Frailty in the Elderly: Contributions of Sarcopenia and Visceral Protein Depletion

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In any given population of free-living individuals 65 years of age and older, a substantial proportion (in the range of 6% to 25%) suffers from many of the elements of the syndrome of frailty. Although the syndrome is complex and still lacks a standard definition, there is a growing consensus about the signs and symptoms as well as the pattern of biological correlates that characterize this disorder. Patients who are afflicted with frailty typically exhibit loss of muscle strength, fatigue easily, are physically inactive, and have a slow—and often unsteady—gait, with an increased risk (and fear) of falling. They are likely to have a poor appetite and to have undergone a recent, unintentional loss of weight. Frail individuals are more likely than the nonfrail to experience impaired cognition and depression. They die sooner. Frailty, of course, is frequently complicated by a variety of coexistent illnesses. Among the biological correlates of frailty are sarcopenia (now readily measurable by dual-energy x-ray absorptiometry [DXA]), osteopenia (with an increased susceptibility to fracture), and activation of the inflammatory and coagulation systems, with a rise in inflammatory cytokines and several markers of coagulopathy. Age-dependent changes in a number of hormones also appear to promote the development of frailty in the elderly, particularly via their effects on muscle mass and strength, bone density, and by contributing to activation of the catabolic cytokines. In particular, serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) decline progressively during aging, and an association between reduction in the levels of these hormones and the involution of advancing age has been proposed. It is not yet known whether, in comparison with their nonfrail counterparts, frail individuals consistently manifest larger reductions in GH and IGF-1 (and other anabolic hormones). More research is needed before it will be known whether the benefits of administering GH to the frail elderly will outweigh the disadvantages. The poor appetite and weight loss that occur in many frail individuals are likely to be accompanied by a degree of visceral protein depletion (with its attendant morbidity), which can be estimated by making serial measurements of indicators of visceral protein status such as transthyretin (TTR), retinol-binding protein (RBP), and albumin. One characteristic of the frailty syndrome that distinguishes it from the effects of aging per se is the potential reversibility of many of its features. Progressive resistance training is feasible for many elderly individuals—even the oldest old—and, by increasing muscle mass and strength, can ameliorate or reverse important aspects of physical frailty. To the extent that visceral protein depletion has been caused by an inadequate intake of calories and protein, consumption of a more adequate diet can result in betterment of the frail patient's nutritional status, as determined by clinical improvement and favorable changes in TTR, RBP, and albumin.
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FRAILTY is a term that has been used increasingly in recent years to describe a somewhat amorphous syndrome in elderly individuals that leaves them especially vulnerable to falls, impairment of function, illness, and premature death (Table 1). The syndrome is more common in women than men.[1] Definitions of frailty vary, depending on the author(s) describing the condition. As Walston et al[2] put it, "The biological basis of frailty has been difficult to establish owing to the lack of a standard definition, its complexity, and its frequent coexistence with illness." According to van den Beld and Lamberts,[3] "frailty is characterized by generalized weakness, impaired mobility and balance and poor endurance. Loss of muscle strength is an important factor in the process of frailty, and is the limiting factor for an individual's chances of living an independent life until death." Potential causes of frailty include sarcopenia, neuroendocrine decline, and immune dysfunction.[1] Strawbridge et al[4] have conceptualized frailty as involving problems or difficulties in 2 or more of the following functional domains: physical, nutritive, cognitive, and sensory. In a cohort of respondents aged 65 to 102 years, one fourth scored as being frail, reporting reduced activities, decreasing mental health, and lower life satisfaction. Frail subjects are said to have significantly increased levels of catabolic cytokines and reduced hemoglobin levels, together with a normocytic, subclinical anemia.[5-7] Weight loss predicts early mortality among free-living frail elders.[8]

RELATION OF FRAILTY TO ACTIVATION OF THE INFLAMMATORY AND COAGULATION SYSTEMS

Within the last few years an increasing number of reports have suggested the existence of a physiological basis to the frailty syndrome that is characterized in part by an increase in markers of inflammation and coagulopathy. In an effort to establish the biological correlates of frailty, Walston et al[2] studied 4,735 community-dwelling adults $\geq$ 65 years of age (Cardiovascular Health Study participants). Frail, intermediate, and nonfrail subjects were identified by exclusion criteria and "a validated screening tool." Of this cohort, 6.3% were identified as frail, 45.3% as "intermediate," and 48.3% as not frail. Frail versus nonfrail participants had increased levels of C-reactive protein, factor VIII, and D-dimer. These differences remained after exclusion of individuals with cardiovascular disease and diabetes and after adjustment for age, sex, and race.

A recent prospective study reported by Cohen et al[9] was

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Table 1. Frailty in the Elderly: Some Clinical Characteristics and Biological Correlates

Symptoms and Signs	Biological Correlates
Muscle weakness	Increased blood levels of catabolic cytokines:
Fatigue	C-reactive protein
Inactivity	Interleukin-6 (IL-6)
Slow and/or unsteady gait	Elevated markers of blood coagulation:
	D-dimer
Weight loss	Factor VIII
Loss of appetite	Reduced hemoglobin levels:
Reduced endurance	Normocytic subclinical anemia
Impaired cognition	Hormonal declines:
	Growth hormone
	Insulin-like growth factor-1 (IGF-1)
	Testosterone (in men)
	Dehydroepiandrosterone (DHEA)
	Estradiol (E2) (in men)
	Hormonal increases:
	Cortisol production (especially postmenopausal women)
	Luteinizing hormone (in men)
	Body composition changes:
	Sarcopenia
	Osteoporosis
	Visceral protein decrease:
	Transthyretin (TTR) ↓
	Retinol-binding protein ↓
	Serum albumin ↓

designed to determine the effects of markers of inflammation (interleukin-6 [IL-6]) and coagulation (D-dimer) on mortality and functional status in participants in the Duke Established Populations for Epidemiologic Studies of the Elderly. Of this group, 1,722 had IL-6 and D-dimer measurements, which, in 1992, were categorized into quartiles. The relative risk of mortality was 1.28 for those with only IL-6 levels in the highest quartile, 1.53 for subjects with only D-dimer levels in the highest quartile, and 2.00 for those with levels of both in the highest quartile, as compared with those who were not in either of the highest quartiles. Cohen et al[9] found that those with high IL-6 and high D-dimer levels had the greatest decline in all measures of function.

Roubenoff[5] has suggested that IL-6 and other cytokines could function through direct catabolic effects or, more indirectly, by inducing anorexia, lowering growth hormone (GH) and insulin-like growth factor-1 (IGF-1) concentrations, or by triggering loss of muscle cells in the elderly—even in the absence of overt inflammatory disease. As Ershler and Keller[10] point out, estrogen and testosterone (which diminish with age) are among several factors that downregulate IL-6 gene expression. They propose that the age-associated increase in IL-6 could help to account for some of the phenotypic changes that occur in the elderly, including decreased lean body mass, osteopenia, low-grade anemia, lymphoproliferative disorders, and Alzheimer's disease.

In an epidemiologic study involving participants in the Health, Aging, and Body Composition Study on 3,075 black and white men and women aged 70 to 79 years of age, Visser et al[11] found that elevated cytokine levels (obtained by combining the levels of IL-6 and tumor necrosis factor-alpha [TNF-α]) were associated across gender and race groups with lower muscle mass (measured by computed tomography and dual energy x-ray absorptiometry [DXA]) and lower muscle strength (measured by isometric grip strength). In their words, "Higher cytokine levels, as often observed in healthy older persons, may contribute to the loss of muscle mass and strength that accompanies aging."

ENDOCRINE CHANGES ASSOCIATED WITH FRAILTY

Age-dependent declines in a number of hormones have been implicated in the causation of frailty in the elderly—particularly via their effects on muscle mass and bone density. In men, aging is associated with substantial mean decreases in bioavailable testosterone (bT), estradiol (E2), and dehydroepiandrosterone (DHEA) and its sulfate (DHEAS).[12-14] Serum luteinizing hormone levels increase with age in elderly men and correlate inversely with bT and several indicators of frailty.[15] Compared to men, postmenopausal women appear to maintain an elevated cortisol production, which is directly related to most measures of GH secretion.[16] Serum levels of GH and IGF-1 decline progressively during aging, and an association between reduced GH and IGF-1 levels and the involution of aging has been proposed.[17] In aging and severe GH deficiency, muscle mass and strength are decreased along with loss of bone mass (osteopenia), with increased risk of fracture.[18] In addition, the relative proportion of total and (particularly) visceral fat is increased.[17]

MEASUREMENT OF SARCOPENIA AND ITS PREVALENCE

Sarcopenia is a major contributor to frailty; yet, muscle mass has only recently begun to be quantified in substantial numbers of elderly individuals by means of such sophisticated body composition methods as DXA and magnetic resonance imaging (MRI).[19] Assessment of total body protein (TBP) from body nitrogen (TBN) content, as opposed to measurement of muscle mass, is best accomplished by total body in vivo neutron activation (neutron capture) analysis (IVNAA).[20] (Gamma ray nuclear resonance absorption [γ-NRA], used to detect the N in explosives placed in air-cargo containers, offers promise of being able to measure TBN at radiation doses at least one order of magnitude lower than those imposed by IVNAA.[21]) According to Hansen et al,[22] TBP declines curvilinearly with age, with an accelerated decrease after 65 years. Although loss of skeletal muscle protein is primarily responsible for the age-related decline in TBP, the contribution of visceral protein depletion to development of the frailty syndrome may prove to be important.

Apart from any involutional effects of aging-related hormone changes, a major contributor to the decline in muscle size and function in aging individuals is simple disuse arising for the most part from chronic physical inactivity. During senescence, there is a gradual loss of both motor nerves and muscle fibers, particularly of the fast-twitch [IIa] fibers, with impaired function of the surviving myocytes.[23] The resulting loss of muscular strength results in increased risk of falling, physical frailty, and disability. Inadequate intake of protein and calories

is a potentially important (and remediable) cause of both sarcopenia and visceral protein depletion. This decline in food intake is in part attributable to the physiologic anorexia of aging, caused in part by an increase in the level of circulating cytokines,[5] and also by alterations of stomach-fundus compliance and release and activity of cholecystokinin.[24] Accumulation of fat can mask the presence of sarcopenia in elderly men and women.[25] There is also growing evidence suggesting that the unintentional decrease in body weight known to predict early mortality in the elderly entails loss of a higher proportion of lean body mass (LBM) than fat.[26] It is not known which component of LBM loss is most responsible for the increased risk of premature death.

New developments in body composition technology have made it possible to quantify muscle mass and distinguish muscle from LBM.[19] In a cross-sectional survey of body composition data (based on biological impedance analysis measurements) from the Third National Health and Nutrition and Examination Survey, Janssen et al[27] found that, in subjects aged $\geq$ 60, the prevalence of class II sarcopenia (the presence of a skeletal muscle mass index [SMI] below 2 standard deviations from the sex-specific mean for adults aged 18 to 39) was 10% in women and 7% in men. The likelihood of functional impairment and disability was approximately twice greater in the older men and thrice greater in the older women with class II sarcopenia than in the older men and women with a normal SMI.

TOTAL BODY PROTEIN DEPLETION VERSUS SARCOPENIA

TBP content varies depending on sex, age, stature, muscular development, and other factors. The body of a healthy 70-kg man of average height and build might be expected to contain about 10.5 kg of protein, of which about 53% (5.6 kg) is intracellular.[28] When one is concerned about protein depletion, the component of greatest interest is intracellular protein (ie, the protein within the cells of the heart, liver, kidneys, skeletal muscle, etc). It is this protein component that constitutes the major part of the body's "labile" protein reserve. The body cannot afford to lose very much of its limited supply of intracellular protein. For example, depletion of the baseline body cell mass (BCM) by about 45% may be lethal,[29] and loss of lesser amounts is accompanied by substantial morbidity. In a group of 32 healthy young male volunteers who underwent 6 months of experimental semistarvation (The Minnesota Experiment[30]), a decrease in the fat-free mass index (FFMI [FFM_{kg}/ht_m^2])[31] of approximately 17% after 6 months of caloric restriction was associated with near prostration, severe weakness, depression, and other serious signs and symptoms of advanced semistarvation.[30]

Given the availability of new methods that permit fairly accurate estimation of TBP, it is now be possible to determine the clinical significance in elderly individuals of various degrees of body protein depletion. Both sarcopenia and visceral protein depletion may be reflected in the measurement of TBP in the frail elderly. It is therefore important to attempt to distinguish the contribution to TBP loss of the sarcopenia that results from physical inactivity from that of visceral protein depletion caused by illness and/or an insufficient intake of dietary calories and protein. Possession of this kind of information about elderly patients who exhibit the frailty syndrome should prove to be indispensable in their diagnosis and care. When an elderly individual eats poorly and at the same time becomes increasingly sedentary, some combination of body fat loss, sarcopenia, and visceral protein depletion will inevitably ensue. The investigative challenge is to assess the individual contribution of each of these components to the morbidity associated with protein-calorie malnutrition (PCM).

There is little evidence to suggest that loss of stored triglyceride per se will be damaging to overweight people; to the contrary, the health of such individuals may improve when excess fat is lost. However, a chronic energy deficit can cause mean fat cell size to shrink below "normal." People (including certain weight-reduced formerly obese individuals) whose fat cells become too small may develop signs and symptoms suggestive of semistarvation.[32]

MARKERS OF VISCERAL PROTEIN STATUS

As discussed above, muscle mass can be quantified by means of several body composition methods, as well as by measurement of the creatinine/height index. In contrast, assessment of visceral protein status is more difficult. At present, the preferred approach to the assessment of "visceral" protein status is to measure the levels in plasma of the so-called visceral protein markers, such as transthyretin (TTR) and retinol-binding protein (RBP). Because these proteins have a short half-life they serve as useful indexes of a patient's nutritional status, with reduced TTR and RBP concentrations suggesting the presence of PCM. Decreasing concentrations of these markers indicate that protein malnutrition is worsening, while rising concentrations suggest spontaneous improvement or a favorable response to nutritional intervention. Because of the lability of TTR and RBP, they are particularly useful as indicators of the short-term trajectory of nutritional depletion or repletion. Serum albumin, on the other hand, turns over more slowly; therefore, a low albumin level—in the absence of complicating factors such as liver disease—can be a useful marker for PCM of longer duration.

Brugler et al[33] have reported the results of a pilot project designed to examine the feasibility of a full-scale study to assess the value of TTR and albumin for detecting and monitoring PCM in hospitalized patients. These authors pointed out that there is ". . . a large patient population (30%-55%) at risk for PCM, and an even larger population experiencing declining nutritional status during hospitalization . . ."

The pilot study demonstrated that these 2 markers provide important information predictive of outcomes for those they identify at risk of PCM. According to Brugler and coworkers, "The patients who entered the study with, or developed, low transthyretin and albumin levels experienced poorer health outcomes and higher costs of care."

Vellas et al[34] investigated the relationships among nutritional markers in 155 older persons (53 men and 102 women; mean age, 78 years [range, 56 to 97]). The participants were housed in a geriatric evaluation unit (n = 105) or free-living in the community (n = 50). The Mini Nutritional Assessment (MNA)

scores were found to be significantly correlated to nutritional intake ($P < .05$ for energy and carbohydrate) and biological nutritional parameters ($P < .001$ for albumin and TTR). In another study of nutritional status in 261 people 65 to 103 years of age newly admitted to a community resident home, Christensson et al[35] found that PCM—diagnosed on the basis of body mass index (BMI), triceps skinfold thickness, arm muscle circumference, serum albumin, and TTR—was present in 29% of the residents who entered municipal care from their own homes, and 43% of the residents who entered from hospital care. Among the factors associated with PCM were reduced fluid intake, deteriorated appetite, reduced mobility, need of help during meals, and gastrointestinal symptoms.

Because IGF-1 concentrations in blood serum are known to decline with advancing age, Arai et al[36] studied IGF-1 levels in 49 centenarians and investigated the possible relationship between IGF-1 and BMI, lipid parameters, nutritional indices, physical and cognitive function, and frequency of hip fracture. In the centenarians, the mean levels of IGF-1 were low, indicating an age-associated decrease in this indicator, even in the extremely old. A strong association of IGF-1 with TTR and RBP was demonstrated; however, there was no association with albumin, transferrin, or BMI. These findings indicate that, like TTR and RBP, serum IGF-1 levels in the oldest old reflect their short-term nutritional status. It was also noted by the authors that the centenarians with lower IGF-1 levels had a higher prevalence of definitive dementia.

TREATMENT OPTIONS

It has been shown convincingly that high-intensity, progressive resistance training can give rise to significant increases in strength and muscle mass in the elderly—even in individuals ≥ 90 years—and thereby ameliorate or reverse important aspects of the syndrome of physical frailty.[37,38] It has also been reported that physical exercise is a potent stimulus of GH secretion, while aging and obesity are associated with a decrease in GH secretion. Holt et al[39] found that, in older men performing a maximal exercise test, peak GH was higher in older lean men than in older overweight men. In the older men, there was an inverse correlation between measures of fat mass and GH secretion. The treatment and preventive implications of these observations are evident.

If visceral protein depletion has been caused by a chronically reduced intake of energy and protein, it is likely that consumption of a more adequate diet will result in improvement in the elderly patient's nutritional status. Measurement of baseline blood levels of serum albumin, TTR, RBP, and IGF-1 will help the clinician determine whether visceral protein depletion is present, and its extent. Subsequent monitoring of these indicators will disclose whether or not the malnourished patient is responding favorably to nutritional intervention.

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