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Frailty and Sarcopenia: The New Geriatric Giants

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ABSTRACT

In the last decade, it has become clear that older persons who are frail or sarcopenic have very high rates of functional deterioration, hospitalization, and death. Recently, it has become recognized that simple screening questionnaires, e.g., the FRAIL and SARC-F, perform as well as more complex testing for the physical phenotype screen and sarcopenia. In this article, we provide a simple algorithm for the management of frailty. The multiple factors responsible for the pathogenesis of sarcopenia are reviewed, focusing on the importance of age-associated loss of motor units innervating muscle. Management of sarcopenia includes resistance exercise, leucine-enriched protein, and vitamin D. A number of newer drugs are under development. General practitioners should be encouraged to screen for frailty and sarcopenia in older persons. (REV INVES CLIN. 2016;68:59-67)

Key words: Frailty. Sarcopenia. Geriatrics. Screening tools. Aging.

In 1976 Bernard Isaacs documented the giants of geriatrics as: impaired vision and hearing, instability and falls, incontinence (fecal and urinary), and intellectual impairment (dementia and delirium)[1,2]. He considered these the conditions that were present in frail older persons. Frailty can be considered to be a state of vulnerability that increases the chance of an older person having functional deterioration, hospitalization, or death[3]. In 2001 Fried, et al.[4] suggested that a physical phenotype (weakness [grip strength], slowness [walking speed], low level of physical activity, self-reported exhaustion, and unintentional weight loss > 4.5 kg in one year) (Table 1) would be useful to recognize frail individuals. It is particularly useful for recognizing persons at high risk of developing functional impairment (loss of activities of daily living)[5]. This approach has become enormously successful for research purposes, but has not been included in general geriatric practice[6-9].

Recently, a simple five question FRAIL scale has been developed which is easily utilized in the clinical setting (Table 2)[10-12].

The term "sarcopenia" was introduced into the literature by Irv Rosenberg in 1995[13]. It was defined as an abnormal loss of muscle associated with aging and it has been validated to predict functional decline[14]. However, Manini and Clark[15] pointed out that it was muscle power and not muscle mass that

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Table 1. Fried's frailty phenotype[4]

A.	Characteristics of frailty
	Shrinking: Weight loss (unintentional)
	Sarcopenia (loss of muscle mass)
	Weakness
	Poor endurance (exhaustion)
	Slowness
	Low activity
B.	Cardiovascular Health Study Measure
	Baseline: > 4.5 kg lost unintentionally in prior year
	Grip strength: lowest 20% (by gender, body mass index)
	"Exhaustion" (self-report)
	Walking time/15 feet: slowest 20% (by gender, height)
	Kcals/week: Lowest 20% (males < 383 Kcals/week; females: < 270 Kcals/week)
C.	Presence of Frailty
	Positive for frailty phenotype: ≥ 3 criteria present
	Intermediate or pre-frail: 1 or 2 criteria present

Table 2. The FRAIL Scale: A rapid, validated scale for the detection of frailty

	3 or more positive answers – frail
	1 or 2 positive answers – pre-frail
F	atigue (have felt tired most or all of the time in past 4 weeks)
R	esistance (have difficulty or unable to climb a flight of stairs)
A	erobic (have difficulty or unable to walk a block)
I	llness (have more than 5 illnesses)
L	oss of weight (have lost more than 5% of weight in past 6 months)

Adapted with permission from Morley, et al.[10].

was the predominant feature that led to loss of functional status. Thus, in 2010 the European Consensus on the Definition and Diagnosis of Sarcopenia changed the definition of sarcopenia to be "muscle loss together with a loss of function as measured by either walking speed or grip strength[16]. Subsequently, four other similar definitions of sarcopenia were published with somewhat different cutoff points[17-20]. In view of the finding that the six FRAX questions without measuring bone mineral density were predictive of fracture risk, we developed a five-question scale (SARC-F) to detect muscle dysfunction in older persons[21-23] (Table 3).

We believe that frailty and sarcopenia should now be recognized as the new geriatric giants. The availability of rapid scales allows primary care physicians to recognize these conditions and to either treat them or refer persons with these syndromes to a geriatrician[24].

FRAILTY PHENOTYPE

There is now international consensus that frailty is a measurable clinical syndrome that recognizes persons at increased vulnerability to stress who may have treatable conditions[10]. It is felt that all persons over 70 years of age should be screened for frailty. Utilizing the physical phenotype of Fried (Cardiovascular Health Study) or FRAIL, persons are considered frail if they have three or more criteria, and pre-frail if they have one or two components. Frailty overlaps with disability, but not all

Tabla 3. SARC-F screen for sarcopenia

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of ten stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the last year?	None = 0 1-3 falls = 1 4 or more falls = 2

Adapted with permission from Malmstrom, et al.[21].

disabled persons are frail and about 70% of the frail are not disabled[25]. Sarcopenia is one of the causes of frailty, but similarly, not all frail persons are sarcopenic and not all sarcopenic persons are frail[26].

There are numerous other frailty scales that have been developed. Some of these are similar to the physical phenotype of frailty (e.g., Study of Osteoporotic Fractures[27], the Frailty Instrument for Primary Care[28], or the Survey of Health Ageing and Retirement in Europe, SHARE-FI)[29]. Others are broader and include psychosocial factors, e.g., the Groningen and Tilburg Frailty Indices[30-33].

The prevalence of physical frailty increases with aging from under 5% in community dwelling persons aged 65-75 years to about 25% in persons who are 85 years of age or older34. Table 4 provides examples of the prevalence of physical frailty in community dwelling persons in different countries[35-55].

A separate approach to frailty has been developed by Rockwood, et al.[56] utilizing the Canadian Health Survey. This has been termed the Frailty Index (FI). This is developed by summing the number of diseases and physical and psychosocial deficits present in an older person. Scales vary from 30 to 100 items. While the FI is highly predictive of poor outcomes, it is much more a comorbidity or multimorbidity index than a true frailty measure. It fails to separate frailty from the underlying comorbidities that may be its cause and it includes disabilities that it is supposed to predict. As such, one can question whether or not it is a true frailty index, though it clearly has a utility as a predictive index.

MANAGEMENT OF FRAILTY

The FRAIL index can be used as a guideline for management. It has been successfully used in the community to recognize frail persons[57]. Persons who answer that they are fatigued should be screened for depression using either the Patient Health Questionnaire 9 (PHQ-9) or the Geriatric Depression Scale[58]. Sleep apnea is a common cause of fatigue and should be excluded by querying whether or not the person stops breathing at night, snores excessively, or falls asleep while driving or in the middle of a conversation. Hypothyroidism, vitamin B_{12} deficiency, and anemia are common causes of tiredness. Low blood pressure, especially orthostatic hypotension or postprandial hypotension, also cause fatigue[59,60].

Problems with the questions about resistance and aerobic activity suggest sarcopenia. This can be treated with resistance exercise, 1,000 IU vitamin D and a leucine-enriched essential amino acid supplement (see section on sarcopenia treatment).

Persons who have multiple illnesses usually have polypharmacy, which often leads to drug side effects[61-63]. Anticholinergic drugs are particularly likely to lead to central nervous system side effects and fatigue[64,65]. Reduction of polypharmacy often can reduce drug side effects and improve quality of life[66,67].

Weight loss in older persons has a variety of treatable diseases, which can be recognized using the MEALS-ON-WHEELS mnemonic[68-70]. For persons with chronic obstructive pulmonary disease, multiple small meals may overcome the dyspnea associated with the thermic effect of eating[71]. Further caloric supplementation can slow the progression of weight loss[72-74].

Figure 1 provides a simple algorithm for the treatment of frailty.

SARCOPENIA

Sarcopenia is an inevitable consequence of aging as demonstrated by the decline in the women's world record for the long jump, which is 7.44 m for the young and 1.72 m for ninety year olds. Aging results in muscle fiber size heterogeneity with a predominant loss of Type II muscle fibers and a decline in satellite cells[75]. Sarcopenia needs to be differentiated from cachexia, which is due predominantly to an increase in proinflammatory cytokines due to diseases[76,77]. Fiber size variability is not present in cachexia.

A major component of muscle loss with aging is due to a loss of motor units innervating muscle[78]. Over the lifespan there is a loss of approximately 25% of motor neurons innervating type II muscle fibers[79]. Damage to motor units can be detected by measuring circulating C-terminal agrin[80]. The accelerated loss of muscle mass that occurs in persons with diabetes mellitus is due to the decreased muscle innervation coupled with decreased blood flow to muscle[81-83].

Tabla 4. Prevalence of frailty in older persons in different countries

Country	Age (years)	Percentage (%)	Notes
USA, CHS[7]	65-74	3.9	
	85+	25.0	
AAH[36]	49-65	2.7 (7.5)	ADL dependence included in parenthesis
	58-74	8.6	
WHAS[35]	70-79	11.3	Women only
Canada GLOW[38]	55+	15.0	Women only
Mexico SADEM[39]	60+	15.7	
Brazil FIBRA-RJ[40]	65+	9.1	
Peru[41]	60+	27.8	
Columbia[42]	60+	12.2	Rural, living in Andes
Europe[37]	65+	17.0	5.8% in Switzerland 27.3% in Spain
United Kingdom[43]	65+	8.1	
Ireland[44]	65+	6.0	
Turkey[45,53]	65+	27.8 (10)	FRAIL in parenthesis
China[46]	60+	15.1	Only included diabetics
Japan[47]	65+	9.3	
Hong Kong[11]	65+	14.0	
Taiwan[48]	65+	4.9	
Korea[49]	65+	7.8	
Malaysia[50]	60+	5.7	
Singapore[51]	55+	2.5	
Australia, Western[54,55]	70+	20.6	Men only using FRAIL scale
	70+	5.6	Women only
Australia Longitudinal Study on Women's Health[52]	85+	16.2	Women only

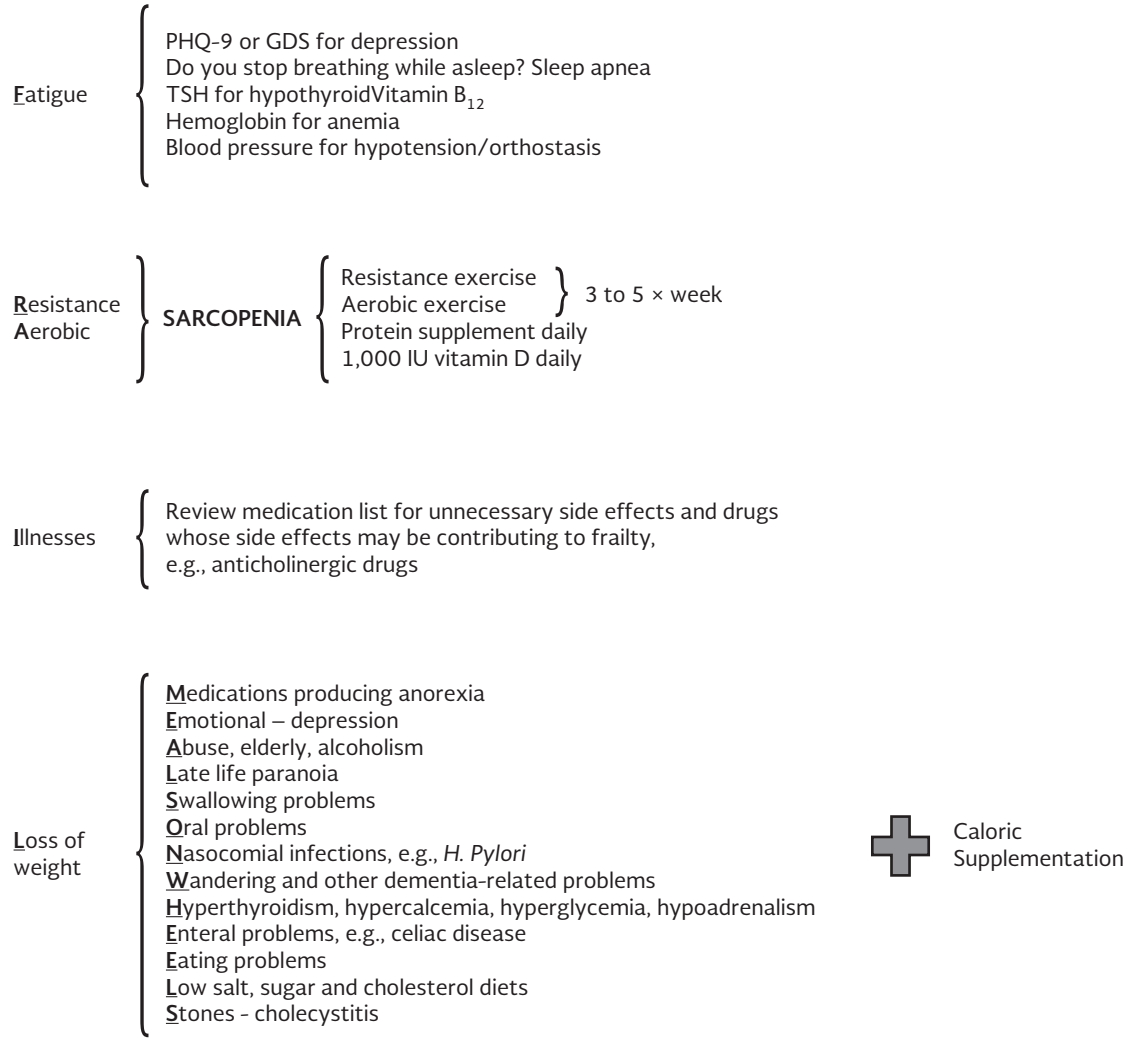
AAH: Action Against Hunger; ADL: activities of daily living; SADEM: Study on Aging and Dementia: CHS: Cardiovascular Health Study; WHAS: Women's Health and Aging Studies.

The development of sarcopenia with aging appears to be related to a variety of age-related factors. Anabolic hormones, especially testosterone, show a decline of about 1% per year from the age of 30 years[84]. This decline is closely related to both the loss of muscle and strength that occurs with aging[85]. The decline in growth hormone leads to a decline in insulin-like growth factor-1 and mechano growth factor[86]. This decline is related to the loss of muscle mass, but not necessarily muscle power[87]. With aging, there is an anorexia of aging which leads to muscle loss[88]. There is also a decline in activity with aging, further causing muscle to be less functional[89]. Levels of 25(OH) vitamin D decline longitudinally with aging[90]. This is both due to a decrease in the ability of cholecalciferol in the skin to make 25(OH) vitamin D and a decline in vitamin D absorption, as well as a decrease in sun exposure and the use of sunblock[91]. Decreased blood supply to the muscles due to atherosclerosis leads to muscle hypoxia. Insulin resistance associated with aging results in increased fat infiltration into muscle, leading to a decline in muscle function[92]. Parabiosis experiments between young and old mice have found a role of the circulating factor –growth differentiation factor-1– in age-related muscle loss[93]; Low-grade proinflammatory cytokine production that occurs with aging results in loss of muscle mass and function[94]. Finally, mitochondrial dysfunction that is associated with aging leads not only to oxidative damage of muscle, but also a reduction in the ability to generate energy to allow muscles to function properly[95]. The factors involved in the pathophysiology of sarcopenia are outlined in table 5.

MANAGEMENT OF SARCOPENIA

Since the original manuscript by Fiatarone, et al.[96] demonstrating that resistance exercises can improve strength in 90-year-old nursing home residents, numerous papers have been published supporting the utility of

Figure 1. Algorithm for management of frailty.



resistance exercise in improving muscle strength in persons with sarcopenia[97]. The LIFE study found that aerobic exercise slowed lower limb functional decline[98]. Singh, et al.[99] showed that resistance exercise twice a week for a year markedly improved clinical outcomes in older persons following hip fracture[100].

There is evidence that older persons who have lost muscle require 1.0-1.2 g/kg/day of protein to restore the loss of muscle mass[100,101]. This protein should be leucine-enriched essential amino acid based[102]. A number of studies have suggested that the addition of protein to exercise can further increase muscle performance[103-106]. The PROVIDE study showed that protein supplementation together with vitamin D increased muscle mass and the ability to do chair stands in persons with sarcopenia[107].

Replacement of vitamin D in vitamin D-deficient persons increases muscle strength and prevents falls[108,109]. Vitamin D supplementation does not increase muscle mass.

Testosterone can increase muscle mass in persons with low testosterone[110,111]. Higher doses of testosterone are required to improve muscle strength and/or power[112-114]. Testosterone improves function in older persons with frailty[115-117]. Testosterone activates beta-catenin to increase muscle mass and at high doses recruits satellite cells to enhance muscle strength[118]. In general, testosterone has minimal side effects[119,120]. However, there is some evidence that within the first year of treatment, testosterone increases cardiovascular disease[121]. This may be due to excessive increase in hematocrit where this is poorly monitored or due

Table 5. Factors involved in the pathophysiology of sarcopenia

Factor	Effect	
	Loss of muscle mass	Loss of muscle strength
1. Decreased physical activity	Yes	Yes
2. Decreased food (protein) intake	Yes	No
3. Decreased testosterone	Yes	Yes
4. Decreased growth hormone and Insulin Growth Factor I	Yes	No
5. Decreased DHEA	Small	No evidence
6. Vitamin D deficiency	No	Yes
7. Insulin resistance	No	Yes
8. Decreased growth differentiation factor-1	Yes	No evidence
9. Atherosclerosis	Yes	Yes
10. Decreased motor units	Small	Yes
11. Proinflammatory cytokine excess	Yes	Yes
12. Mitochondrial dysfunction	No	Yes

DHEA: dehydroepiandrosterone.

to increased relaxation of the coronary arteries resulting in rupture of unstable plaques[122]. A number of selective androgen receptor modulators have been developed. Unfortunately, to date they have not been demonstrated to be more effective than testosterone and there is insufficient evidence to determine if they have a better safety profile[123,124].

Growth hormone increased muscle mass and nitrogen retention[125,126]. It does not improve muscle strength and thus should not be used to treat sarcopenia.

Ghrelin is a hormone that is produced from the fundus of the stomach and enhances growth hormone release, food intake, and memory[127]. Anamorelin, a ghrelin agonist, has been shown to increase food intake and muscle mass, but not muscle function, in persons with cancer[128].

Antibodies to myostatin and the activin II receptor have been developed. Myostatin antibodies increase muscle mass and muscle fiber diameter in mice[129]. There is some evidence that they may have similar effects in humans with sarcopenia[130]. Activin II receptor ligand traps have powerful effects on increasing muscle and bone mass, but side effects have led to their development being halted[131]. Novartis has developed a direct antibody to the activin II receptor that has shown positive effects in persons with inclusion body myositis[132].

Other drugs under development to treat sarcopenia include the angiotensin converting enzyme inhibitor (perindopril), fast skeletal troponin activators (tirasemtiv) and mixed beta agonist/antagonist (espindolol)[133-135].

OSTEOSARCOPENIA

There is increasing evidence that osteoporosis and sarcopenia frequently coexist[136]. Men with sarcopenia have an increased risk of hip fracture[137]. Exercise increases muscle strength and muscle contraction directly enhances bone mineral density and bone quality[138]. In addition, vitamin D has direct effects on bone and muscle[139]. However, recent studies have suggested that the interaction between muscle and bone is due to an extremely complex bidirectional communication between both muscle and bone chemokines[140]. Further, both adipose tissue and cartilage also produce paracrine substances that modify the function of muscle and bone. Among the myokines that modulate bone are proinflammatory cytokines, myostatin, fibroblast growth factor-2, insulin-like growth factor-1, Tmem119, and osteoglycin[141]. Bone chemokines include the osteocyte-derived prostaglandin E2 and WnT3a as well as osteoblastic products such as osteocalcin and sclerostin. Under-carboxylated osteocalcin also plays a hormonal role by increasing the function of insulin receptors to increase glucose entry into cells.

COGNITIVE FRAILTY

Cognitive frailty has been defined as physical frailty coupled with cognitive impairment (CDR 0.5)[142]. The concept was first recognized in older Mexican Americans in 2008[143] and in 2011 was also described in the Mexican study of Nutritional and Psychosocial Markers of Frailty[144]. Persons with the combination of cognitive impairment and the physical frailty phenotype are more likely to develop disability, a decline in instrumental activities of daily living, and hospitalization[145]. The coexistence of physical frailty and cognitive impairment is not surprising given the fact that proinflammatory

cytokines play a role in the pathophysiology of both conditions[146], and white matter hyperintensity is related to both cognitive impairment, decline in walking speed, and falls[147]. The IAGG consensus conference on "Brain Health" has stated that there is a need for further research into this important relationship[148].

CONCLUSIONS

Over the last decade, frailty and sarcopenia have risen to become the true modern giants of geriatrics. While frailty and sarcopenia overlap, about a third of persons with sarcopenia do not have frailty, and similarly, all frail persons do not have sarcopenia[149,150]. The recent development of rapid, simple screening tests for both conditions (FRAIL and SARC-F) has made it easy for clinicians to identify them. In this article we provide a simple algorithm to treat both physical frailty and sarcopenia. It is hoped that this approach to secondary prevention will lead to a reduction in disability in older persons.

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