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Prevention and Treatment of Frailty in the Postmenopausal Woman

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Frailty is a complex subject, and all aspects of frailty are intertwined. This article identifies and discusses the individual aspects of frailty. These aspects, including sarcopenia, nutrition, obesity, relative strength, inflammatory markers, osteopenia and osteoporosis, aerobic capacity, absolute strength, balance, and prevention of frailty, must be reunited, albeit in varying combinations, if the effects of frailty on women are to be understood and treated. This article does not exhaust the topic, but covers what the authors consider to be the major issues.

Definitions of frailty

Frailty can be intuitively defined as the characteristics of an individual who is thin and weak. Vulnerability, fragility, and lack of resilience are also generally considered characteristics of frail individuals. A broad definition of frailty, developed by Buchner and coworkers [1] in the Seattle arm of the Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) study, states that frailty is any loss of physiologic reserves that predicts or increases the susceptibility to disability. These reserves include relative strength, bone density, and aerobic capacity, and might also include cognitive abilities, motor skills, linguistic ability, various types of memory, visual acuity, and hearing acuity. When young people become temporarily incapacitated from illness or injury, they lose some muscle mass, strength, and aerobic capacity. However, they have enough in reserve that they can recover from the illness or injury using what strength remains to return to preillness levels. If older individuals have lived sedentary lives, they will

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have gradually lost so much strength that they have little or no reserves; illness or injury will weaken them and they will not have the ability to recover completely. Many families report that grandparents are never the same after the flu or a fall; their reserves, which were once abundant, are gone.

Because frailty can exist before it is obvious, and because it is such a central problem with aging, considerable effort has been expended to clearly define the concept. Using factor analysis, Speechley and Tinetti [2] identified nine variables that loaded heavily on a construct called frailty. Those variables were divided into three subgroups: (1) predictors of future loss of physiologic reserve (eg, age >80 years, depression, sedative use, sedentary lifestyle), (2) indicators of current loss (eg, decreased muscle strength in shoulder or knee, visual loss), and (3) clinical measures of disability (eg, measurements of gait, balance, and lower extremity disability). The frailty syndrome has also been elucidated by Fried, Bandeen-Roche, and coworkers [3], who characterize frailty as a medical syndrome caused by aggregate declines in multiple molecular, cellular, and physiologic systems, and is indicated by weight loss, exhaustion, low energy expenditure, weakness, and slowness. In proportional hazards models, frail women had a higher risk for losing the ability to perform activities of daily living (ADLs) or instrumental ADLs (IADLs), and a greater risk for institutionalization and death, independent of multiple potentially confounding factors.

Sarcopenia

Sarcopenia, the loss of muscle mass and strength that occurs with aging, is a term coined by Rosenberg in 1988 [4] to describe one of the most noticeable changes that occurs in older women. It has generally been considered a normal part of aging and does not seem to require the presence of disease [5]. However, because most data are cross-sectional, and the speed and degree of loss varies greatly among individuals, defining the limits of "normal" is an ongoing process. Consequently, discussion is ongoing about how much loss of muscle mass is an inevitable part of aging, and how much is caused by disuse [6,7]. Numerous studies of older athletes have found that for those who have maintained an active lifestyle, the loss of muscle mass is much less than would be predicted by age [8].

Muscle mass is also lost after illness or surgery. Each day of bed rest results in an estimated 1% loss of muscle strength [9], and an estimated 75% of hip fracture patients will lose so much muscle mass that they will never regain previous levels of function [10].

Clearly a link exists between muscle loss and disability. Janssen and colleagues [11], developed a scale of muscle loss with certain cut points below which odds for disability significantly increased. Encouragingly, even very frail nursing home residents in their 70s, 80s, and 90s can improve muscle strength by as much as 100% through resistance training, resulting in improvement in gait velocity and stair-climbing ability [12].

Because production of hormones, such as growth hormone, testosterone, and estrogen, are known to be related to strength and diminish with age, treatment of muscle loss with hormones has been investigated. Studies suggest that although some improvements can be attributed to growth hormone, the unwanted side effects are numerous and the improvements minimal [13]. Testosterone replacement therapy is considered a possible treatment of frailty for older men. Although some experts suggest that this treatment might have beneficial effects on muscle mass and strength, determining whether adverse side effects counterbalance any possible benefits is impossible. Despite the fact that testosterone levels in women are also linked to muscle mass and strength and that testosterone production diminishes with age in women, few studies have examined testosterone replacement for older women as a treatment of loss of muscle mass, and none has shown unequivocal improvement in health-related outcomes [14]. Although hormone replacement therapies have been used to try to reverse sarcopenia, strength training is the preferred treatment of age-related muscle wasting [15].

Nutrition

Aging is associated with altered sensations of thirst, hunger, sense of smell, and satiety [16,17]. When older people have no obvious reason to eat, the frequent result is diets lacking in the variety necessary to provide adequate nutrition. Older women may be at higher risk for micronutrient malnutrition because of difficulty with shopping and meal preparation and simple disinclination to prepare complex meals when the meal will be eaten alone (among women aged $\geq$75 years, 51% live alone [18]). Not unreasonably, older persons tend to adapt their diets to individual functional difficulties, such as chewing, self-feeding, shopping for basic necessities, carrying a shopping bag, cooking a warm meal, or using fingers to grasp or handle. These problems can lead to monotonous food consumption and, as a consequence, inadequate nutrient intake. Reporting difficulties in three or more nutrition-related activities has been shown to significantly increase the risk for inadequate intake of energy [19,20]. Bartali and colleagues [19] found evidence that low intakes of energy and selected nutrients are independently associated with frailty. Semba and colleagues [21] found that low serum micronutrient (various vitamins and minerals) concentrations are an independent risk factor for frailty among disabled older women, and that the risk for frailty increases with the number of micronutrient deficiencies.

Individuals do not need to be thin to be malnourished. In a study examining the nutritional status of rural, homebound elderly, virtually all were deficient in recommended nutrients, but only 5% of those interviewed were underweight (body mass index [BMI] $<$18.5). In fact, 22% were overweight (BMI 25.0–29.9) and 33% were obese (BMI $>$30.0) [22]. Overweight

and obese older women, particularly those living alone, may be at greater nutritional risk than men who have a high BMI [23].

Experts have suggested that, although older people's caloric needs may diminish with age, their need for protein may not, and the current recommended dietary allowance of 0.8 g per kilogram of weight per day is probably insufficient to meet the needs of most older people [24,25].

Inadequate diet, and especially inadequate protein, results in low energy, which leads to reduced activity and therefore loss of muscle mass and aerobic capacity, which then diminishes appetite. This vicious circle is further exacerbated by the fact that poor diet, inadequate activity, and (often) inadequate intake of water contribute to constipation, which also diminishes appetite and discourages physical activity (Fig. 1).

Some suggest that aerobic activity can improve the absorption of nutrients in malnourished older individuals, and resistance training seems to effectively lower dietary protein needs by improving the efficiency of protein absorption [25,26]. Some studies have suggested that supplementation with essential amino acids can help offset the muscle wasting produced by prolonged bed rest [27], but no evidence exists that it is a useful way to maintain muscle mass in community-living elders. A study investigating nutritional supplementation and strength training in frail nursing home residents found that nutritional supplementation alone had no effect on muscle mass, and

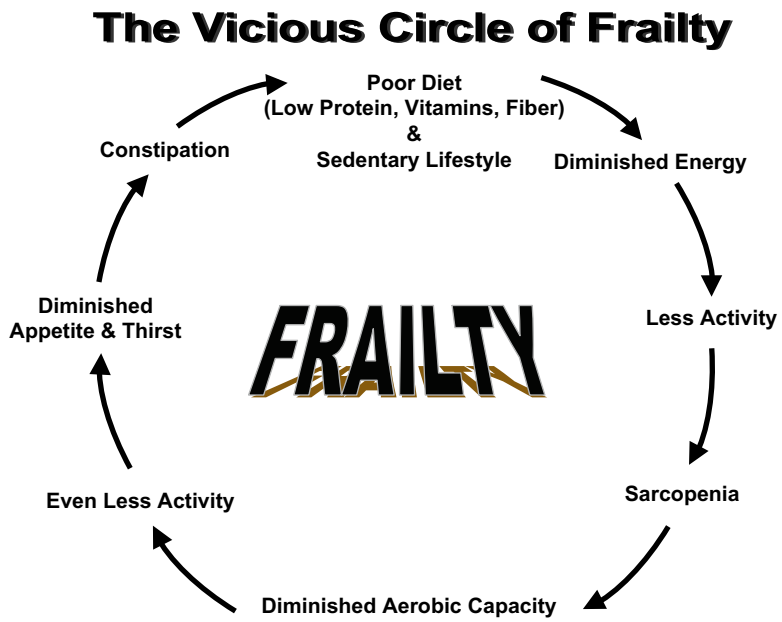

Fig. 1. The Vicious Circle of Frailty links poor diet and hydration, reduced energy and physical activity, and sarcopenia.

that the supplementation was related to diminished caloric intake in those who did not participate in resistance training. The resistance training had a significant positive effect on strength, gait speed, and overall physical activity [12]. Evans [25] stated that resistance training seems to have the greatest potential for stopping or reversing sarcopenia in malnourished older individuals. This article's authors would add that it should be combined with proper diet and aerobic exercise.

Clearly, educating older women, and the general population, about the importance of eating adequate amounts of fruits, vegetables, and protein is essential. Proper diet must be combined with enough exercise to stimulate appetite and elimination and maintain enough muscle mass to enable individuals to continue performing (at least) ADLs.

Obesity

An obese individual rarely comes to mind when thinking of a frail person, but in fact the two are not mutually exclusive, and are actually closely linked. By the time an obese woman reaches 80 years of age, she will almost certainly evince the symptoms listed by Speechley, Tinetti, Fried, and Bandeen-Roche [2,3] of sedentary lifestyle, weakness, exhaustion, low energy expenditure, slowness, difficulty with gait and balance, and lower extremity disability. Obesity as a factor is further elucidated in the following section on relative strength.

Relative strength

As Buchner and deLateur [28] pointed out, an intuitive understanding exists that strength and ability to function are closely interrelated. They were the first to understand that, in terms of function, the key is not absolute strength, but strength relative to height and weight. A woman may be able to leg press 100 lb, but if she weighs 300 lb, she will not be able to stand up. This relationship has recently been corroborated in a longitudinal study that found that *sarcopenic obesity*, or low muscle mass in relation to fat mass, predicted onset of IADL disability in community-dwelling elders who had no disability [29]. Those who did not develop subsequent disability had significantly higher activity levels than those who developed disabilities, whether obese or not.

Inflammatory markers

Indicators of frailty can be found among blood tests. Low Insulin-like growth factor-1 (IGF-1) levels have been shown to be associated with markers of frailty, especially inflammatory markers, such as interleukin 6 (IL-6) [30]. This finding might partially explain the effectiveness of

low-dose aspirin in the prevention of heart attacks. That is, not only does the acetylsalicylic acid decrease the tendency of platelets to aggregate, it also has an anti-inflammatory effect. High levels of cytokines, particularly IL-6, are often observed in elderly people and can apparently accelerate sarcopenia, because IL-6 inhibits the production of IGF-1, an important anabolic stimulus for muscle growth [5].

The apparent interaction between elevated inflammatory markers and reductions in growth factor signals may be a root cause of progressive muscle wasting [31]. Cappola and colleagues [32] found that older women who had the lowest levels of IGF-1 and high levels of IL-6 showed the greatest decrements in walking performance and functional ability, and increased mortality.

Therapies directed toward inflammatory factors have been available for many years, but their efficacy in treating muscle wasting is either questionable or has not been tested [31]. Reducing the blood levels of IL-6 has not been shown to be as effective in preventing frailty as has, for example, lowering total and low-density lipoprotein cholesterol in preventing coronary artery disease. More likely, correcting frailty causes reduction in the levels of IL-6 and C-reactive protein.

Although a common assumption is that age is the underlying cause of increased inflammatory markers, evidence shows that it may be related to inactivity. McFarlin and colleagues [33] investigated the relationship among age, physical activity, and biomarkers of inflammation. The findings of that study supported previous reports, which inferred that acute exercise or a physically active lifestyle may possess anti-inflammatory properties.

Osteopenia and osteoporosis

One of the most obvious results of increased frailty is the higher incidence of fractures in older women. After menopause, bone turnover continues, but more bone is lost than is built. Because women frequently have small bones, as age increases this loss of bone density results in more porous, and therefore more fragile, bones. A fall that might result in a quickly forgotten bruise at 20 years of age may result in a fractured hip at 80 years of age. Although hip replacements have helped maintain mobility for some individuals who fracture hips, the femur must be dense enough to receive the implant, which can be a problem for older women, whose bones are often brittle and porous [34].

Discussion is ongoing about whether lipid-lowering drugs slow bone turnover, thereby improving bone mineral density. One large case-control study (498,417 cases) in Denmark suggests that among lipid-lowering drugs, statins, but not non-statins, protect bone density [35]. The Women's Health Initiative Observational Study (93,716 women) in the United States concluded that statin use did not improve fracture risk or bone density and that the cumulative evidence does not warrant use of statins to prevent or treat osteoporosis [36].

As in sarcopenia, some evidence shows that testosterone replacement therapy may slow or reverse bone loss in older women and men, but no large randomized controlled studies have adequately investigate the safety and efficacy of this treatment [14].

Aerobic capacity

Another aspect of aging and frailty is diminished aerobic capacity. It is common knowledge that maximal aerobic capacity declines with age, although the decline is much less debilitating if regular physical activity is part of the aging person's lifestyle. Although the possible peak workload diminishes with age, trained older athletes still perform better than most sedentary young individuals [37]. Older women's participation in vigorous aerobic activities is only now becoming socially acceptable, so the available data on women who have maintained a very active lifestyle are limited. Currently, studies referring to active lifestyles often consider women who report an hour of activity a week to be active. Even using that lenient criterion, active lifestyles are consistently linked to better function and overall health. Studies that measure actual aerobic fitness, such as the recent studies by Barlow and colleagues [38], Kara and colleagues [39], and Ades and colleagues [40], report an inverse relationship among aerobic fitness and hypertension, cognitive function, and overall function in women.

It is becoming much more common for older women to participate and even compete in aerobic activities such as rowing, running, tennis, cross-country and downhill skiing, swimming, water aerobics, and hiking. It will be interesting to see what will be discovered when there are more very active older women.

Absolute strength

Although seeking a concise definition of frailty and understanding its underlying causes are interesting and useful, identifying an indicator that can be quickly identified without multiple sophisticated tests is also helpful. A very simple indicator of frailty does seem to exist: absolute grip strength seems to be inversely proportional to disability. As part of the Women's Health and Aging Study, Rantanen and colleagues [41,42] found that absolute grip strength was a powerful predictor of cause-specific and total mortality. Presence of chronic diseases or the mechanisms underlying decline in muscle strength associated with chronic disease, such as poor nutritional status, disuse, and depression, all of which are independent predictors of mortality, did not explain the association. They concluded that handgrip strength may predict mortality through mechanisms other than those leading from disease to muscle impairment. In a study of 75- and 80-year-old community-dwelling individuals, Portegijs and colleagues [43] found that a high level of regular physical activity seemed to compensate for low muscle

strength, resulting in lower mortality than would normally be predicted by the low muscle strength.

Balance

Another problem associated with frailty is loss of balance. As women age, many experience repeated falls, often resulting in hip fracture or other injury. Loss of balance can sometimes be attributed to conditions such as Parkinson's disease, vestibular disorders, vision problems, stroke, or side effects of drugs. Often no cause is obvious. Understandably, fear of falling increases as falls increase, usually resulting in diminished activity, even if no injury resulted from the fall [44,45]. Diminished activity leads to loss of muscle mass and bone density, which lead to more falls and more injuries. Fortunately, this downward spiral can be reversed with exercise [12,46,47].

Prevention of frailty

With the ever-increasing number of active and strong older women, the fact that frailty is not an inevitable part of aging is becoming apparent. This condition can at least be postponed, and at best prevented.

Each section that addresses aspects of frailty ends with the same refrain: exercise is the key to prevention of frailty. As other authors have shown (such as in the articles on bone health and those on prevention and management of compression fractures found elsewhere in this issue), building physiologic reserves during adolescence and young adulthood is important. Even more important, however, is developing and maintaining the habit of regular exercise to develop and maintain these physiologic reserves. This activity must be as integral to normal life as brushing the teeth.

Several important types of activity prevent frailty. One type is strength training, which wards off sarcopenia and helps maintain bone density and balance. Another type is aerobic exercise, which maintains cardiovascular health. Flexibility and balance exercises should also be included in an exercise program. The question, of course, is how, in this time of ever-diminishing need to be active, exercise can be integrated into daily life; how can sedentary patients be convinced to become more active.

The authors believe this question must first be answered at a personal level. Do physicians themselves participate in regular exercise to show that they understand its importance? And if not, can they expect patients to believe them if they do not demonstrate what they claim is so vital? Finding time in a busy day for some exercise is no less challenging for patients than for physicians.

The problem is rarely lack of general knowledge that exercise is beneficial; most people are already aware that exercise should be part of life, so physicians do not need to spend much time explaining this to patients. However, many people are not aware of the long-term effects of not exercising,

nor are they aware that many of the effects are reversible. Many people think that they must join a gym or an organized exercise group to achieve the appropriate levels of physical activity. Although group support has been shown to help maintain exercise adherence [48], perceived lack of time and lack of value for exercise are major barriers to exercise [49]. Another significant barrier is the misconception that bed rest, or a lot of rest, is beneficial, when in fact it rapidly accelerates loss of muscle mass, strength, and cardiovascular decline [50].

Although some debate continues about how much information is retained after a physician visit, elderly adults who receive exercise advice from their physician have been shown to perform more moderate to heavy levels of exercise per week than those who did not [51]. Physicians must communicate the need and importance of daily exercise to all patients [52].

Explaining to patients how physicians themselves manage to fit exercise into their busy lives, to help patients understand how this can be done, can also be helpful. Box 1 provides some suggestions. The authors, who exercise regularly, have found that these guidelines work.

If patients are not exercising at all, suggesting incremental changes in behavior works best. Even considering a major lifestyle change might seem overwhelming to them. Rather than asking them to buy weights, tell them to go the pantry and get a couple cans of soup or bags of rice (something soft is preferable because it is easier to grasp and hurts less when dropped, but cans also work well) and put them on their favorite chair. This way, when the patients sit down to watch television, they can do 10 biceps curls; when a new show comes on, they can do 10 more. Voila! They have an exercise schedule! Because evidence shows that presenting patients with written material after giving exercise advice increases adherence [55], physicians should literally give them a list of things they can do with the "new toys." For example:

1. Place the cans or bag on each knee and raise them to shoulder level.
2. Take one in the left hand and touch it to the right hip, then touch the right one to the left hip.
3. Bend over and touch them to the floor several times.

Physicians should also add several blank lines to the list and provide patients with an assignment: they should add two new exercises that use the toys and must demonstrate them at the next visit. Successive approximations should be rewarded. If patients return with only one new exercise, they should still be praised and encouraged to think of another exercise for next time.

Some additional suggestions include doing a hula dance while brushing teeth, which will strengthen abdominal and leg muscles and is fun. When grocery shopping, they can walk half an aisle on the toes and the other half on the heels, and can do a few biceps curls with a milk jug. If they

Box 1. Suggestions for finding ways to fit exercise into your life

1. Think about why exercise is important to you. Do you want to maintain or regain mobility or strength, flexibility, or balance? Do you want to lose or keep off some fat? Do you want to improve or maintain aerobic capacity? Do you want to find new friends or enjoy the company of old ones? Whatever the reasons are, they are valid for you. Remember them and remind yourself of them often.
2. Set reasonable goals. Very few people have an hour a day to spend at the gym, and even fewer want to. Most people can find half an hour during the day, even if it is divided into two or three parts, when they can fit something in. It has been shown that multiple short bouts of brisk exercise reap almost the same benefits as one half-hour bout for previously sedentary individuals [53]. The most important part is doing it.
3. Keep the goals short-term. Commit to 1-week intervals rather than ''the rest of my life.'' As Bandura [54] pointed out, *chunking*, or dividing tasks into manageable bits, makes getting the task done much easier.
4. Plan ahead and be specific. Opportunities for exercise rarely ''just appear.'' ''I'll try to get a walk in some time today'' usually means that the day will be over and the walk will not have happened. Look for specific time in the day and literally put it in the schedule. Do the planning for exercise in 1-week chunks.
5. Do not think about it too much and do not allow yourself to question whether you really have time or whether you really feel like it. You have time because you already planned it, and you will certainly feel better after it is done.

have a sense of humor, physicians can suggest that the grocery aisles, or any long halls, are great places to practice ''silly walks''; this is not only good exercise but is also fun, and if the activity is fun, patients are more likely to repeat the exercise.

Physicians should keep in mind that patients who do not exercise probably do not know how [56], and therefore simply telling them they should is not likely to produce a change in behavior. Physicians should discuss ways to get some movement into their lives and provide patients with written suggestions to take home, because all patients forget what doctors tell them to do, especially if it is something novel.

At no age does one no longer need to be active to maintain good health. The recommendations from the Centers for Disease Control and Prevention/American College of Sports Medicine [57–59] that every adult in the

United States should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week do not put an upper age limit on the guidelines. Throughout the lifespan, regular exercise is vital. No one wishes to one day discover that she has fallen and cannot get up.

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