	Reference
Oral supplements			
Protein/calorie	No change	NH patients	(14)
Protein/calorie, 360 kcal/d	No change	Frail NH patients	(15)
Protein/calorie, 400 kcal/d	↑ weight	Malnourished NH patients	(30)
24 oz. medical nutritional suppl.	↑ intake[b]	High risk NH patients	(77)
Various liquid supplements	Negative mean weight change	High risk NH patients	(24)
Tube feedings[c]			
Nasogastric	Negative mean weight change	LTC patients (age 20–95)	(19)
	Negative mean weight change	Stroke patients with dysphagia	(47)
Gastrostomy (PEG)	Slight ↑ weight	Stroke patients with dysphagia	(47)
	↑ weight	Outpatients (age 18–93)	(34)
	No change	NH patients	(23)
Jejunostomy	↑ weight	Outpatients (age 26–71)	(9)
Orexigenic drugs			
Megestrol acetate, 800 mg/d	↑ body weight	NH patients	(87)
Flavor-enhancers			
6 flavors added to foods	↑ intake	Retirement home residents	(65)
Food flavors and MSG	↑ intake	Elderly hospital patients	(65)

Abbreviations: NH = nursing home, LTC = long-term care, PEG = percutaneous endoscopic gastrostomy.

[a]Using increased food intake and/or body weight as a measure of effectiveness.

[b]Body weight was not reported.

[c]For obvious reasons, food intake is artificially controlled with tube feedings.

not all (14, 15, 24), studies of oral supplements a modest improvement in food intake and body weight is achieved.

Tube feedings must be considered when there is an intestinal obstruction or if the patient is unable to ingest sufficient calories and other nutrients. Whereas ultimate health outcomes (complications, survival times) may not be improved (40), this approach can be used to produce modest increases in nutrient intake and body weight. Clinical indications and patient/family preferences dictate either the nasogastric, gastrostomy (percutaneous endoscopic gastrostomy), or jejunostomy route. The limited available literature (see Table 1) shows the most favorable outcomes from the percutaneous endoscopic gastrostomy route. Complication rates from surgical and endoscopic tube placement are high (32–70%) (51) and thus, the decision to place the tube must be carefully considered by the health care provider and the patient/surrogate.

Beyond these methods, efforts are being made to enhance the appeal of food to elderly patients and thereby increase food intake and head off subsequent malnutrition. Several orexigenic drugs have been considered, but many have not been successful and/or have adverse side effects. In one study the synthetic progestin megestrol acetate increased appetite, and (eventually) weight in nursing home patients who had lost 5% or more of their body weight (87). Dronabinol (tetrahydrocannabinol, a cannabis derivative with FDA approval for use in AIDS and cancer) is also being studied for applicability in elderly patients.

The addition of simulated food flavors to nutritious foods in order to enhance consumption may provide benefit by improving food consumption. Schiffman & Warwick (66) used this approach and found increased food consumption when food flavors (roast beef, ham, natural bacon, maple, and cheese) were added to the diets of nursing home residents. These investigators have also used food flavors to enhance food intake in hospitalized elderly patients (65). These were short-term studies, so potential effects on long-term weight gain are likely but unproven. If a sustained increase in calorie consumption can be accomplished this would eventually produce an increase in body weight.

When nutritional frailty is identified, it is important to consider a therapeutic plan that includes several simultaneous interventions. As mentioned earlier, nutritional frailty rarely has only one cause. A guideline for planning and prioritizing appropriate interventions has recently been developed for use in the nursing home. An expert panel of medical caregivers and academicians (the Council for Nutrition, Clinical Strategies in Long-Term Care) formulated a set of guidelines for the diagnosis and treatment of involuntary weight loss in the long-term care setting (11, 75). The guidelines are triggered by one of three indicators of nutritional frailty: (*a*) involuntary weight loss of 5% in 30 or 10% in 180 days or less, (*b*) a BMI $\leq$ 21 kg/m^2 (based roughly on the requirements of Congressional legislation), or (*c*) 25% of more of food uneaten for two-thirds of meals over 7 days. This clinical guide incorporates potential causes of weight loss and suggested interventions. Suggestions for family, food, and environmental changes, guidelines for laboratory assessment, and acute illness, pain, and depression are all considered in this set of guidelines.

Interventions to Address Sarcopenia

ANABOLIC INTERVENTIONS   A number of interventions have been evaluated to counter sarcopenia in older adults. Anabolic interventions that have been tested include supplementation with testosterone, growth hormone, dehydroepiandrosterone, creatine, and chromium picolinate. Studies of testosterone have been characterized by variability in method and dosing of testosterone replacement. Taken together, the studies demonstrate a modest increase in lean body mass, bone mineral density, and grip strength (66, 69, 73). The long-term safety of testosterone replacement with respect to prostate cancer and cardiovascular disease remains to be determined. A number of studies have shown that growth hormone increases muscle mass but not muscle strength (50). Unfortunately, growth hormone has many side effects in older adults, including fluid retention, gynecomastia, and orthostatic hypotension (71). Although dehydroepiandrosterone products, found routinely in health food stores, claim to improve muscle weakness, study findings have been conflicting regarding improvement in muscle mass and strength. To date, results are more promising in males than in females (16, 41). Creatine has been argued to increase stores of phosphocreatine in the muscle and replenish phosphocreatine and adenosine triphosphate during exercise. Several studies suggest a potential benefit of creatine, especially when combined with exercise, but more studies are needed to confirm these findings (53, 54). Data on chromium picolinate suffered from methodologic weaknesses in earlier studies. A recent study by Campbell and co-workers (8) did not demonstrate any positive effects of chromium picolinate on body composition and muscle function.

PROGRESSIVE RESISTANCE TRAINING AND SARCOPENIA   The most promising intervention for increasing muscle mass and strength in older persons is progressive resistance training. A number of studies show improved muscle mass, strength, balance and endurance in older adults who participate in strength training exercise (37, 46). In Fiatarone's study of very elderly adults, a combination of strength training and protein calorie supplementation was more likely to increase calories consumed than protein calorie supplementation alone, although this trend did not reach statistical significance (14). More studies are needed to evaluate the impact of a combination of strength training and anabolic hormones and/or strength training and nutritional supplementation on nutritional frailty.

Human Interventions for Cytokine Activity and Immune Function

An array of agents demonstrate inhibitory action on pro-inflammatory cytokines and are beginning to be evaluated in patients with cachexia. Pentoxifylline decreases TNF-α production by reducing TNF-α messenger RNA transcription (13). In AIDS patients, however, pentoxifylline has not contributed to weight gain (27). No studies have been performed to date using pentoxifylline in older adults. Thalidomide decreases TNF-α levels by increasing the breakdown of

TNF-α messenger RNA. Initial trials in patients with HIV cachexia have been promising for increasing weight; no studies to date have been reported in the geriatric population (86). Megestrol acetate (megace) has been used in cancer patients to increase appetite and weight gain. It appears to work through a number of different mechanisms, including reducing the production of IL-1, IL-6, and TNF-α (36). In a study of nursing home residents, those receiving 800 mg/day of megace demonstrated maximum weight gain at 12 weeks following treatment. Individuals with elevated cytokine levels at baseline were most likely to respond to megace with increased weight gain (87, 88). Omega-3 fatty acids alter cyclooxygenase and lipooxygenase activity and secondarily inhibit cytokine production. Omega-3 fatty acids show promise in animals by increasing food intake in cytokine-related cachexia; however, no studies to date have been reported in cachectic geriatric patients (74). N-acetyl cysteine and S-adenosyl methionine have both been shown to modulate concentrations of pro-inflammatory cytokines such as TNF, IL-1, and IL-6. These agents have been studied in other conditions of chronic inflammation and may have promise for treatment of geriatric cachexia (20, 38).

To conclude, a number of different agents have been shown to inhibit pro-inflammatory cytokine activity in animal models. Many of these agents have been evaluated in HIV disease, cancer, and other chronic inflammatory conditions. More research is needed to determine the impact of these agents among patients with geriatric cachexia.

SUMMARY

Nutritional frailty is a common problem in older adults, characterized by unintentional loss of body weight and lean body mass and accompanied by disability that often signals the beginning of a terminal decline. Because nutritional frailty rarely has only one cause, treatment requires a therapeutic plan that includes several simultaneous interventions. Interventions that show the most promise include flavor enhancers, progressive resistance training (to treat sarcopenia and possibly stimulate improved food intake), and agents to inhibit and modulate cachexia-producing pro-inflammatory cytokines. Much work remains to be done to identify which approaches will be of greatest benefit in older patients with nutritional frailty.

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