Editorial

Something About Frailty

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FRAILTY is a commonly used term indicating older persons at increased risk for morbidity and mortality (1). In some ways, it is analogous in older persons with the term “failure to thrive” in young children. Unfortunately, it has been poorly defined in the medical literature.

There is general agreement that frailty is not adequately defined as purely a decline in functional status, although functional status is itself a predictor of poor outcomes (2–5), and Gealey (6) found that persons perceived to be frail also showed functional impairment. Brown and colleagues (7) defined frailty as a state that “occurs when there is diminished ability to carry out the important practical and social activities of daily living.” Hougaard (8) defined frailty as “a random effects model for time variables, where the random effect (frailty) has a multiplicative effect on hazard.” Rockwood and colleagues (9) suggested that the essential feature of frailty is the “notion of risk due to instability” and called for a more precise operationalization of the term. Lipsitz (10) defined frailty etiologically using a mathematical chaos theory approach suggesting that frailty occurs when the responses of an organism “lose complexity in resting dynamics and [show] maladaptive responses to perturbations.” Using the concept of synmorphosis, Bortz (11) has suggested that frailty is a result of early disease in multiple systems leading to impaired muscle strength, mobility, balance, and endurance.

Recently, two groups have attempted to operationalize the definition of frailty. Fried and colleagues (12) have provided a specific list of objective, measurable criteria for frailty. Using their definition, they found frailty to be present in 6.9% of older community-dwelling persons and to be more common in women. Their definition differed from disability and comorbidity in this population and was a predictor of future functional decline and morbidity. Brown and colleagues (13) suggested that frailty could best be predicted by obstacle course performance, hip abduction strength, the semitandem portion of the Romberg test, and coordination on the pegboard test.

A number of shorter tests to screen for frailty have also been developed. Vellas and colleagues (14) suggested that an abnormal one-leg standing balance was a simple and inexpensive marker of frailty. Miller and colleagues (15) found timed one-leg balance to be a predictor for frailty in inner-city elderly African-Americans. Lundin-Olsson and colleagues (16) utilized the Timed Up and Go (TAG) test done with and without carrying a glass of water. The TAG consists of rising from an armchair, walking 3 meters, turning around, and sitting down again. They found that persons who took 4.5 seconds or longer to complete the task when carrying the glass of water than when doing it without the extra task could be classified as frail. Brody and colleagues (17) produced a simple self-reported screening instrument that had a 50.7% sensitivity and a 97.8% specificity for predicting persons at risk of frailty. There is a need to compare these simpler tests to the more complex tests discussed in the previous paragraph.

Frailty is the precursor of functional deterioration, which leads to recurrent hospitalization, institutionalization, and death (Figure 1; 4–6,18–23). Frail persons have a decrease in social activity (12,24,25). This is compounded by the fact that frailty is often associated with incontinence, a major factor in decreasing social activity and leading to institutionalization (26–28). Frailty leads to a decline in mobility (29,30) and is independently associated with osteopenia (31). This combination leads to falls associated with hip fracture and a subsequent fear of falling (32–34). Finally, frail persons appear to be at an increased risk of developing stroke (35).

There are many causes of frailty, all of which can interact to prod the individual on the downward spiral of frailty. The geriatrician can make little impact upon some of these factors. These include chronological age, genes, and previous education level (12,36–39). It would appear that having apolipoprotein E4, a risk factor for both Alzheimer’s disease and atherosclerosis, is a particularly good marker of future frailty (40–43). Ongoing studies in centenarians comparing the highly functional versus the less functional and persons who are younger should yield, over the next decade, some extremely exciting data on the genetic components of frailty (44–53).

For simplicity’s sake, based on the literature, we suggest that there are four major intrinsic factors—sarcopenia and related metabolic pathogenic factors, atherosclerosis, cognitive impairment, and malnutrition—that are responsible for the pathogenesis of frailty (Figure 2). Frailty’s severity can further be determined by a series of social factors such as low income, low education, and lack of family, church, or other societal supports (54). We have also identified a set of potentially treatable precursor conditions that can lead to these major determinants of frailty. They are anorexia; inactivity, lack of exercise, and fear of falling; pain; diabetes mellitus; depression; and delirium. Pain limits mobility and exercise activity (55–58). Diabetes mellitus enhances the perception of pain (59,60), accelerates atherosclerosis
causes depression, and is associated with cognitive impairment (59,64–66). It has been shown to increase functional impairment, increase injurious falls, and decrease social activity (67–74). Both depression and delirium worsen the outcome from other diseases and independently cause functional decline (60,64,75–78).

Sarcopenia or the “melting of flesh” is a term that describes the loss of muscle mass and diminishment of muscle function that occurs with aging. As a pathological entity, it has been operationally described as an appendicular lean body mass less than two standard deviations below that of a young healthy population corrected for height in meters squared (79). The prevalence of sarcopenia has been calculated to range from 6% to 12% in persons older than 60 years of age to more than 50% in the old-old (80–82). With the development of sarcopenia, there is a decrease in the ratio of skeletal muscle to adipose tissue free body mass (83). Women have a smaller ratio of muscle to fat, and African-Americans have a greater ratio in old age. Visser and colleagues (84) have suggested that it is muscle strength rather than muscle mass that determines lower limb performance. With aging, there is a decline in the synthesis rate of mixed muscle protein, myosin heavy chain, and in mitochondria proteins, along with an anatomic loss of Type IIa fibers, all of which contribute to the pathogenesis of sarcopenia (79,85). A number of genetic factors have been identified as putative factors involved in the maintenance of fat-free mass in the Quebec Family Study (86). These include the insulin growth factor-1 receptor on 15q and neuropeptide Y and the growth hormone releasing hormone receptor on 7p. Two markers of an unidentified gene(s) were identified on 18q12. Rat studies have suggested a relationship of muscle fibers with mitochondrial DNA deletions to the development of sarcopenia (87). There is some evidence that apoptosis resulting in muscle fiber loss with aging is related to mitochondria enzyme activity (88). Myostatin is a gene that inhibits the growth of muscle. The mRNA for myostatin does not appear to decline with age, suggesting a potential role for myostatin in age-related sarcopenia (89).

A number of studies have suggested that the decline in testosterone that occurs in men over the lifespan is related to loss of muscle mass. Free testosterone index is the best index of muscle mass loss and is a strong indicator of the decline in strength with aging in men (90,91). Testosterone replacement increased muscle mass in older persons (92), and in persons who are truly hypogonadal, it also increased strength and bone mineral density (92–97). Insulin-like growth factor-1 (IGF-1) is also related to loss of muscle in men and women (98). Transgenic mice overexpressing IGF-1 have greater muscle force and did not show the decline in dehydroepiandrosterone receptors that is responsible for excitation-contraction uncoupling (99). Excitation-contraction uncoupling is the major mechanism responsible for underlying skeletal muscle weakness in aging mammals. Both testosterone and growth hormone increase IGF-1. Growth hormone treatment appears to increase muscle mass but not strength (100). Growth hormone does not appear to be a suitable agent for the management of sarcopenia both because of its increased effect on mortality in older persons (100–102) and because it increases free radical damage to muscle (103). There is evidence that the decline in muscle mass and strength in women may also be related to testosterone (104). Growth hormone secretion is higher in women with high body cell mass compared to those with sarcopenia (105). While dehydroepiandrosterone and its sulfate decline dramatically with age, there are limited data suggesting that it can reverse sarcopenia (106).

Another major cause of sarcopenia appears to be the effect of increased cytokines on muscle leading to reduced protein synthesis (107–112). In particular, interleukin-6 appears to play a role in accelerating sarcopenia and frailty (111–113). Loss of nerve motor endplates with aging leads to discoordinated firing of the muscles (114). Pain results in loss of lean muscle mass (115), a decrease in the ability of a
person to exercise to maximum effect, and a decline in function (116). Atherosclerosis leads to an accelerated loss of muscle units.

While not all investigators would consider atherosclerosis a major cause of frailty, it clearly is a prime etiological factor. Poor blood flow to the legs leads to decreased blood flow to the nerves and muscles, aggravating sarcopenia and decreasing the availability of oxygen to muscles. Minor strokes within the central nervous system can lead to cognitive impairment, and coronary artery atherosclerosis can cause deterioration of cardiac output and a decline in VO\textsubscript{2\text{max}}.

Overwhelmingly, immobility or lack of exercise appears to be the major factor in the pathogenesis of sarcopenia (117,118). Yarasheski and colleagues (119) found that resistance exercise increased mixed muscle protein synthesis rate. Both balance and muscle strength are predictors of frailty (120). Improvement in lower extremity strength is related to improved physical performance in frail community-dwelling elders (120,121).

It is now well established that a physiological anorexia of aging can play an important role in the decline of function in older persons (122,123). When an older person develops malnutrition, he or she becomes cachexic with severe loss of muscle strength (124). Cachexia appears to be predominantly associated with excess elaboration of cytokines (108,122). Malnourished older persons also have vitamin deficiencies leading to cognitive impairment (125) and to elevated homocysteine levels that can lead to accelerated atherosclerosis (126). The decline in vitamin levels also decreases the defense mechanisms against free radicals (127). Malnutrition is a strong determinant of frailty (122). A decline in serum cholesterol levels, which represents both malnutrition and cytokine excess, is an excellent marker for frailty in older persons (128,129).

Cognitive dysfunction leads to frailty either directly or indirectly due to decreased food intake (113). Binder and colleagues (130) showed that decreased cognitive processing speed as measured by trail making B or the Cancellation Random Figure Test were associated with a decline in a standardized physical performance test.

The metabolic factors associated with frailty are outlined in Figure 3.

During the past decade, our understanding of both the definition of frailty and its pathophysiology has come a long way. In many ways, frailty is the bread and butter of the geriatrician’s existence. It is a syndrome that often goes unnoticed by the general internist or the subspecialist. It is in the management of frailty that the art of geriatrics is best expressed. During the past few years, the articles in the Journal have clearly demonstrated the efficacy of resistance and balance exercises at reversing elements of frailty (131–145). There is increasing evidence that hypogonadism in older men is associated with functional decline (146) and that testosterone replacement in these men will improve function (147). Aggressive nutritional support with calories and vitamins can delay frailty (124,148). Appropriate treatment of depression (149,150), delirium (151), diabetes (152), osteoporosis (153), and hypertension (154,155) can all prevent the onset or acceleration of frailty. Providing appropriate social support and perhaps treatment for early cognitive impairment represents other modalities to improve the outcome of the frail older person. Aggressive treatment of pain will allow the older person to continue to function and exercise and will prevent the onset of sarcopenia (116). Determining the appropriate levels of health promotion and disease prevention represent a major intellectual challenge for the gerontological team (156). All of this needs to be carried out while remembering the hazards of polypharmacy in the older person (157–159).

As geriatricians, it is important as we devise approaches to the management of frailty that we allow our older friends to maintain as much autonomy as possible. To this end, Miller and colleagues (160) examined the preferences of seniors for frailty remedial strategies. Older persons’ enthusiasm for exercise was lower than the levels of participation necessary for reversal of frailty. Seniors tended to prefer stretching, chair-based, walking, and dynamic balance exercises over lifting weights, dancing, and hormone-based therapy. Most subjects preferred home-based rather than group exercises. Vitamin therapy was preferred over hormones as has been consistently seen in articles on complementary and alternative medicine published in the Journal (161–164). Clearly, geriatricians need to increase the awareness of strategies for the prevention of frailty in the general population as well as in our own patients.

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Figure 3. Metabolic causes of frailty. DHEA = dehydroepiandrosterone; IGF-1 = insulin-like growth factor-1.
References


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