Continuing Medical Education

SARCOPENIA AND FUNCTIONAL DECLINE: PATHOPHYSIOLOGY, PREVENTION AND THERAPY

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ABSTRACT

Twenty years ago, the term 'sarcopenia' has been introduced to describe the ageing related loss of skeletal muscle mass. Since then, sarcopenia has been intensively studied and prevalence values have been reported in fifteen papers covering several continents and races. However, consistency regarding the outcome measures and corresponding cut-off values defining sarcopenia is lacking. Most approaches are based on estimations of muscle mass and proposed cut-off values might be too strict, thus reducing their use in daily practice. From a clinical viewpoint, the assessment of muscle performance (grip strength and endurance) can be proposed as a screening tool showing sufficient sensitivity. The pathophysiology of sarcopenia is multifactorial, and important changes at the tissue level have been identified. Close relationships with inflammatory processes have been demonstrated and there is strong evidence for the involvement of a chronic low-grade inflammatory activity. Sarcopenia is aggravated by a complex interaction of several factors among which aging, disuse, immobilization, disease and malnutrition. A comprehensive geriatric assessment should allow the clinician to estimate the relative contribution of these factors and to elaborate appropriate management. From all interventions studied, intensive resistance training seems the most efficient to counter sarcopenia, even in the very old geriatric patients. Significant ameliorations (up to >50% strength gain) can be expected after six weeks of training at a rhythm of 2-3 sessions per week. From a preventive viewpoint, all elderly patients should be advised to start such an exercise program and continue it as long as possible. To date, most pharmacological interventions to counter sarcopenia include drugs with anabolic effects. Unfortunately, their effect is questionable and no clear guidelines exist for the prescription of these products in the context of sarcopenia.

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1. DEFINING SARCOPENIA

One of the most intriguing age-related changes is the loss of skeletal muscle mass. In order to draw the attention of clinicians, scientists and policy-makers to this phenomenon, Rosenberg suggested in 1988 to

give it a name derived from the Greek such as 'sarcomalacia' or 'sarcopenia' (1, 2). The term sarcopenia has been adopted by the scientific community, and increasing efforts have been addressed to explore the determinants of this phenomenon (3).

Originally, sarcopenia refers to the age-related decline in lean body mass. In fact, most human physiologic systems regress with ageing, independently of substantial disease effects, at an average linear loss rate of 0.34-1.28% per year between the age of 30 and 70 years (4). Conceptually, sarcopenia can therefore be considered as the effect of ageing on muscle mass; affecting all ageing humans. Although sarcopenia is a typical phenomenon of the aged, cross-sectional data indicate that skeletal muscle atrophy starts around the age of 30-40 years and progresses insidiously (5, 6). The loss of muscle mass is primarily due to a decrease in the number of both type I (slow twitch) and type II (fast twitch) muscle fibres and a reduction of the size of the remaining muscle fibres, with a preferential atrophy of the type II fibres (5, 7). The progression of sarcopenia has high inter-individual variability (8), with mean linear loss rates per year between the age of 30 and 70 going from 0.7% to 1.5%. Besides atrophy, muscle fibres also present a tendency to shorten and their orientation within the muscle (pennation angle) changes towards a less optimal configuration (9). An important consequence of this muscle atrophy and qualitative changes is the accompanying muscle weakness. Moreover, the process accelerates dramatically above the age of 70 years with losses of strength up to 3.5 % per year (10).

Several authors proposed, given the parallelism, to redefine sarcopenia in analogy to osteoporosis. In this concept, the actual muscle mass (MM) of an elderly subject is compared to the mean MM of a young, healthy and gender-matched reference group. The difference in MM can then be expressed in standard deviations (SD) by means of a t-score (((actual MM) - (gender-specific normative score of healthy young persons))/ SD(gender-specific normative score of healthy young persons)). Several 'skeletal muscle indices' (SMI) have been proposed in order to correct MM for individual anthropometry, such as MM/height^2 or MM/body mass. From a statistical viewpoint, sarcopenia has first been defined as SMI t-score<-2SD by Baumgartner et al. (11). In order to allow for stratification, Janssen et al (12) defined 2 degrees of severity of sarcopenia according to the SMI t-score (Class-1 if -1>t-score>-2 and Class-2 if t-score<-2). However, it appears that the cut-off-values for sarcopenia depend strongly on the method used for MM-determination (such as Dual Energy X-ray Absorptiometry or Bio-Impedance) as well as on the reference population used in the calculation of t-scores. In table 1, an overview of the available literature concerning the prevalence of sarcopenia is provided. As can be seen, a wide variability in prevalence has been reported, going from 0 to 100 % in males and females aged 60 years and older. Prevalence values were markedly low in studies using a reference group including subjects older than 40 years, which can be explained by lower cut-off values defining sarcopenia (13, 14). Also, the prevalence of sarcopenia seems to be underestimated in overweight and obese persons when correcting MM for height^2. It has become clear now that a high body weight can mask sarcopenia in elderly persons (15). The influence of body weight on the relationship between sarcopenia and physical functioning has been demonstrated by Estrada et al (16). In fact, the use of an SMI correcting for body weight might be a more valid approach in order to study the impact of sarcopenia on physical disability. Especially for overweight and obese subjects a correction for total body weight or fat mass seems most appropriate when interpreting MM values (e.g. by expressing MM per kg total body weight or MM/fat mass ratio) (17).

We can conclude that to date, no satisfying definition based on muscle mass for diagnosing sarcopenia is available. Definitions of sarcopenia based on t-scores <-2 SD, which is a pure statistical approach, for skeletal muscle mass (absolute or corrected) is insufficient for clinical use. Conceptually, it is difficult to consider a subject presenting e.g. a t-score=-1 or a t-score=-1.7 as not presenting sarcopenia. From a preventive and therapeutic approach, the criteria for defining sarcopenia should be sufficiently sensitive. When considering the available prevalence data for sarcopenia as summarized in table 1, it seems justified to regard at least 50% of the elderly above the age of 70 years as presenting muscle weakness and atrophy, justifying interventions to counter the process.

Interestingly, the loss of muscle strength in ageing is more important than can be explained by atrophy alone. Consequently, prevalence values of sarcopenia are considerably higher when based on muscle performance (using grip strength 95% in male and 71% in female aged older than 85years) compared to muscle mass (using calf muscle cross-sectional area 68% in male and 6% in female aged older than 85 years) (18). Therefore, in clinical settings the evaluation of muscle capacity might be more instructive for decision making than muscle mass.

Table 1. Prevalence of Sarcopenia as reported in the literature (between 1998-2008).

Source	Method	Population	Reference	Criterion	Cut points	Prevalence		
						Category	Male	Female
Baumgartner ea. (11)	*ASM	New Mexico, USA Hisp: 221M, 209F N-Hisp: 205M, 173F	†N-Hisp, 107M, 122F aged 18-40yrs	ASM/height^2 T-score<-2	M<7.26kg/m^2 F<5.45kg/m^2	<70yrs 70-75yrs 75-80yrs >80yrs	Hisp=16.9% N-Hisp=13.5% Hisp=18.3% N-Hisp=19.8% Hisp=36.4% N-Hisp=26.7% Hisp=57.6% N-Hisp=52.6%	Hisp=24.1% N-Hisp=23.1% Hisp=35.1% N-Hisp=33.3% Hisp=35.3% N-Hisp=35.9% Hisp=60.0% N-Hisp=43.2%
Melton ea. (13)	DXA	Minnesota, USA 98% white 345M, 349F	146M, 138F aged 20-50yrs	SM/height^2 T-score<-2	M<9kg/m^2 F<6kg/m^2	60-69yrs 70-79yrs ≥80yrs	4.0% 16.0% 34.0%	6.0% 11.8% 4.1%
Iannuzzi ea (109)	DXA	Connecticut, USA Caucasian whites 142M, 195F	Baumgartner ea. (11)	ASM/height^2 T-score<-2	M<7.26kg/m^2 F<5.45kg/m^2	≥65yrs >80yrs	26.8% 52.9%	22.6% 31.0%
Janssen ea. (12)	BIA	NHANES III, USA 2224M, 2278F aged≥60yrs	3116M, 3298F aged 18-39yrs	SMI T-score 1)-1≥T≤-2 (Class1) 2)T<-2 (Class2)	1)M37-31% F28-22% 2)M<31% F<22%	60-69yrs 70-79yrs ≥80yrs	1)47% 2)6% 1)42% 2)7% 1)43% 2)7%	1)59% 2)9% 1)57% 2)11% 1)61% 2)11%
Tanko ea. (110)	DXA	Ballerup, Denmark 754F aged 18-85 yrs	subgroup 216F aged 18-39 yrs	1)LTMa 2)LTMa/height2 a)T-score<-2 b)-1≥T≤-2	1a)<14kg 2a)<5.4kg/m^2 1b)<16.6kg 2b)<6.1kg/m^2	40-49yrs 50-59yrs 60-69yrs >70yrs	- - - 	1a)7.4% 2a)3.3% 1b)26.4% 2b)29.7% 1a)14.3% 2a)3.8% 1b)35.8% 2b)32.1% 1a)20.1% 2a)9.4% 1b)43.5% 2b)24.0% 1a)40.2% 2a)12.3% 1b)40.3% 2b)32.9%
Rolland ea. (111)	DXA	§Toulouse, France 1311F aged 80±4 yrs	Baumgartner ea. 1998 (11)	ASM/height^2 T-score<-2	F<5.45kg/m^2	>70yrs	-	9.5%
Gillette-Guyonnet ea. (112)	DXA	§Toulouse, France 1321F aged ≥75 yrs	Baumgartner ea. 1998 (11)	ASM/height^2 T-score<-2	<5.45kg/m^2	76-80yrs 86-95yrs	- -	8.9% 10.9%
Kenny ea. (113)	DXA	189F aged 59-78 yrs using ERT≥2yrs	Baumgartner ea. 1998 (11)	ASM/height^2 T-score<-2	<5.45kg/m^2	59-78yrs	-	23.8%
Castillo ea. (14, 114)	BIA	California, USA 694M, 1006F aged 55-98yrs	1838M, 1555F aged 15-64yrs (115)	FFM T-score<-2	M<47.9kg F<34.7kg	60-69yrs ≥85yrs	1.0% 11.5%	0.8% 9.7%
Lauretani ea. (18)	CT, dynamometry, grip strength	Tuscany, Italy 349M, 424F, aged ≥65yrs	25M, 22F aged 20-29yrs	T-score<-2 1)Calf muscle area 2)KE torque 3)LE power 4)Grip strength	1)M<6058cm^2 F<4286cm^2 2)M<397N/dm F<311N/dm 3)M<162W F<160W 4)M<41kg, F<19kg	65-74yrs 75-85yrs >85yrs	1)16.1% 2)20.9% 3)57.8% 4)60% 1)35.1% 2)36.1% 3)88.7% 4)83.5% 1)68.2% 2)81.8% 3)100% 4)95.5%	1)2.75% 2)52.2% 3)98% 4)40% 1)11.2%% 2)73.1% 3)100% 4)47.8% 1)5.7% % 2)85.7% 3)100% 4)71.4%
Newman ea. (116)	DXA	Tennessee & Pennsylvania, USA 1435M, 1549F (41% Black) aged 70-79 yrs	same cohort	sex-specific P20 1)LTMa/height^2 2)Residuals$	1)M<7.23kg/m^2 F<5.67 kg/m2 2)negative residual	BMI<25 BMI25-30 BMI≥30	1)50.4% 2)32.8% 1)8.9% 2)15.4% 1)0% 2)11.5%	1)51.9% 2)23.0% 1)7.1% 2)21.7% 1)0% 2)14.4%
Janssen ea. (117)	BIA	NHANES III, USA 2223M, 2276F aged≥60yrs	same cohort	SMI2 cutpoints‡ 1)high risk 2)moderate risk	1)M≤8.50kg/m2 F≤5.75kg/m^2 2)M8.51-10.75kg/m2 F5.76-6.75kg/m^2	≥60yrs	1)11.2% 2)53.1%	1)9.4% 2)21.9%
Lau ea. (118)	DXA	Hong Kong, China 261M, 264F aged ≥70yrs	28M, 83F aged <40yrs	T-score<-2 1)LTM 2)ASM 3)ASM/height^2 4)SM	1)M<34.3kg, F<28.4kg 2)M<15.6kg, F<11.7kg 3)M<5.7kg/m2, F<4.8kg/m^2 4)M=21.1kg, F=15.6kg	70-74yrs 75-79yrs ≥80yrs	1)15.9% 2)19.1% 3)10.2% 4)19.1% 1)29.9% 2)29.8% 3)15.4% 4)29.8% -	1)59.4% 2)34.8% 3)10.1% 4)34.8% 1)62.3% 2)34.6% 3)6.2% 4)34.6% 1)58.5% 2)43.1% 3)6.2% 4)43.1%
Estrada ea. (16)	DXA	Connecticut, USA 189F aged 68±5yrs	1)Baumgartner ea. 1998 (11) 2)Janssen ea. 2002 (12)	T-score<-2 1)ASM/height^2 2)SMI	1)<5.45kg/m^2 2)<22.1%	BMI<25 BMI25-30 BMI>30	- - -	1)36.7% 2)8.5% 1)9.2% 2)40.0% 1)0% 2)85.7%
Foley ea. (119)	BIA	NHANES III, USA 6789M, 6981F 1556 aged 20-60yrs 1308 aged ≥70yrs	Janssen ea. 2002 (12)	SMI T-score 1)-1≥T≤-2 (Class1) 2)T<-2 (Class2)	1)M37-31% F28-22% 2)M<31% F<22%	whole sample	1)27.2% 2)4.5%	

DXA=Dual Energy X-ray Absorptiometry, CT=Computerised Tomography, BIA=Bioelectrical Impedance Analysis, MRI=Magnetic Resonance Imagery, ASM=Appendicular muscle mass, FFM=Fat Free Mass, NHANES III=Third National Health and Nutrition Survey, Hisp=Hispanic, N-Hisp=Non-Hispanic White, M=Male, F=Female, P20=20th Percentile of sample distribution, SM=ASMx1.33, SMI=Skeletal Muscle Index ((muscle mass / body mass) x 100), SMI2=Skeletal Muscle Index 2 (muscle mass/height^2), LTM=Lean Tissue Mass, LTMa=Appendicular Lean Tissue Mass, KE=Knee extension, LE= Leg extension, ERT=Estrogen Replacement Therapy, *estimated ASM (kg) = 0.2487(weight) + 0.0483(height) - 0.1584(hip circumference) + 0.0732(grip strength) + 2.5843(sex) + 5.8828 (validated by DXA based on a subsample of 199 subjects, R^2 = 0.91, standard error of estimation=1.58 kg), †Rosetta Study (120), §EPIDOS-study (121), $Residuals of a Linear Regression: LTMa(kg)=-22.48+24.14xHeight(m)+0.21xTotal Fat Mass(kg) for Male, LTMa(kg)= -13.19+14.75xHeight(m)+0.23xTotal Fat Mass(kg) for Female, ‡Cutpoints associated with self-reported physical disability in activities of daily life

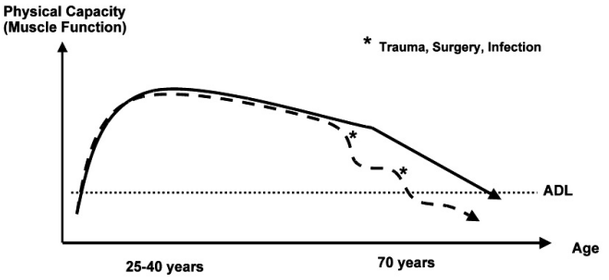

Figure 1 - Accelerated Loss of Muscle Performance due to Catabolic Processes During Inflammatory Conditions. *The plain line represents the evolution of skeletal muscle capacity with increasing age. The dotted line represents the threshold value for muscle capacity necessary for performing activities of daily life (ADL) in a comfortable manner. Inflammatory conditions are accompanied by severe muscle wasting, which can lead to important loss of functional performance and can be threatening for the independence of elderly persons (dashed line). Typically inflammatory situations are trauma, infection and surgery(*).*

Finally, it remains particularly difficult to predict at which stage sarcopenia will lead to physical disability. In general, the accumulated muscle weakness due to sarcopenia at the age of 50 years (theoretically up to 20%) does not lead to major limitations in daily activities (ADL); however, the additional muscle senescence up to the age of 70 years and over leads very often to significant strength losses and reduced functional capacity (19). Above the age of 70 years most persons live near their maximal capacities and simple tasks like rising from a chair or walking stairs require efforts above 80% of the maximum capabilities (20). It is obvious that, in elderly persons already presenting a certain degree of sarcopenia, a pathology induced supplementary muscle weakness can very rapidly lead to disability and additional morbidity. (21, 22). These events, therefore, are particularly dangerous and represent a high risk for loss of independence (23). As shown in figure 1, situations like trauma, infection or surgery at higher age can lead to a more rapid strength loss towards or below the threshold value necessary for self care and ADL.

According to the World Health Organization (24) Belgium ranked 5th among countries with the highest prevalence of aged population (22.3% aged >60 years). In 2025 Belgium is expected to rank 6th with 33.2% of the population aged >60 years. According to the Belgian National Institute for Statistics (25), in 2010 approximately 5% of the Belgian population will be aged ≥80 years, and this number is expected to increase to 10% in 2050. Consequently, there is an urgent need for optimal prevention and management of sarcopenia, in Belgium and similar countries.

2. PATHOPHYSIOLOGY OF SARCOPENIA

As shown in table 2, the contributing factors can be subdivided into decreased anabolic and increased catabolic processes, for both of which endogenous and exogenous factors can be recognised. At the level of the individual person, the relative contribution of these factors can show important variability. In each geriatric patient confronted with muscle weakness, a comprehensive evaluation of the causative factors will be necessary for further clinical management.

2.1 Ageing-related factors

2.1.1 Immune changes

Aging, even in healthy persons, is commonly accompanied by slightly elevated concentrations of circulating IL-6 and TNF-α, a phenomenon corresponding to a chronic low-grade inflammatory profile (26). Also, minor elevations in CRP concentration are proposed by some authors to be related to biological aging (27). Several studies demonstrate that elderly persons with higher concentrations of circulating IL-6 and TNF-α show lower muscle mass and muscle strength (6, 28, 29). The underlying mechanisms involved are not yet completely understood and not all elderly persons present this basal low-grade inflammatory profile. Age-related changes of the immune system, including altered T-cell function, might contribute to this

Table 2. Factors Contributing to Sarcopenia.

	Type	Factor
↓ Anabolism	Endogenous	↓ Hormonal stimulation (Growth Hormone, IGF-1, Testosterone, Oestrogen)
		Loss of motorneurones, denervation of muscle fibres
		↑ non-contractile tissue in muscle
	Exogenous	↓ Physical activity
		Bed rest, immobilisation
		Malnutrition
↑ Catabolism	Endogenous	↑ Basal inflammatory profile (IL-6, TNF-α)
	Exogenous	Stress-induced inflammation: Life events, Depression
		Disease

phenomenon (30). The mechanisms by which inflammation contributes to muscle atrophy and muscle weakness are further developed in section 2.2 of this review.

2.1.2 Connective tissue alterations

Muscle weakness due to sarcopenia is more important than can be explained by atrophy alone. The more pronounced atrophy of type-2 (fast twitch) compared to type-1 (slow twitch) muscle fibres might explain the important loss of muscle strength and muscle power (the capacity to generate a high force in a short time) seen in sarcopenia (5). In fact, the absolute loss of muscle power with ageing is even more important than the loss of maximal strength (18), indicating that contraction-speed is also impaired. Intriguingly, when normalized to cell size, the contractile strength and velocity of isolated muscle fibres are not significantly affected by ageing (31). Supplementary loss of muscle contractile properties might be due to age-related alterations in the connective tissues surrounding the muscle fibres (endomysium, perimysium and epimysium). Age-related augmentation of the proportion of connective tissue and fat in the muscle (32), together with the formation of additional intermolecular cross-links leads to profound changes in composition of the muscle-tendon complex as well as its mechanical properties (33). These processes are responsible for an increasing proportion of insoluble extracellular matrix and thickening of the tissues, as well as increasing mechanical stiffness and loss of elasticity (33). Remarkably, tendons of elderly persons seem to loose their stiffness leading to inefficient force transmission from the muscle to its bony insertions and supplementary weakness (9).

2.1.3 Altered cyto-protective mechanisms.

The aforementioned inflammatory processes related to sarcopenia (both systemic and at the tissue level) are thought to be intensified by a concomitant age-related decline in cellular protection mechanisms, i.e. Heat Shock Protein (Hsp) expression. Under normal conditions Hsp's are present at low levels. Hsp's become intensely expressed during various stress-situations (e.g. hyperthermia, oxidative stress, infection) and then protect the cellular integrity by acting as 'chaperones' for intracellular proteins. Several Hsp families are identified, which can be classified according to their molecular weight. (34). Especially the 'Hsp70 chaperoning machine' (HspA-family) is the most inducible by stress (35). Alterations in Hsp70 expression are thought to be involved in age-related dysfunctions such as sarcopenia (36).

Basal, unstimulated levels of several Hsp appear to increase with aging (37-40), indicating that a continuous, low grade damage is taking place. This basal increase of Hsp70 is related to the degree of inflammation, as it is reflected by circulating IL-6 and TNF-α levels. On the other hand, it has been shown that stress induced Hsp70 expression becomes significantly attenuated in older individuals (41, 42). It can, therefore, be assumed that, although the Hsp protection mechanism is stimulated during aging, the protection that is provided must be disproportionately lower than needed.

It has been shown that intensive strength training results in a beneficial alteration of the inflammatory profile. Also, a decrease of basal levels of Hsp70 in cells other than muscle cells has been found, indicating an effect at the systemic level (43). Moreover, when cells were stressed, they reacted better when elderly were strength trained, indicating that the aging related suppression had been neutralized.

2.2 Disease and malnutrition

In this review we focus on the aging and disuse aspects. It is clear, however, that a wide variety of clinical disorders can contribute to muscular weakness at older age. Most cardiovascular and pulmonary diseases for instance are known to have a detrimental effect. Worsening of sarcopenia occurs during inflammation, and will be seen with infection, trauma, surgery, burns, tissue infarction and cancer (see (44) for review). Besides the regulation of the immune reaction against external aggression, several pro-inflammatory cytokines are involved in the catabolic processes associated with inflammation. Particularly TNF-α, IL-1β and IL-6 are known to have cytotoxic and proteolytic properties (45, 46). Elevated concentrations of these cytokines in the blood, during inflammatory pathology, are related to severe muscle wasting and cachexia (47, 48). The exact mechanisms by which inflammatory cytokines promote myofibrillar proteolysis are not yet completely understood. Recent insights revealed an up-regulation of the ubiquitin-proteasome pathway and calcium-activated pathway of calpains, thus inducing muscle protein breakdown (49, 50). Moreover, it appears that TNF-α, by increasing the cellular production of reactive oxygen species (ROS) and nitric oxide (NO), can depress muscle contractibility, which might be related to symptoms like fatigue or weakness during inflammatory conditions (see (49) for review).

Also, inhibition of the formation of new myofibrils by inflammatory cytokines has been reported (49, 51).

The influence of nutritional deficiency on sarcopenia is undeniable. Mainly insufficient protein intake will unfavourably influence the muscular system. Strictly speaking, hypovitaminosis D, which is extremely common in elderly people, cannot be considered as a nutrition problem. At old age, the production of vitamin D in the skin, after exposure to UV light, decreases importantly. Since vitamin D has been recognized to be of importance not only for the skeleton, but also for the muscular system, hypovitaminosis D is thought to contribute to muscular weakness and to falls in the elderly persons (52). Elderly women with osteoporosis and presenting with hypovitaminosis D were shown to have a worse grip strength than those with a normal vitamin D level (53).

2.3 Disuse

Lack of physical activity is a well known precipitating factor for sarcopenia (8). At higher ages, most people become physically less active. For example, only one on two Belgian citizen attains a minimum of 2.5 hours of moderate physical activity per week, and this proportion decreases to one in five at the age of 75 years and over (54). Although one might expect that master athletes, who maintain high levels of sports activities at higher ages, remain preserved from skeletal muscle senescence, their mean rate of strength decline seems to correspond to that seen in non-athletes(± 1% per year) (55, 56). Even Olympic-style weight lifters experience losses of muscle power at a rate of 1.5% per year (55, 57). Nevertheless, individuals who started weight lifting at young age and maintained this training through lifetime, end up at higher ages with similar isometric knee extensor strength and type II fibre area in M Vastus Lateralis as young not strength training persons (58, 59).

3. SCREENING FOR MUSCLE WEAKNESS

In aging research, grip strength has often been used as an indicator of general muscle strength, since it is a parameter easy to measure. Indeed, age-related changes in grip strength are well described (60) and appear to run parallel to the strength losses in other muscle groups (18). Therefore, grip strength is a useful tool in the clinical evaluation of geriatric patients (18). Severe inflammation, as seen during acute infections, dramatically worsens sarcopenia-induced reduction in grip strength (22). Also, in well-functioning elderly persons chronic low-grade inflammation is associated with a worse degree of sarcopenia and reduced grip strength (28). Low grip strength is recognized as one of the characteristics of frailty, as are inflammation and the sensation of fatigue (61, 62). Therefore, the evaluation of grip strength merits broader attention and should be part of the comprehensive geriatric assessment. In table 3 reference values for maximal grip strength are provided based on a population of 530 healthy subjects as described by Merkies et al. (60). Also, age -and gender-specific threshold values are given.

As described above, due to sarcopenia, older or ill persons will function closer to their limit of maximal strength (20). Since daily activities in the elderly often require sustained intense muscle contractions (e.g. when bearing shopping bags), these may be more challenging given the reduced muscle strength, and could explain the common sensation of fatigue. This tiredness during daily activities is not a trivial symptom but a predictor of disability in older individuals (63). In a general population, the sensation of fatigue is very common (in respectively 20.4% and 14.3% of women and men) (64); it is predominantly (in 98%) present in residents of long-term care facilities (65). Contrary to maximal grip strength, the physical resistance of the muscles to fatigue is not often measured as part of the clinical evaluation of elderly patients. Recently, we have described a simple test for muscle fatigue resistance in elderly patients, expressed as the time for grip strength to decrease to 50% of its maximum during sustained contraction (66). Also, we have demonstrated that muscle fatigue resistance is closely related to the clinical condition of elderly patients (21, 22). For the assessment of fatigue resistance, the subject is first asked to squeeze the large bulb of the Martin Vigorimeter (Elmed, Addison, USA) as hard as possible (see figure 2). The highest of three attempts is

Table 3. Reference values (in Kpa) for maximal grip strength

	Male		*Female*	
Age	*Threshold value*	*Median*	*Threshold value*	*Median*
70-74 years	66 KPa	91 KPa	54 KPa	67 KPa
75-79 years	57 KPa	82 KPa	48 KPa	63 KPa
80-84 years	50 KPa	75 KPa	43 KPa	59 KPa
≥85 years	37 KPa	64 KPa	35 KPa	54 KPa

All reference values are valid for the dominant and non-dominant hand using the Martin Vigorimeter. The threshold value corresponds to the p=0.05 level. Adapted from Merkies et al.(60)

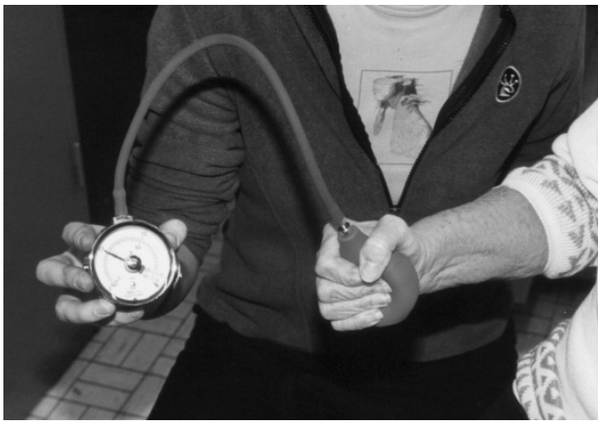

Figure 2. *Assessment of grip strength and fatigue resistance using the martin Vigorimeter.*

noted as the *maximal grip strength* (in KPa). Then, the subject is instructed to squeeze again the bulb of the vigorimeter as hard as possible and to maintain this maximal pressure. The time (in seconds) during which grip strength drops to 50% of its maximum is recorded as *fatigue resistance*. By consequence, the outcome on the fatigue resistance test is a measure relative to each individual's maximal strength.

Since functional performance depends as well on the strength that can be deployed as on the time during which the strength development can be sustained, we have integrated both parameters into a useful muscle endurance outcome defined as *Grip Work* (67). This can be easily estimated using the equation: Grip Work = Maximal Grip Strength * 0.75 * Fatigue Resistance. The calculation of grip work starts from the assumption that the strength drops linearly during the fatigue resistance test. In a recent study, we have confirmed the validity of that assumption by monitoring continuously the changes in grip strength during the fatigue resistance test in a large and diverse sample of 291 subjects among which 100 young subjects (49 male, 51 female, aged 23±3 years), 100 community-dwelling elderly (49 male, 51 female, aged 74±5 years) and 91 hospitalized geriatric patients (30 male, 61 female, aged 83±5 years). An excellent correlation (Pearson's r=0.97, p<0.001) was found between the values for Grip Work as estimated using the aforementioned equation and the real work output measured, thus supporting the use of this parameter reflecting the real delivered work output. (unpublished data)

Since Grip Work estimates the ability to sustain maximal strength in time it is relevant during daily activities that need sustained muscle activity (e.g. when lifting, manipulating or bearing objects). From a functional viewpoint, the generated force output of muscles is efficient when it allows performing daily activities in a comfortable manner. In this context body mass can be of critical importance. Therefore, expressing grip work relative to body weight (Grip Work / Body Mass) might be an excellent parameter on order to estimate and follow-up functional muscle performance (67, 68).

Based on our previous work (references (67, 68) and unpublished data), we provide here some guidelines for the clinical interpretation of grip work outcomes in elderly patients. For grip work, 2500 KPa*sec in female and 3000 KPa*sec in male were optimal cut-off values in order to discriminate frail and disabled hospitalised geriatric patients from community-dwelling elderly without significant functional disability and healthy young subjects (area under the curve (AUC) = 84%, sensitivity=80%, specificity=70% for female; AUC=86%, sensitivity=90%, specificity=70% for male). When grip work is expressed in kg body weight, 40 KPa*sec/kg can be a useful cut-off value for both elderly male and female in a clinical setting (AUC=83%, sensitivity=80%, specificity=68%). These cut-off values were chosen in order to obtain high sensitivity and acceptable specificity for using grip work as a screening tool in elderly persons (aged 70 years and over). Future research involving larger populations will allow for a further refinement of the proposed cut-off values.

4. PREVENTION AND THERAPY

4.1 Physical exercise to counteract sarcopenia

There exists a body of evidence showing that physical exercise is beneficial in elderly and effective in improving muscle strength (69, 70). Physical exercise can be prescribed in a wide variety of modalities, depending on the intensity (load or resistance, number of repetitions, number of series), duration, frequency and type (weight-lifting, walking or running, bicycling, etc.). Resistance training, preferentially at high intensity, appears to be the most appropriate physical exercise modality in order to improve muscle strength in elderly persons (71, 72). This type of training consists classically of three series of ten to twelve repetitions at 70 to 80% of the one repetition maximum (1RM = the weight that can be moved maximum once over the whole range of movement). A frequency of one to three exercise sessions per week leads to optimal results. With this training regimen sarcopenia can, at

least partly, be countered within a short time. Strength gains from 30 % up to 170 % can be obtained already after six to eight weeks intensive resistance exercise in elderly persons, even in the oldest old (>90 years) (69, 73-75). The mechanisms by which muscle strength increases are not yet completely understood. Short-term gains in muscle strength are primarily due to neurological adaptations, including increased motor unit firing frequency and improved motor unit recruitment (69). After training for eight weeks and longer, hypertrophy of both type 1 and type 2 muscle fibres becomes measurable, thus resulting in e.g. increased lean mid-thigh cross sectional area of 9% and more (73, 75-77). The benefits of resistance training upon the recovery of muscle strength in the elderly are undeniable. Nevertheless, it has to be noted that most studies investigating the effects of intensive strength training in elderly deal with healthy subjects and take place in strictly controlled laboratory conditions. However, also in institutionalised patients presenting multiple medical problems, there is evidence for positive effects of physical training on muscle strength, mobility and range of motion (73, 78, 79). Even in frail patients with moderate dementia (average score on the Mini Mental State Examination = 17.8, SD=7.2) resistance training is feasible and leads within six weeks to improvement of strength, sit-to-stand time, gait speed and timed up-and-go performance (80). Moreover, resistance training is beneficial in the rehabilitation of older patients presenting rheumatoid arthritis (81-83), chronic heart failure (84), in frail hospitalised geriatric patients (85) and in elderly patients after hip surgery (86).

Strength gains tend to level off after eight weeks of strength training (76) and seem to be maintained (minimal loss) up to twelve weeks after stopping the training (87). After twelve weeks of detraining, muscle strength as well as muscle cross-sectional area decrease significantly (87-89) and some data reveal more important strength losses in elderly compared to young subjects during a detraining period (87). Habitual daily activity seems to be insufficient to maintain the strength gains, and at least one strength training session per week is necessary in order to avoid significant muscle strength and size loss over six months follow-up (90).

4.2 Intensive exercise requires intensive coaching

Most studies on intensive strength training for elderly persons confirm the safety of this training regime and adverse effects are only rarely reported. However, when they are clearly defined in the study design, adverse effects are reported more often (70), and serious incidents appear to occur from time to time (91). Therefore, the level of coaching needs to be adapted to the individual profile of the patient.

For frail geriatric patients, exercise sessions should be supervised by a professional such as a physical therapist (in Belgium designated as "kinesitherapist"). In a first approach (first 2-3 weeks), 2-3 sessions a week should be planned during which the optimal exercise modalities are identified and the patient gets acquainted with the movements. Afterwards, the frequency of the supervised sessions can be progressively lowered to one per week while, simultaneously, a home-based exercise program is established (e.g. using dumbbells or elastic bands for providing sufficient resistance). This schedule should be continued as long as possible (at least for one year; in some countries, as in Belgium, the health insurance authority provides increased reimbursement for frail geriatric patients presenting muscle weakness and increased fall risk). Also, for institutionalised geriatric patients (e.g. living in a nursing home) these resistance exercise sessions should be provided and a rehabilitation room should be accessible with at least some basic devices enabling strength training.

Non-disabled community-dwelling elderly can be referred to a strength training program e.g. in a fitness centre. Also for this category of elderly persons, an exercise program consisting in resistance exercises at high intensity should be systematically provided and maintained as long as possible. However, these elderly persons are often not free of pathology (such as cardio-vascular disease, rheumatologic and/or osteo-articular pathology, diabetes, etc.) and use frequently several drugs that might influence the exercise capacity (such as drugs with cardiovascular effects). By consequence, exercise instructors are often afraid of complications in their elderly clients and exercise sessions for elderly are too often designed at a too low intensity. Therefore, "apparently healthy" elderly subjects should be screened for risk for complications during intensive physical training. Specific recommendations in a screening report addressed to the exercise monitors should enable an individually designed strength training schedule at sufficient intensity for obtaining optimal strength gains.

Previously, we have developed a simple classification system, which stratifies health categories corresponding to an increasing risk for complications during physical exercise (see table 4), and which can be used

Table 4: Health categories for risk stratification of complications during physical exercise in elderly persons.

Health Category	Description *	Clinical examples
A A1	Completely healthy; no medication	
A2	Completely healthy; using only preventive medication	Hormonal replacement therapy, aspirin, ...
B B1	Functioning normally; presence of stabilised, non cardiovascular disease; absence of cardiovascular abnormalities	treated hypothyroidism, stable diabetes, ...
B2	functioning normally; using medication with cardiovascular effect, no overt cardiovascular disease other than normalized arterial hypertension	Arterial hypertension; β blocking agent, ...
C	(history of) cardio-vascular pathology or abnormal ECG.	Bundle branch block; angina, CABG; ...
D	presenting signs of acute or active disease at the moment of examination.	bronchospasm, swollen joints, influenza, ...

Table adapted from Bautmans et al (92), * Status after questioning, physical examination, ECG, and laboratory examination of blood, serum & urine according to the SENIEUR protocol (122). CABG: coronary artery bypass graft

by physicians in the context of exercise prescription (92). The classification system was primarily designed to allow the establishment of recommendations concerning the exercise schedule (type, duration and intensity) of elderly persons in the absence of direct medical supervision. Therefore, the classification system is rather conservative and it is easy for an individual to be considered at risk for complications. Roughly, participants in category **A** (completely healthy) will have no particular limitations for exercising; for those in category **B1** (functioning normally, but presenting chronic non-cardiovascular disorders) the instructions will vary with the nature of the health problem; those in category **B2** will only exercise at higher intensity (e.g. up to 80% of maximal heart rate or higher) when guided by an instructor qualified for training elderly persons; those in category **C** will only be allowed to exercise under supervision of an instructor and with medical guidance of the training program; those in category **D** will not exercise unless cleared by a physician.

In figure 3 we propose a flowchart showing the different steps in clinical decision making when dealing with geriatric patients suffering from muscle weakness. All elderly patients should be screened for muscle weakness by means of anamnesis, grip strength and fatigue resistance assessment. From a preventive point of view, subjects without apparent muscle weakness should be encouraged to start a strength training program. Depending on the risk for complications, the level of supervision needs to be adapted. When elderly patients show clear signs of muscle weakness (mobility problems and/or low grip strength values), the causative factors should be inventoried as well as their relative contribution. After medical treatment (where possible), the patient is referred to strengthening exercises under adapted supervision depending on the risk for complications. When patients exercise under

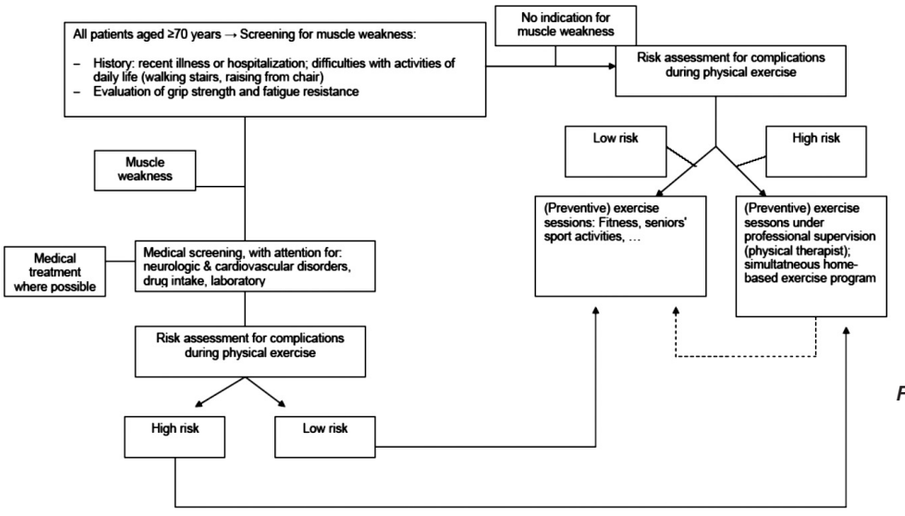

Figure 3. *flowchart showing the different steps in clinical decision making when screening for muscle weakness in geriatric patients.*

individual supervision of a physical therapist, a home-based exercise program should be designed in order to allow for long term continuation of the exercises.

4.3 Dietary intervention

Multinutrient supplementation for frail and very elderly persons has been shown to be ineffective without simultaneous high-intensity resistance exercise training (93). Since nutritional support will often result in reduction of the normal intake, supplementation will only be useful if it introduces products that are essential to counter sarcopenia. It is clear, as well in prevention as in treatment of sarcopenia, that a sufficient amino acid and caloric supply is essential. Although controversy remains about the need to supply mainly essential amino acids (94, 95), elderly persons will respond, albeit somewhat slower than younger persons, to such supplements (96).

4.4 Pharmacologic treatment

Hypovitaminosis D, although extremely common at higher age, remains too often untreated. Although no cure of sarcopenia can be expected from vitamin D, it is advised to treat hypovitaminosis D systematically whenever it is detected or suspected. (97). A daily dose of 800 IU of vitamin D is needed in order to prevent falls. Recently, it has been stressed that this dose may not be sufficient, and that higher doses may be needed to obtain normalization of circulating 25-OH-vitamin D levels.

Theoretically, several categories of drugs might be considered as a supportive therapy in the treatment of sarcopenia. Most of the products discussed below have documented anabolic properties. Unfortunately, either their effect is weak, or else important adverse drug effects are to be feared.

It is well known that anabolic steroids have an effect on the muscular system. There has been a renewed interest in these drugs and some evidence indicates that they might be useful in the context of sarcopenia. Nandrolone decanoate, both in long term administration in elderly women with osteoporosis (older than 70 years) (98) and short term administration in men with COPD (average age of 66 years) (99), resulted in a slight improvement of muscle mass and of some parameters of muscle function.

Although a positive effect on muscle mass and grip strength has been described after testosterone treatment in older men, the guidelines for prescribing androgen products remain ambiguous (100, 101). Difficulties arise mainly in the definition of androgen insufficiency, the substitution level to be attained, and the target group for whom androgen treatment might be useful. Certainly for frail, sarcopenic patients, insufficient data are presently available and more clinical studies are needed. Weak androgenic products, such as DHEA, do not appear to be interesting as a treatment option, since at best only subjective effects have been found (102, 103). The use of Growth Hormone or of Insulin-Like Growth Factor 1 has been shown to have little or no benefit in the improvement of sarcopenia (104). Also, their administration appears to be frequently accompanied by disturbing adverse effects.

Some reports point to a positive effect of Angiotensin Converting Enzyme Inhibitors on muscle strength, lower extremity muscle mass and on exercise capacity (105, 106). There remains some doubt whether these products directly affect the skeletal muscle or whether the observed effects are due to improvement of latent heart failure.

At present, apart from vitamin D, no pharmacological treatment can be advised for the routine management of sarcopenia. Although some products might be useful, their place in the approach of sarcopenia has been insufficiently documented. Recently, some promising reports on 5'-Adenosinemonophosphate-Activated Protein Kinase (AMPK) agonists have been made (107, 108). Pharmacological stimulation of AMPK appears to mimic training in mice and improves endurance even in the absence of training. Whether these products have a place in treatment of sarcopenia in human subjects will need further studies.

5. CONCLUSION

The last two decades, sarcopenia has been intensively studied and prevalence values have been reported in fifteen papers covering several continents and races. However, there is a lack of consistency regarding the outcome measures and corresponding cut-off values in order to efficiently screen for sarcopenia. Most approaches are based on estimations of muscle mass or volume and the corresponding cut-off values proposed might be to strict, thus reducing their use in daily practice. From a clinical viewpoint, the assessment of muscle performance (grip strength and endurance) can be proposed as a screening tool showing enough sensitivity to identify elderly patients presenting a sufficient degree of muscle weakness justifying further assessment and intervention. The pathophysiology of

sarcopenia is multifactorial, and important changes at the tissue level have been identified. Close relationships with inflammatory processes have been demonstrated and there is strong evidence for the involvement of a chronic low-grade inflammatory activity occurring at higher ages. Sarcopenia is aggravated by a complex interaction of several factors among which aging, disuse, immobilization, disease and malnutrition. A comprehensive geriatric assessment should allow the clinician to estimate the relative contribution of these factors and to elaborate appropriate management. From all interventions studied, intensive resistance training seems the most efficient to counter sarcopenia, even in the very old geriatric patients. Significant ameliorations (up to >50% strength gain) can be expected after 6 weeks training at a rhythm of 2-3 sessions per week. Given the dose-response relationship, the resistance must be sufficiently high (70-80% maximal strength) and depending on the patient's profile appropriate supervision and coaching needs to be provided. From a preventive viewpoint, all elderly patients should be advised to start such an exercise program and continue as long as possible. Besides local benefits at the muscle itself, also systemic responses are induced by intensive strength training in elderly persons such as better cellular protection mechanisms and probably reduction of the chronic low-grade inflammatory activity. To date, most pharmacological interventions to counter sarcopenia include drugs with anabolic effects. Unfortunately, no clear guidelines exist for the prescription of these products in the context of sarcopenia.

REFERENCES

1. Rosenberg IH. Summary comments. *Am J Clin Nutr.* 1989; 50: 1231-3.
2. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr.* 1997; 127: 990S-1S.
3. Morley JE. Editorial: The top 10 hot topics in aging. *J Gerontol A Biol Sci Med Sci.* 2004; 59A: 24-33.
4. Sehl ME, Yates FE. Kinetics of human aging: I. Rates of senescence between ages 30 and 70 years in healthy people. *J Gerontol A Biol Sci Med Sci.* 2001; 56: B198-208.
5. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci.* 1988; 84: 275-94.
6. Marcell TJ. Review Article: Sarcopenia: Causes, Consequences, and Preventions. *J Gerontol A Biol Sci Med Sci.* 2003; 58: M911-6.
7. Frontera WR, Hughes VA, Lutz KJ, Evans WJ. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. *J Appl Physiol.* 1991; 71: 644-50.
8. Doherty TJ. Invited review: Aging and sarcopenia. *J Appl Physiol.* 2003; 95: 1717-27.
9. Narici MV, Maganaris CN. Plasticity of the muscle-tendon complex with disuse and aging. *Exerc Sport Sci Rev.* 2007; 35: 126-34.
10. Aniansson A, Grimby G, Hedberg M. Compensatory muscle fiber hypertrophy in elderly men. *J Appl Physiol.* 1992; 73: 812-6.
11. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *American journal of epidemiology.* 1998; 147: 755-63.
12. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002; 50: 889-96.
13. Melton LJ, 3rd, Khosla S, Crowson CS, O'Connor MK, O'Fallon WM, Riggs BL. Epidemiology of sarcopenia. *J Am Geriatr Soc.* 2000; 48: 625-30.
14. Castillo EM, Goodman-Gruen D, Kritz-Silverstein D, Morton DJ, Wingard DL, Barrett-Connor E. Sarcopenia in elderly men and women: The Rancho Bernardo study. *American Journal of Preventive Medicine.* 2003; 25: 226-31.
15. Gallagher D, Ruts E, Visser M, Heshka S, Baumgartner RN, Wang J, et al. Weight stability masks sarcopenia in elderly men and women. *Am J Physiol Endocrinol Metab.* 2000; 279: E366-75.
16. Estrada M, Kleppinger A, Judge JO, Walsh SJ, Kuchel GA. Functional impact of relative versus absolute sarcopenia in healthy older women. *J Am Geriatr Soc.* 2007; 55: 1712-9.
17. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis.* 2008; 18: 388-95.
18. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol.* 2003; 95: 1851-60.
19. Hurley MV, Rees J, Newham DJ. Quadriceps function, proprioceptive acuity and functional performance in healthy young, middle-aged and elderly subjects. *Age Ageing.* 1998; 27: 55-62.
20. Hortobagyi T, Mizelle C, Beam S, DeVita P. Old adults perform activities of daily living near their maximal capabilities. *J Gerontol A Biol Sci Med Sci.* 2003; 58: M453-60.
21. Mets T, Bautmans I, Njemini R, Lambert M, Demanet C. The influence of celecoxib on muscle fatigue resistance and mobility in elderly patients with inflammation. *Am J Geriatr Pharmacother.* 2004; 2: 230-8.
22. Bautmans I, Njemini R, Lambert M, Demanet C, Mets T. Circulating Acute Phase Mediators and Skeletal Muscle Performance in Hospitalized Geriatric Patients. *J Gerontol A Biol Sci Med Sci.* 2005; 60: 361-7.
23. Hoenig H, Rubenstein LZ. Hospital-associated deconditioning and dysfunction. *J Am Geriatr Soc.* 1991; 39: 220-2.
24. WHO. Active Ageing: a policy framework. March 2009 [cited; Available from: http://whqlibdoc.who.int/hq/2002/WHO_NMH_NPH_02.8.pdf
25. Bevolkingsvooruitzichten 1995-2025. In: Federaal Planbureau Brussel B, ed.: Nationaal Instituut voor de Statistiek.
26. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol.* 2004; 39: 687-99.

27. Kushner I. C-reactive protein elevation can be caused by conditions other than inflammation and may reflect biologic aging. *Cleve Clin J Med*. 2001; 68: 535-7.
28. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci*. 2002; 57: M326-32.
29. Payette H, Roubenoff R, Jacques PF, Dinarello CA, Wilson PW, Abad LW, et al. Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. *J Am Geriatr Soc*. 2003; 51: 1237-43.
30. Zanni F, Vescovini R, Biasini C, Fagnoni F, Zanlari L, Telera A, et al. Marked increase with age of type 1 cytokines within memory and effector/cytotoxic CD8+ T cells in humans: a contribution to understand the relationship between inflammation and immunosenescence. *Exp Gerontol*. 2003; 38: 981-7.
31. Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J, Trappe T. Single muscle fibre contractile properties in young and old men and women. *J Physiol*. 2003; 552: 47-58.
32. Kent-Braun JA, Ng AV, Young K. Skeletal muscle contractile and noncontractile components in young and older women and men. *J Appl Physiol*. 2000; 88: 662-8.
33. Avery NC, Bailey AJ. Enzymic and non-enzymic cross-linking mechanisms in relation to turnover of collagen: relevance to aging and exercise. *Scand J Med Sci Sports*. 2005; 15: 231-40.
34. Hightower LE, Hageman J, Vos MJ, Kubota H, Tanguay RM, Bruford EA, et al. Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones. 2008.
35. Vos MJ, Hageman J, Carra S, Kampinga HH. Structural and functional diversities between members of the human HSPB, HSPH, HSPA, and DNAJ chaperone families. Biochemistry. 2008; 47: 7001-11.
36. Lee CE, McArdle A, Griffiths RD. The role of hormones, cytokines and heat shock proteins during age-related muscle loss. Clinical nutrition (Edinburgh, Scotland). 2007; 26: 524-34.
37. Njemini R, Bautmans I, Lambert M, Demanet C, Mets T. Heat shock proteins and chemokine/cytokine secretion profile in ageing and inflammation. Mech Ageing Dev. 2007; 128: 450-4.
38. Njemini R, Lambert M, Demanet C, Kooijman R, Mets T. Basal and infection-induced levels of heat shock proteins in human aging. Biogerontology. 2007.
39. Njemini R, Lambert M, Demanet C, Mets T. Heat shock protein 32 in human peripheral blood mononuclear cells: effect of aging and inflammation. J Clin Immunol. 2005; 25: 405-17.
40. Njemini R, Lambert M, Demanet C, Mets T. The effect of aging and inflammation on heat shock protein 27 in human monocytes and lymphocytes. Exp Gerontol. 2006; 41: 312-9.
41. Njemini R, Abeele MV, Demanet C, Lambert M, Vandebosch S, Mets T. Age-related decrease in the inducibility of heat-shock protein 70 in human peripheral blood mononuclear cells. J Clin Immunol. 2002; 22: 195-205.
42. Njemini R, Demanet C, Mets T. Inflammatory status as an important determinant of heat shock protein 70 serum concentrations during aging. Biogerontology. 2004; 5: 31-8.
43. Bautmans I, Njemini R, Vasseur S, Chabert H, Moens L, Demanet C, et al. Biochemical changes in response to intensive resistance exercise training in the elderly. Gerontology. 2005; 51: 253-65.
44. Delves PJ, Roitt IM. The immune system. Second of two parts. N Engl J Med. 2000; 343: 108-17.
45. Mackinnon L. Exercise and immunology. Champaign, Illinois: Human Kinetics 1992.
46. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999; 340: 448-54.
47. Baracos V, Rodemann HP, Dinarello CA, Goldberg AL. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. N Engl J Med. 1983; 308: 553-8.
48. Kotler DP. Cachexia. Ann Intern Med. 2000; 133: 622-34.
49. Zoico E, Roubenoff R. The role of cytokines in regulating protein metabolism and muscle function. Nutr Rev. 2002; 60: 39-51.
50. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. N Engl J Med. 1996; 335: 1897-905.
51. Argiles JM, Alvarez B, Carbo N, Busquets S, Van Royen M, Lopez-Soriano FJ. The divergent effects of tumour necrosis factor-alpha on skeletal muscle: implications in wasting. Eur Cytokine Netw. 2000; 11: 552-9.
52. Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. Molecular Aspects of Medicine. 2005; 26: 203-19.
53. Mets T. Calcium, vitamin D, and hip fractures. Incidence of falls may have decreased. Bmj. 1994; 309: 193.
54. Bietlot M, Demarest F, Tafforeau J, Van Oyen H. Gezondheidsenquête 1997 en 2001. De gezondheid in België, zijn gemeenschappen en gewesten. 2001 [cited; Available from: http//www.iph.fgov.be/epidemio/epinl/index4.htm
55. Hawkins SA, Wiswell RA, Marcell TJ. Exercise and the master athlete--a model of successful aging? J Gerontol A Biol Sci Med Sci. 2003; 58: 1009-11.
56 Wiswell RA, Hawkins SA, Jaque SV, Hyslop D, Constantino N, Tarpenning K, et al. Relationship between physiological loss, performance decrement, and age in master athletes. J Gerontol A Biol Sci Med Sci. 2001; 56: M618-26.
57. Meltzer DE. Age dependence of Olympic weightlifting ability. Med Sci Sports Exerc. 1994; 26: 1053-67.
58. Klitgaard H, Mantoni M, Schiaffino S, Ausoni S, Gorza L, Laurent-Winter C, et al. Function, morphology and protein expression of ageing skeletal muscle: a cross-sectional study of elderly men with different training backgrounds. Acta Physiol Scand. 1990; 140: 41-54.
59. Brown M. The master athlete. Orthopaedic Physical Therapy Clinics of North America. 1997; 6: 253-66.
60. Merkies IS, Schmitz PI, Samijn JP, Meche FG, Toyka KV, van Doorn PA. Assessing grip strength in healthy individuals and patients with immune-mediated polyneuropathies. Muscle Nerve. 2000; 23: 1393-401.
61. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older Adults: Evidence for a Phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56: M146-57.
62. Syddall H, Cooper C, Martin F, Briggs R, Aihie Sayer A. Is grip strength a useful single marker of frailty? Age Ageing. 2003; 32: 650-6.
63. Avlund K, Vass M, Hendriksen C. Onset of mobility disability among community-dwelling old men and women. The role of tiredness in daily activities. Age Ageing. 2003; 32: 579-84.
64. Chen MK. The epidemiology of self-perceived fatigue among adults. Prev Med. 1986; 15: 74-81.

65. Liao S, Ferrell BA. Fatigue in an older population. *J Am Geriatr Soc*. 2000; 48: 426-30.
66. Bautmans I, Mets T. A fatigue resistance test for elderly persons based on grip strength: reliability and comparison with healthy young subjects. Aging Clin Exp Res. 2005; 17: 217-22.
67. Bautmans I, Gorus E, Njemini R, Mets T. Handgrip performance in relation to self-perceived fatigue, physical functioning and circulating IL-6 in elderly persons without inflammation. BMC Geriatr. 2007; 7: 5.
68. Bautmans I, Njemini R, Predom H, Lemper JC, Mets T. Muscle endurance in elderly nursing home residents is related to fatigue perception, mobility, and circulating tumor necrosis factor-alpha, interleukin-6, and heat shock protein 70. *J Am Geriatr Soc*. 2008; 56: 389-96.
69. Hurley BF, Roth SM. Strength training in the elderly: effects on risk factors for age-related diseases. Sports Med. 2000; 30: 249-68.
70. Latham NK, Bennett DA, Stretton CM, Anderson CS. Systematic review of progressive resistance strength training in older adults. J Gerontol A Biol Sci Med Sci. 2004; 59: M48-61.
71. Latham NK, Andersen-Ranberg K, Bennett DA, Stretton CM. Progressive resistance training for physical disability in older people (Cochrane Review). The Cochrane Library. 2003; 2.
72. Williams GN, Higgins MJ, Lewek MD. Aging skeletal muscle: physiologic changes and the effects of training. Phys Ther. 2002; 82: 62-8.
73. Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians. Effects on skeletal muscle. Jama. 1990; 263: 3029-34.
74. Roth SM, Ferrell RF, Hurley BF. Strength training for the prevention and treatment of sarcopenia. J Nutr Health Aging. 2000; 4: 143-55.
75. Harridge SD, Kryger A, Stensgaard A. Knee extensor strength, activation, and size in very elderly people following strength training. Muscle Nerve. 1999; 22: 831-9.
76. Pyka G, Lindenberger E, Charette S, Marcus R. Muscle strength and fiber adaptations to a year-long resistance training program in elderly men and women. J Gerontol. 1994; 49: M22-7.
77. Trappe S, Williamson D, Godard M, Porter D, Rowden G, Costill D. Effect of resistance training on single muscle fiber contractile function in older men. *J Appl Physiol*. 2000; 89: 143-52.
78. Rydwik E, Frandin K, Akner G. Effects of physical training on physical performance in institutionalised elderly patients (70+) with multiple diagnoses. Age Ageing. 2004; 33: 13-23.
79. Bautmans I, Van Hees E, Lemper JC, Mets T. The feasibility of whole body vibration in institutionalised elderly persons and its influence on muscle performance, balance and mobility: a randomised controlled trial [ISRCTN62535013]. BMC Geriatr. 2005; 5: 17.
80. Thomas VS, Hageman PA. Can neuromuscular strength and function in people with dementia be rehabilitated using resistance-exercise training? Results from a preliminary intervention study. J Gerontol A Biol Sci Med Sci. 2003; 58: 746-51.
81. van den Ende CH, Breedveld FC, le Cessie S, Dijkmans BA, de Mug AW, Hazes JM. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. Ann Rheum Dis. 2000; 59: 615-21.
82. Van Den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy for rheumatoid arthritis. Cochrane Database Syst Rev. 2000: CD000322.
83. Rall LC, Meydani SN, Kehayias JJ, Dawson-Hughes B, Roubenoff R. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheum. 1996; 39: 415-26.
84. Pu CT, Johnson MT, Forman DE, Hausdorff JM, Roubenoff R, Foldvari M, et al. Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. *J Appl Physiol*. 2001; 90: 2341-50.
85. Sullivan DH, Wall PT, Bariola JR, Bopp MM, Frost YM. Progressive resistance muscle strength training of hospitalized frail elderly. Am J Phys Med Rehabil. 2001; 80: 503-9.
86. Hauer K, Specht N, Schuler M, Bartsch P, Oster P. Intensive physical training in geriatric patients after severe falls and hip surgery. Age Ageing. 2002; 31: 49-57.
87. Lemmer JT, Hurlbut DE, Martel GF, Tracy BL, Ivey FM, Metter EJ, et al. Age and gender responses to strength training and detraining. Med Sci Sports Exerc. 2000; 32: 1505-12.
88. Hakkinen K, Alen M, Kallinen M, Newton RU, Kraemer WJ. Neuromuscular adaptation during prolonged strength training, detraining and re-strength-training in middle-aged and elderly people. Eur *J Appl Physiol*. 2000; 83: 51-62.
89. Taaffe DR, Marcus R. Dynamic muscle strength alterations to detraining and retraining in elderly men. Clin Physiol. 1997; 17: 311-24.
90. Trappe S, Williamson D, Godard M. Maintenance of whole muscle strength and size following resistance training in older men. J Gerontol A Biol Sci Med Sci. 2002; 57: B138-43.
91. Kallinen M, Sipila S, Alen M, Suominen H. Improving cardiovascular fitness by strength or endurance training in women aged 76-78 years. A population-based, randomized controlled trial. Age Ageing. 2002; 31: 247-54.
92. Bautmans I, Lambert M, Mets T. The six-minute walk test in community dwelling elderly: influence of health status. BMC Geriatr. 2004; 4: 6.
93. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. The New England journal of medicine. 1994; 330: 1769-75.
94. Fujita S, Volpi E. Nutrition and sarcopenia of ageing. Nutrition research reviews. 2004; 17: 69-76.
95. Dreyer HC, Volpi E. Role of protein and amino acids in the pathophysiology and treatment of sarcopenia. Journal of the American College of Nutrition. 2005; 24: 140S-5S.
96. Drummond MJ, Dreyer HC, Pennings B, Fry CS, Dhanani S, Dillon EL, et al. Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging. *J Appl Physiol*. 2008; 104: 1452-61.
97. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. BMJ. 2005; 330: 524-6.
98. Frisoli A, Jr., Chaves PH, Pinheiro MM, Szejnfeld VL. The effect of nandrolone decanoate on bone mineral density, muscle mass, and hemoglobin levels in elderly women with osteoporosis: a double-blind, randomized, placebo-controlled clinical trial. The journals of gerontology. 2005; 60: 648-53.
99. Creutzberg EC, Wouters EF, Mostert R, Pluymers RJ, Schols AM. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest. 2003; 124: 1733-42.
100. Practice Committee of the American Society for Reproductive Medicine Treatment of androgen deficiency in the aging male. Fertility and sterility. 2006; 86: S236-40.

101. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2006; 91: 1995-2010.
102. Baulieu EE, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: contribution of the DHEAge Study to a sociobiomedical issue. Proceedings of the National Academy of Sciences of the United States of America. 2000; 97: 4279-84.
103. Nair KS, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *The New England journal of medicine*. 2006; 355: 1647-59.
104. Giovannini S, Marzetti E, Borst SE, Leeuwenburgh C. Modulation of GH/IGF-1 axis: potential strategies to counteract sarcopenia in older adults. *Mechanisms of ageing and development*. 2008; 129: 593-601.
105. Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Williamson J, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet*. 2002; 359: 926-30.
106. Sumukadas D, Struthers AD, McMurdo ME. Sarcopenia--a potential target for Angiotensin-converting enzyme inhibition? *Gerontology*. 2006; 52: 237-42.
107. Jorgensen SB, Jensen TE, Richter EA. Role of AMPK in skeletal muscle gene adaptation in relation to exercise. *Appl Physiol Nutr Metab*. 2007; 32: 904-11.
108. Narkar VA, Downes M, Yu RT, Embler E, Wang YX, Banayo E, et al. AMPK and PPARdelta agonists are exercise mimetics. *Cell*. 2008; 134: 405-15.
109. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *J Gerontol A Biol Sci Med Sci*. 2002; 57: M772-7.
110. Tanko LB, Movsesyan L, Mouritzen U, Christiansen C, Svendsen OL. Appendicular lean tissue mass and the prevalence of sarcopenia among healthy women. *Metabolism*. 2002; 51: 69-74.
111. Rolland Y, Lauwers-Cances V, Cournot M, Nourhashemi F, Reynish W, Riviere D, et al. Sarcopenia, calf circumference, and physical function of elderly women: a cross-sectional study. *J Am Geriatr Soc*. 2003; 51: 1120-4.
112. Gillette-Guyonnet S, Nourhashemi F, Andrieu S, Cantet C, Albarède JL, Vellas B, et al. Body composition in French women 75+ years of age: The EPIDOS study. *Mechanisms of Ageing and Development*. 2003; 124: 311-6.
113. Kenny AM, Dawson L, Kleppinger A, Iannuzzi-Sucich M, Judge JO. Prevalence of sarcopenia and predictors of skeletal muscle mass in nonobese women who are long-term users of estrogen-replacement therapy. *J Gerontol A Biol Sci Med Sci*. 2003; 58: M436-40.
114. Erratum to article by: Castillo EM, Goodman-Gruen D, Kritz-Silverstein D, Morton DJ, Wingard D, Barrett-Connor E. Sarcopenia in elderly men and women: The Rancho Bernardo Study: Am J Prev Med 2003;25:226-31. *American Journal of Preventive Medicine*. 2004; 27: 265-.
115. Pichard C, Kyle UG, Bracco D, Slosman DO, Morabia A, Schutz Y. Reference values of fat-free and fat masses by bioelectrical impedance analysis in 3393 healthy subjects. *Nutrition*. 2000; 16: 245-54.
116. Newman AB, Kupelian V, Visser M, Simonsick E, Goodpaster B, Nevitt M, et al. Sarcopenia: alternative definitions and associations with lower extremity function. *J Am Geriatr Soc*. 2003; 51: 1602-9.
117. Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *American journal of epidemiology*. 2004; 159: 413-21.
118. Lau EMC, Lynn HSH, Woo JW, Kwok TCY, Melton LJ, III. Prevalence of and Risk Factors for Sarcopenia in Elderly Chinese Men and Women. *J Gerontol A Biol Sci Med Sci*. 2005; 60: 213-6.
119. Foley RN, Wang C, Ishani A, Collins AJ, Murray AM. Kidney function and sarcopenia in the United States general population: NHANES III. *American journal of nephrology*. 2007; 27: 279-86.
120. Gallagher D, Visser M, De Meersman RE, Sepulveda D, Baumgartner RN, Pierson RN, et al. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol*. 1997; 83: 229-39.
121. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet*. 1996; 348: 145-9.
122. Ligthart GJ, Corberand JX, Fournier C, Galanaud P, Hijmans W, Kennes B, et al. Admission criteria for immunogerontological studies in man: the SENIEUR protocol. *Mech Ageing Dev*. 1984; 28: 47-55.