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Special Issue
Sarcopenia: from theoretical approach into clinical practice

Guest Editor
Francesco Landi

ORIGINAL INVESTIGATION

Psychological distress among a sample of Iranian older adults

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Introduction. Psychological distress is one of the most important predicting factors of mental health among older adults. Therefore, this study aimed to identify status and associated factors of psychological distress among older adults in Gorgan City.

Method and material. A cross-sectional design was conducted on a convenience sample of 190 community-dwelling older adults aged 60 years and over in Gorgan, Iran. The Kessler psychological distress (K10) was used to measure psychological distress. Data analysis was conducted using the Statistical Package for Social Science (SPSS) version 22.

Results. Out of 190 participants around 53% were female. The mean age of the respondents was 69.88 ± 7.58. The prevalence of severe psychological distress was found to be 13.2%. The results of multiple linear regression showed a significant model ($F_{(8,181)} = 9.02$, $p < 0.001$), wherein sex, subjective income, and chronic disease were significantly associated with psychological distress.

Conclusions. The results of this study indicate slightly a high level of psychological distress among older adults, particularly in vulnerable groups including women, the poor, low educated people, and older adults with co-morbidity. Therefore, it is recommended that policy-makers take into account vulnerable older adults when providing comprehensive mental health programs for aged population.

Key words: Psychological distress, Older adults, Iran

INTRODUCTION

Population aging is a global phenomenon which is accompanied by substantial economic and social consequences [1]. The growth of aged population will be expected to increase from 694 million in 1970 to 1.2 billion in 2050 [2]. Iran, like other countries around the world, is experiencing aging population. Although aged population now accounts for 9.3% of the Iran population, it is projected to reach 20% by 2050 [3].

Regarding high life expectancy, the prevalence of chronic illnesses is being increased among elderly people, therefore well-being from different aspects including psychological or physical would be the most important issue at advanced ages [4]. There is a significant relationship between psychological well-being and health outcome. Low level of psychological well-being could result in higher allocation rate budget on health and social care in aged population [5]. In light of mentioned above, early identification of psychological distress in later life not only could shorten the duration of suffering but also promote the quality of life [6].Psychological distress is generally defined as *"emotional suffering characterized by symptoms of depression and anxiety that may be tied in with Somatic symptoms"* [7].

From aspect of holistic approach, psychological distress would substantially originate from specific socio-economic background including marital status

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(separated, widowed and divorced), low educated people, lower income, unemployment, mental distress, substance abuse, social network, family structure and living in village or small town [8]. Furthermore, previous studies have indicated that there is strong association between psychological distress and increased risk of mortality [9], cardiovascular disease [10], diabetes [11], hypertension [12] and epilepsy [13].

Some individuals are so vulnerable towards psychological distress. For example, elderly women are sensitive group especially who have primary education, because poor education may be major obstacle for having predominant participation in society and being active from aspect of cognition. As a result, the mentioned issue will lead to psychological distress among old women [14 15]. Older women experience the impact of events including widowhood, isolation, feeling of insecurity, sense of helplessness, substandard health, physical illness, and lack of attention more intensively than older men [16]. The aim of this study was to identify the status and associated factors of psychological distress among older adults in Gorgan City.

MATERIAL AND METHOD

A cross-sectional study design was conducted on a sample of 190 Iranian community-dwelling older adults using a convenience sampling technique in Gorgan. The city of Gorgan is located in north-eastern part of Iran which leads to Caspian Sea from south-east. Her total area is 40 km^2 and has a Mediterranean climate [17]. According to the last National Iranian census in 2016, total population of Gorgan city is 365682 which has 30635 elderly persons at the age of 60 and over [18].

Data collection was conducted from July 2016 to September 2016. The participants were 190 aged people 60-year-old and over who were recruited from a day care center and community-dwelling older adult in Gorgan city. The exclusion criteria were as cognition impairment (based on abbreviation mental test (AMT) and not willing to continue the process of project.

The majority of the participants attended to daycare center on Sundays and Thursdays, because most leisure activates and educational programs were commonly held during those days. Therefore, two trained-enumerators involved in data collection. A face-to-face technique was carried out.

Kessler psychological distress scale (k10) was used to measure non-psychological distress in the anxiety- depression spectrum. The responses were classified into five point Likert Scale ("all of the time" = 5, "a little of the time = 2", some of the time = 3, most of the time = 4, "none of the Time = 5"); the total score was ranged between 10 (no distress) 50 (sever distress) [19]. The reliability of this scale in other studies that were conducted in other countries was 0.84-0.94 [20-23]. In this study the internal reliability of this scale was obtained 0.88.

Socio-demographic variable

Socio-demographic variables were including age, sex, marital status, living status, level of education, employment status, income satisfaction, chronic disease (Hypertension, diabetes, Cardiovascular disease, Gastrointestinal disease, Cerebrovascular disease, kidney disease, Pulmonary disease, musculoskeletal disorders, Anemia) – information related to chronic disease was obtained through self-report technique. Furthermore, variables such as sex, marital status, living status, level of education and employment status were coded in a binary format, male (coded as 1) in comparison with female (coded as 0), marital status (unmarried coded as 0, married coded as 1), living status (alone coded as 0, others coded as 1), Level of educational (No formal education coded as 0, formal education coded as 1), employment status (unemployment coded as 0, employment coded as 1).

Statistical analysis

Data analysis was conducted using the Statistical Package for Social Sciences (SPSS 22). Descriptive analysis such as ranges, frequency distribution, percentage, means and standard deviation were used. Analytic statistic including bivariate analyses were performed using Pearson correlation, independent t-test, multiple linear regression. Preliminary exploratory data was carried out to determine missing value, detect outliers and access for normality.

RESULTS

In this survey, 190 older adults were studied. The mean age was 69.88 ± 7.58 with a range between 60 and 90 years old. In terms of gender distribution, the sample was equally distributed (52.6%, n = 100) Table I presents the distribution of the aged population based on socio-demographic and health characteristic.

The total score related to psychological distress was between 10 and 50, which 12.1% and 13.2% were likely to have a moderate disorder and likely to have a sever disorder, respectively. Table II reports specific classification of Kessler psychological distress (K10) and the mean score was 19.41 ± 8.65.

A series of bivariate analyses including Pearson correlation, independent-samples t-test and multiple linear regression were conducted to assess association between socio-demographic characteristics and psychological distress.

Table I. Distribution of the study population by each socio-demographic and health characteristics.

Variable	Category	N	%	M	SD
Sex	Male	90	47		
	Female	100	53		
Age	60-74 young-old	139	73	69.9	7.6
	75-84 old-old	43	22		
	+85 oldest-old	9	4.7		
Income satisfaction	Absolutely dissatisfy	34	18		
	Dissatisfy	31	16		
	Don't have any opinion	8	4.2		
	Satisfy	86	45		
	Absolutely satisfy	31	16		
Marital status	Married	119	63		
	Unmarried	71	37		
Living status	Alone	42	22		
	With others	148	78		
Level of educational	No formal education	112	59		
	Primary education	52	28		
	Secondary and tertiary education	24	13		
Employment status	Unemployed	146	77		
	Employed	44	23		
The number of chronic disease	0	46	24		
	1	51	27	1.6	1.3
	2	47	25		
	3	46	24		

Table II. Classification of Kessler psychological distress on elderly population.

Categories	N	%	M	SD
10-19 Likely to be well	122	64		
20 = 24 Likely to have a mild				
Disorder	20	11	19.4	
				8.7
25-29 Likely to have a moderate	23	12		
disorder				
30-50 Likely to have a severe	25	13		
disorder				

As Table III shows. The results related to independent t-test were revealed that there was a significant difference between women (M = 22.81, SD = 8.82), men (M = 15.63, SD = 6.68), t (152) = 6.35, $p < 0.001$ and psychological distress.

As expected, older women reported significantly higher level of psychological distress. Furthermore, independent sample t-test was performed to investigate psychological distress between marital statuses among elderly individuals. There was no significant difference in psychological distress between unmarried group (M = 20.76, SD = 8.38) and married group (M = 18.60, SD = 8.73), t (188) = 1.67, $p > 0.05$. However, a significant difference was found from aspect of living status, education level.

In order to assess bivariate association, Pearson correlation was used, the findings showed that there was a negative and significant association between age and psychological distress ($r = -0.16$ $p \leq 0.05$), income satisfaction and psychological distress ($r = -0.22,$ $p \leq 0.05$). Nevertheless, there was a significant and positive correlation between chronic disease and psychological distress ($r = 0.3,$ $p < 0.001$).

The most surprising aspect of the data is that identify socio-demographic and health predictors of psychological distress. Regression analysis was used to predict that socio-demographic and health characteristics could have significant relationship with psychological distress. The results, as shown in Table IV. Indicates that multiple linear regression analysis to predict the psychological distress by socio-demographic factors.

Finding from multiple linear regression analysis revealed a significant model (F (8,181) = 9.02, $p < 0.001$) with sex ($\beta = -0.4$, $p < 0.001$), income satisfaction ($\beta = -0.2$, $p < 0.001$) and chronic disease ($\beta = 0.2$, $p < 0.01$) as socio-demographic and health predictor of psychological distress. However, the multiple linear regression test did not show any significant differences between

Table III. Mean score of psychological distress based on socio-demographic factors.

Variable	Category	N	Mean	SD	t
Sex	Female	100	22.81	8.8	
	Male	90	15.63	6.7	6.35**
Marital status	Unmarried	71	20.76	8.4	
	Married	119	18.6	8.7	1.67*
Living status	Alone	42	21.98	8.5	
	Others	148	18.68	8.6	-2.18
Education level	No formal	112	20.5	8.7	
	Formal	78	17.85	8.4	2.09
Employment status	Unemployed	146	19.82	8.8	
	Employed	44	18.02	8.3	1.21

Note: **p < 0.001, p ≤ 0.05*

Table IV. Results of multiple linear regression analysis to predict psychological distress by socio-demographic factors.

Variable	B	SE	β	t	Collinearity statistics	
					Tolerance	VIF
Age	-0.1	0.1	-0.1	-0.95	0.85	1.2
sex	-7.1	1.5	-0.4	-4.65*	0.51	1.9
Marital status	2.13	1.6	0.12	1.35	0.5	2
Living status	1.62	1.7	0.07	0.96	0.6	1.7
Level of education	-0.6	1.2	-0	-0.48	0.83	1.2
Employment status	1.55	1.5	0.07	1.03	0.74	1.4
Income satisfaction	-1.4	0.4	-0.2	-3.4**	0.97	1
Chronic disease	1.3	0.4	0.23	3.05**	0.89	1.1

Notes: F (8,181) = 9.02, *P < 0.001, **P ≤ 0.05. Sex (male = 1, female = 0), marital status (unmarried = 0, married = 1), Living status (alone = 1, others = 0), Level of education (no formal = 0, formal = 1), Employment status (employed = 1, unemployed = 0).

age, marital status, living status, educational level and employment status and psychological distress among Iranian elders.

DISCUSSION

This study was conducted in a sample of 190 community-dwelling Iranian elderly population in Gorgan city so that investigate significant socio-demographic and health predictors of psychological distress in old age.

The results of this study indicate that five socio-demographic and health factors including age, sex, and marital status, level of educational, living status, income satisfaction, and chronic disease were significant predictors of psychological distress in later life.

The current study found a significant and inverse relation between age and psychological distress among Iranian aged people. This finding detects that with increasing age, psychological distress will be decreased. Therefore, the present findings seem to be consistent with other researches which supported this correlation [24 25]. The possible explanation for positive influence of aging on psychological distress may be related to appraising coping strategies in later life which were more likely resulted in declining of psychological ailments [26 27].

Another finding from the current study detected that there was a significant relationship between psychological distress and sex. The elderly women had reported higher level of psychological distress in comparison with older men. These present findings seem to be consistent with recently study which found several possible explanations for this results, for instance the rate of morbidity among elderly women is higher and numerous of elderly women spend a large partial of their life with disabilities and illnesses [28]. The aged women more likely to experience widowhood in later life and this factor may explain the relatively good correlation between sex and psychological distress [29]. Overall, old women suffer from lower socio-economic resources that leads to poverty, one possible explanation for this discrepancy is lack of security job among females [30]. Elderly women tend to expresses the negative feelings [31]. With advancing age, facial and physical attractiveness among women will be declined [32] which result in increasing psychological distress whereas men may obtain social prestige with age. These expressed factors could be main cause of higher psychological distress among women [33]. Some authors have speculated that social network characteristics could have substantial influence on psychological distress between men and women [34 35]. There is, however, other possible explanations that might be related to lack of adequate access to economical and emotional resources by men and women across life course may lead to sex difference in psychological distress [34]. According to above mentioned, psychological distress among women is higher than men.

Marital status also could be one important predictor of psychological distress among older adults. Although there was no statistically differences between unmarried and married respondents but older people who were unmarried had higher psychological distress. This findings is in agreement with previous study which showed that being single was equally detrimental effects on level of psychological distress among two genders [36]. This result may be explained by the factor that marriage could provide powerful social support for couples that leads to lower level of psychological distress among men and women [37-39]. Other finding documented have reported that social contract may assemble individuals together in an intimate relationship which would be stress-buffering and socially integrative [40]. In sum, the findings of the current study do support the previous research [41]. One the other hand, a study indicated that psychological distress among married men is much less in comparison with married women [42].

Furthermore, another important finding which was emerged from this study is related to pivotal role of education status on psychological distress. The finding of current study is consistent with those of Brannlund and Hammarström using data collected from over the course of 27 years from Sweden participants, found that high education is positively linked to less psychological distress [43]. This result may be explained by the fact that older people who have high level of education could participate in cognitively stimulating activates, have better economic circumstance and engage in more physical activity, as a result these individuals have lower level of psychological distress [44].

In this study, being alone was found to cause psychological distress that is consistent with previous studies [45-47]. As people grow old, there is most likely to report the highest loneliness which is emerged from death of spouse and social disengagement after leaving work or a familiar neighborhood [48]. However, the finding of the current study do not support the previous research which was not indicated any significantly difference between older adults who lived alone and those who lived with others from aspects of psychological distress [49].

Income satisfaction and chronic disease had a significant correlation with psychological distress at a multiple linear regression. Previous studies have demonstrated that clear relationship of lower income with psychological distress [50-52]. Stabilization of income may increase subject's ability to cope with life crises and therefore will diminish psychological distress [53 54].

Further finding from the current study emerging from observed correlation between chronic disease and psychological distress might be explained that distress may contribute to disease progression [55]. This result provides further support for hypothesis that due to increase in chronic disease, demand for psychological treatment will be identified [56]. On the other words, psychological distress may originate from chronic disease may have adverse effect on health-related quality of life [57]. This produced result which corroborate the findings of a great deal of the previous findings in this field [58-61].

CONCLUSIONS

Returning to question posed at the beginning of this study, it is now possible to state that policy makers should pay much more attention to vulnerable elderly people.

LIMITATIONS

A number of important limitations need to be considered. First, the current research is limited by the use of a cross-sectional design, therefore a longitudinal study should be conducted to evaluated cause-and-effect relationships. Second, this project used a self-report technique for gathering data, which has some problems including honesty/image management, understanding and response bias as a result caution must be applied, as findings might not be transferable to aged population in Iran. It is recommended that the further research could be undertaken in the following settings including long-term institutions and hospitals in which older population with various characteristics from aspect of socio-demographic and health have been maintained.

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Conflict of interest

The authors declare no conflict of interest.

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Original Investigation

Medication management ability in older patients: time for a reappraisal

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Background. Adhering to drug regimens is a complex and multidimensional task. Elderly patients usually take an average of seven drugs but most fail to adhere to the prescribed regimen. Several performance-based instruments have been developed to assess a patient's capacity to manage drugs but with inconsistent results.
Aims. The aim of the study was to assess the prevalence of impaired medical management capacity in a sample of the oldest old hospitalized elderly patients and the main clinical factors associated with potential unintentional non-adherence.
Methods. Forty-six consecutive patients were enrolled in the geriatric transitional care unit of Ospedale Policlinico San Martino, Genoa, Italy. All patients received an abbreviated comprehensive geriatric assessment and a hand grip assessment for sarcopenia. Patients' medication management ability was assessed by administering the DRUGS tool 48-74 hours before hospital discharge.
Results. The results showed a negative correlation between age and total medication management score. A positive correlation was detected between functional status, cognitive status, and medication management score. Hand grip strength < 9 kg correlated with a significant worsening of medical management capacity. In contrast, multiple morbidities and the mean number of drugs were not associated with the medical management score.
Conclusions. This preliminary study indicated that drug management capacity mainly relies on frailty markers, such as functional status, sarcopenia, and cognitive performance. Further studies are warranted to identify a subset of medical parameters that can accurately predict impaired medical management ability early, particularly for highly vulnerable elderly patients.

Key words: Drug management ability, Frailty, Functional decline, Oldest old patients, Sarcopenia

INTRODUCTION

The ability to appropriately manage medications is crucial to assure medical adherence, particularly in older adults with multiple morbidities and regimens with several drugs. Older adults usually take an average of seven drugs per day; however, up to 40% fail to take their medications as prescribed [1 2].
Adhering to a drug regimen is a complex task that includes cognitive, physical, functional and socioeconomic abilities. Several instruments have been developed to assess medication management ability in patients who used their own medications or participated in a simulated medication regimen [3-6].
The DRUGS and Med MaiDe instruments [5 6] both use a patients' own medications and show adequate intra and inter-rater reliability, Moreover, the DRUGS tool is correlated with cognitive function, responsiveness to change, and applicability in different clinical settings [7-11].
No systematic assessment of drug management ability has been implemented into routine clinical practice.
To fill this gap in knowledge, the present study assessed

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the medical management ability of hospitalized elderly patients and the main clinical factors associated with potential inability to manage drugs.

SUBJECTS AND METHODS

In total, 100 consecutive patients admitted to the Ospedale Policlinico San Martino, Geriatric unit, Genoa, Italy (January-June 2017) were enrolled. Thirty patients were excluded for clinical instability, six patients died, ten patients refused to participate in the study, and eight patients withdrew from the study. Thus, 46 patients entered the study after written informed consent was obtained. The local ethics committee approved this study.

Patients were included if they were: > 65 years, suffering from moderate multiple morbidities (CIRS < 6) [12], clinically stable and the hospital discharge drug regimen included the target drug packaging (see above).-

Exclusion criteria were end stage chronic disease, (CIRS > 6) and an inability to participate in the study.

Demographic variables, residence, marital status, and in-home assistance data were collected. All patients received abbreviated comprehensive geriatric assessment, including the following tools to assess clinical domains: cognitive status (Mini Mental State Examination [13], MMSE), psychological status (Geriatric Depression scale [14], GDS 15-items), functional status (Basic and Instrumental Activities of Daily Living of Lawton [15] [16], BADL and IADL), physical burden of illness (Cumulative Illness Rating Scale [12], CIRS: Illness Severity Index-SI, and Co-morbidity Index-CI). A hand-grip dynamometer (Camry; EH101 Units: kg/libbers. Maximum capacity 90 kg. Power 2X 1.5 V AAA batteries. Tolerance ± 0.5 kg) was used to assess sarcopenia.

The DRUGS tool [5] was administered 48-72 hours before hospital discharge to assess a person's ability to identify drugs, to open containers, to take out the correct number, and to appropriately verbalize the prescribed drug and dose for the following packaging types:

- pill blister packs;
- tablets;
- child resistant closure droplets;
- insulin (Apidra Solostar) pen;
- inhaler devices (e.g., Aliflus diskus inhaler; Bretaris inhaler).

STATISTICS

Data are expressed as mean ± standard deviation. The non-parametric Pearson's correlation analysis was used to determine the associations between two variables (Fig. 1). The non-parametric *t*-test (Mann-Whitney test) was used to estimate differences between two variables. The non-parametric Kruskal-Wallis analysis was used to estimate differences among three or more variables. A p-value < 0.05 was considered significant. Graph Pad version 5.0 b software (Graph Pad Software, La Jolla, CA, USA) was used to perform the statistical analysis.

Table I. Patients' clinical characteristics based on the abbreviated comprehensive geriatric assessment.

Assessment tool	Mean ± SD
MMSE	20.38 ± 0.35
CIRS	4.15 ± 0.27
CIRS severity	1.98 ± 0.05
IADL	2.62 ± 0.35
BADL	3.13 ± 0.33
GDS	7.20 ± 0.52
Mean drugs	6.17 ± 0.42
Hand-grip (kg)	9.76 ± 0.90

RESULTS

Mean patient (30 females and 16 males) age was 86.64 ± 1.01 years.

A total of 71% of patients lived alone at home and 29% received home assistance.

Most patients' clinical phenotype (Tab. I) was frail, characterized by severe sarcopenia and functional decline.

All patients failed to manage their medication, fulfilling only the first task (e.g., ability to identify drugs) of the four requested for each drug package: (Aliflus diskus: 1.37 ± 0.19; Bretaris: 1.11 ± 0.19; Apidar Solostar: 1.60 ± 0.16; pill blister pack: 2.35 ± 014; tablets 1.33 ± 0.17; child resistant closure droplets: 1.42 ± 0.16).

A negative correlation was observed between age and the DRUGS score (n = 46; r = –0.43, p < 0.001).

In addition, a positive correlation was detected between DRUGS, the BADL (n = 46, r = 0.70, p < 0.0001), the IADL (n = 46; r = 0.65, p < 0.001), the MMSE (n = 46; r = 0.58, p < 0.0001), and hand-grip strength (n = 46; r = 0.42, p < 0.005). Worsening of the DRUGS score was associated with the severity of cognitive deficit (moderate dementia: MMSE 19-11 points) (KW 12.84 p < 0.01) and (severe dementia: MMSE ≤ 10 points) (KW 29.91 p < 0.001), respectively.

Similarly, a moderate functional decline (BADL < 4/6 points) was associated with worsening of the DRUGS score (U 497: p < 0.01).

Handgrip strength < 9 kg correlated with worsening of the DRUGS score (U 338; p < 0.005).

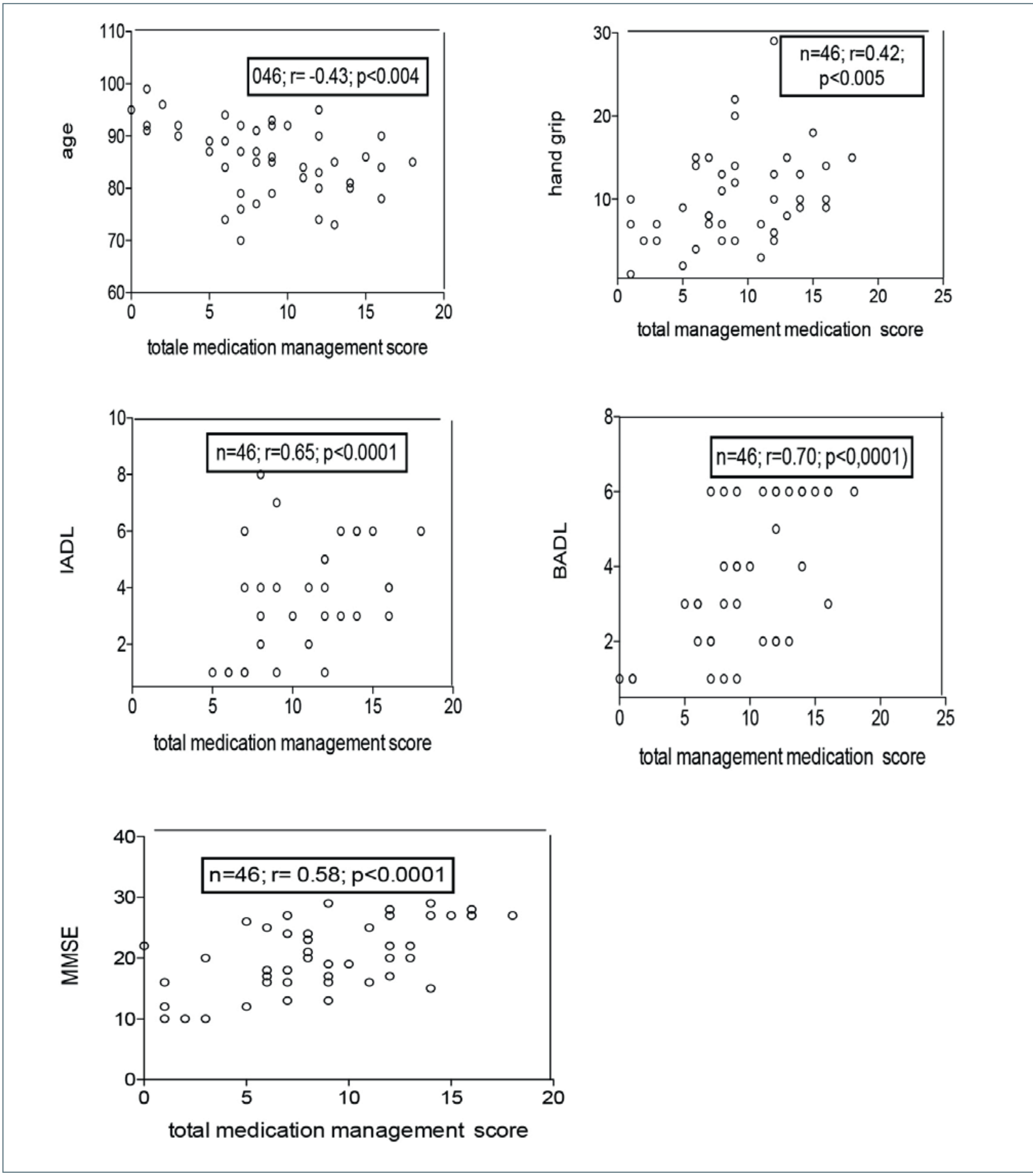

Figure 1. Pearson's correlation analysis between the DRUGs score and age, sarcopenia (hand-grip strength measured in kg), functional status (Basic and Instrumental Activities of Daily Living of Lawton, BADL and IADL), and cognitive status (Mini Mental State Examination, MMSE).

Multiple morbidities were not associated with impaired drug management.

Medication management ability for the Aliflus diskus inhaler was inversely correlated with age ($n = 46$; $r = -0.38$, $p < 0.0008$) but positively correlated with the BADL ($n = 46$; $R = 0.42$, $p < 0.003$), CIRS severity

(n = 46, r = 0.45, p < 0.0018), the CDT (n = 46, r = –0.36, p < 0.001), and the MMSE (n = 46; r = 0.38, p < 0.009). Similarly, management ability for the Bretaris inhaler was inversely correlated with age (n = 46, r = –0.34, p < 0.003) and the MMSE (n = 46, r = 0.51, p < 0.001) but positively correlated with the BADL (n = 46, r = 0.54, p < 0.005) and the IADL (n = 46, r = 0.60, p < 0.0001). In contrast, the medication management ability of child resistant closure droplets correlated with hand-grip strength (n = 46; r = 0.60, p < 0.0001) as well as the Apidra Solostar device (n = 46, r = 0.60, p < 0.0001).
The medication management ability of pill blister packs correlated with sarcopenia (n = 46; r = 0.66, p < 0.0001), the IADL (n = 46; r = 0.62; p < 0.0001), and cognitive status (n = 46; R = 0.43, p < 0.0002).

DISCUSSION

Medical management is a highly integrated process that includes a defined set of mental and physical skills and has also been considered a key to successful aging [17 18] In contrast, the need to receive assistance with medications predicts frailty [19-21].
This exploratory study indicates that the ability of elderly subjects to manage their medications mainly relies on cognitive performance, functional status, and sarcopenia [18 19], which are recognized markers of frailty.
In particular, the present findings show that age (*oldest-old* population) was the main determinant of the inability to manage drugs.
In addition, sarcopenia was associated with an overall worsening of drug management ability and was associated with less ability to use pill blister packs, children closure droplets, and an insulin pen.
The use of inhaler devices unmasks higher integrated processing; indeed, the inability to use an inhaler was associated with cognitive deficit, visuospatial impairment, severity of comorbidities, and functional decline.
Notably, drug management ability declined according to dementia severity and disability as well. Frailty hallmarks are key determinants of effective medical management performance, adherence, and compliance, with direct implications for appropriate clinical management of such a vulnerable population.
Interestingly, multiple morbidities and multiple drug regimens were not associated with drug management ability. Thus, it could be hypothesized that understanding of comorbidity clusters and/or disease severity could better help stratify older adults' higher risk of drug noncompliance. Similarly, particular types of drugs packaging and the complexity of drugs prescriptions, instead of the mere cumulative number of drugs, may primarily account for this impaired ability [21 22].

The limitations of this study are the small size and the single hospital setting with selection bias and underpowered results. Hospital complications, such as delirium and exceedingly poor mobility, may hamper overall drug management ability. Furthermore, a patient's usual drug regimen may undergo changes with which patients may be initially unfamiliar. Even if patients verbalized their difficulty taking such a large number of medications, no systematic survey has been conducted to assess preferences and knowledge of medical management strategies.
The strengths of this study are the real-world assessment of hospitalized *oldest-old* patients, considering a frail clinical phenotype, and the performance-based analysis of a broad set of drugs types and packaging. Hypothetically, a longitudinal assessment, sample size implementation, and a multivariate analysis could add knowledge to this field. In particular, including a wider set of drugs types and a sub-analysis of specific abilities for more complex devices, such as inhalers, could help in the understanding of this true geriatric syndrome.
Further research is needed to select the most predictive clinical parameters to intercept early drug management inability and to assure appropriate drug compliance in vulnerable older patients.

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Conflict of interest

The authors declare no conflict of interest.

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Clinical Observations in Geriatrics

Effect of multi-modal exercises after hemiarthroplasty of hip joint in a 72 year old male Parkinson's disease participant. A case report

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Background. Parkinson's disease is a progressive and deteriorating disease which often affects the mobility of individuals of above 60 years. A fall is one of the risk factor and especially the neck of femur fracture was very common among them. In India, the physiotherapy intervention of Parkinson's patient after hemiarthroplasty was poorly defined when compared to total hip arthroplasty. Thus, we have taken a single case study as an initiative with multi-modal exercise on physical function of Parkinson's patient after the hemiarthroplasty.
Case presentation. A 72-year-old man with symptom of Parkinson's disease and stage 3 of Hoehn and Yahr classification for past 1 year had a fall and underwent hemiarthroplasty for the left sided neck of femur fracture. After post-operative check x-rays and vital signs are normal, we have started multi-modal exercise with initial bed mobility exercise, breathing exercise and chest percussion technique, balance training in sitting and standing with gutter crutch, proprioceptive training, psychological counselling, progress to resistance exercise to quadriceps and stretching the calf muscle for 12 weeks. We have gradually reduced the gutter crutch to walking stick and gradually without walking aids at the end of 12 week protocol. We have continued the exercise for the patient and follow-up at 24 week also to check the status of physical function of patient. We have assessed the patient at the baseline and post-12 week with post-24 week follow-up using sit to stand and timed up and go test performance as an outcome measures. The physical performance showed significant changes in the post-12 week of patient when compared at baseline values and even continued significance at post-24 week of multi-modal exercise also.
Conclusions. Thus, the multi-modal exercises proved to be more beneficial on physical function for the Parkinson's patient with hemiarthroplasty. Even, we have found that the earlier mobilization had promoted the confident of patient and active participation of progression is faster in this case study.

Key words: Parkinsonism, Hemiarthroplasty, Quadriceps strengthening, Balance exercise

CASE PRESENTATION

A 72-year-old right- handed man presented with left neck of femur fracture due to sudden blackout while standing near his house and fall directly on left side. He was immediately hospitalized and the vital signs were normal and general physical examination was unremarkable other than for left sided femoral neck fracture. He had a symptom of Parkinson's disease with stage 3 of Hoehn and Yahr classification for past 1 year and taking medication by supervised neurophysician. His family members who were the informant said that normally a talkative and active person but had become unusually quiet for past 1 year and less active. There was no past history of Diabetes, Hypertension, strokes, mental illness or chronic alcoholism and his cognitive

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state was normal. His recent memory and immediate recall were not impaired. Routine haematological and biochemical laboratory tests were normal. He underwent the hemiarthroplasty of left hip joint after the thorough examination by orthopaedic surgeon. The vital signs have been stable for him during the acute post-operative period. A post-operative check X-ray of left hip (Fig. 1) also revealed no abnormality. After getting the informed consent from the patient, we have started the ankle pumping exercise, isometric exercise to major hip and knee joint muscles with breathing exercise and chest percussion technique, incentive spirometer exercise for 3 session per day. After he was shifted to the separate suite room, orthopaedic surgeon advised the bed mobility exercise and walking with the gutter crutch for his comfort. He was attentive, able to do all this scheduled exercises but because of Parkinson's he had slowness of movement and poor balance while in sitting on the bed side itself. In India, the evidence of multi-modal exercises (various mode of exercises have been illustrated to improve the physical function and quality of life) on patients with Parkinson's disease after hemiarthroplasty was not represented till now. Thus, we planned for balance training exercises in sitting on bed side and standing with gutter crutch support along with quadriceps arc exercise, hip abduction resistance exercise, calf stretching exercise with psychological counselling. He was discharged to his home on day 7. Meanwhile, at the day 5 we have assessed him sit to stand timing from the hand supported chair with the gutter crutch support. When seen a 2 week later at the outpatients we examined the sit to stand timing and also timed up and go test performance to check his physical function. We continued the supervised balance exercise, proprioceptive training and resistance exercise to the quadriceps muscles and hip abductor of both legs, ankle stretching exercise for 40 minutes of duration per session and 5 days a week for total of 12 weeks. We also had a subsequent follow-ups after 24 weeks with timed up and go test for his changes in physical function. He was now independent for basic self-care and performed well on timed up and go test without any walking aids.

Figure 1. Post-operative check x-ray of left hemiarthroplasty.

DISCUSSION

Our patient presented with hemiarthroplasty who had a past 1 year of Parkinson's symptom under medication. Fall is a risk factor for Parkinson's patients especially the hip fracture is very common in those above 60 years [1]. Moreover the repeated fall had been the hectic problem to the Parkinson's patient even after the surgical intervention. This will deteriorate the routine life care and physical function of patient and thereby socio-economic burden to the family member also. This symptom disturb its progression of bed mobility and daily function. Several studies have evaluated the outcome of total hip arthroplasty in Parkinson's disease patients with hip fractures [2]. Unfortunately these surveys are not accurately applicable to a hemiarthroplasty. In order to support the current evidence regarding the outcome of hip hemiarthroplasty in Parkinson's disease patients we carried out a case study as an initiative. It's really challenging for the physiotherapist in the rehabilitation team to make him motivated and start his active life style and thereby to justify the family members. Nocera et al have found that when the severity of the Parkinson's disease increases the knee extensor strength was more weaker [3]. Exercise programs which are focused on improving muscle strength may also improve the physical function in patients with Parkinson's disease [4]. In our study, the multi-modal exercises like balance exercise, proprioceptive training and quadriceps resistance exercise helped him to be independent on his basic life care and improved physical function. In between the episodes, sit to stand test and timed up and go testing revealed the significant changes in the physical function of the subject. Even we have found that reaction time of quadriceps contraction performance on post-12 week and post-24 week have shown significant improvement than from the baseline and post-1week period of multi-modal exercise intervention. Aggressive physiotherapy and early mobilization was advised for patients with Parkinson's disease undergoing hemi-arthroplasty [5]. Moreover our patient had more confident after the physiotherapy intervention and he also able to maintain his balance in sitting and standing with the gutter crutch support. Furthermore, it is generally believed that more the attentive patients throughout the intervention and motivated by the family members in each stage of progression psychologically he will more confident and co-operative throughout the intervention protocol. Mathew et al states that the delay in the post-operative mobilization exercises after hemiarthroplasty in patients with Parkinson's disease were shown poor results in their physical outcomes and few patients attain mortality rate (37%) due to other complication [6]. We had seen this patient was more co-operative and confident on throughout the each stage of intervention protocol. There are some limitations to this study which needs further research. Firstly we have taken the patient with 1 year of Parkinson's symptom and we need to examine the intervention to the patient with history of prolonged period of Parkinson's disease. Secondly, we have taken the patient with cognitive function normal, whereas the Parkinsonism with dementia patients should also be examined for cognitive impairment level and effect of intervention changes on physical function. Nevertheless we believe this case presentation adds to the concept that the balance exercise, proprioceptive training with quadriceps resistance training will promote the hemiarthroplasty underwent Parkinson's with active participation in the community and continued to be healthier aging. The effectiveness of this multi-modal exercises can be compared with the single mode of exercise on physical function of more Parkinson's patients. The positive effect of this multi-modal exercise on balance and physical performance in Parkinson's patient can be implemented to all the elderly people for the healthy aging.

Conflict of interest

The authors declare no conflict of interest.

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Clinical Observations in Geriatrics

Mass involving retromolar trigone in a geriatric lady-diagnostic dilemma

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Polymorphous low grade adenocarcinoma (PLGA) is rarely encountered in routine clinical practice. Our patient, 78 year old lady presented with complaint of ill-fitting denture owing to soft tissue mass in retro-molar trigone. she had undergone multiple surgeries for thyroid malignancy. Thus, PGLA was a surprise diagnosis in this case. The differential diagnosis and subsequent clinical course are discussed in the following manuscript.

Key words: Polymorphous, Adenocarcinoma, Medullary, Carcinoma

CLINICAL PRESENTATION

A 78 year old Indian lady was referred to our out-patients department by her dental surgeon for evaluation of swelling in right retromolar trigone.

Patient was a complete denture wearer for many years and reported to her dentist for progressive ill-fitting of lower denture. Dentist discovered a swelling in the right retromolar trigone as probable cause of poor denture fit and was subsequently referred to us.

On questioning, she was aware of swelling which was slowly enlarging over approximately one year. It was painless, was not associated with any discharge, altered sensation in lip or tongue. It posed no difficulty in mastication, swallowing and phonation. So she did not seek early medical advice. There was no history of fever, weight loss, malaise, fatigue and tobacco consumption in any form.

Her medical history revealed that she underwent hemi-thyroidectomy for medullary carcinoma in 1976. This was followed by completion thyroidectomy in 1989 for recurrence and right radical neck dissection in 1998 for nodal recurrence. She was on thyroxin supplement since then. Apart from this, there was no history of major systemic illness.

Clinical examination revealed scar on right side of neck where nodal dissection was carried out in the past. Intra-orally about 3 cm *2 cm *1 cm firm, non-tender, sessile mass was seen occupying lower right retromolar trigone. Overlying mucosa had no obvious ulceration. Lesion was nontender and partially fixed to underlying bone. Rest of the oral cavity was unremarkable and there was no cervical lymphadenopathy (Figs. 1-2). Baseline hemogram was within normal limits.

DIFFERENTIAL DIAGNOSIS

Based on clinical evaluation, we should consider neoplasms and reactive proliferations as diagnostic possibilities.These are as follows in the order of likelihood.

1 **Metastatic thyroid carcinoma.** This was considered likely because patient had suffered from this disease in the past. Medullary carcinoma is a tumor of the parafollicular (C cells) derived from the neural crest and not from the cells of the thyroid follicle as are other primary thyroid carcinomas. Involvement of lymph nodes occurs in 50-60 per cent of cases of medullary carcinoma and blood-borne metastases are common. Current recommended treatment

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Figure 1. Neck scar.

Figure 2. Mass in the right retromolar trigone.

is by total thyroidectomy and either prophylactic or therapeutic dissection of central and bilateral cervical lymph nodes [1]. Serum calcitonin which serves to detect recurrence was normal in present case. Thus this diagnosis was ruled out in present case.

2 **Minor salivary gland neoplasm.** These account for 10% of all oral cavity malignant neoplasms and 15-23% of all salivary gland malignant neoplasms [2]. This is likely diagnosis due to submucosal location of tumour and advanced age. The precise histotype can only be diagnosed upon biopsy. Immunohistochemistry (IHC) if needed can be done for pathological diagnosis. Incisional biopsy was done for this patient under local anesthesia.

3 **Oral squamous cell carcinoma** is a consideration due to retromolar location and very high incidence of oral cancer in India. However no history of tobacco consumption coupled with submucosal location, non-ulcerated mucosa and absence of cervical lymphadenopathy make this a less likely diagnosis.

4 **Reactive lesions** to be considered include pyogenic granuloma, peripheral giant cell granuloma, traumatic fibroma, (due to denture irritation) [3]. Pyogenic granuloma is more common on labial or buccal gingiva. The surface is frequently ulcerated. Children and pregnant ladies are affected more often. Thus this is unlikely diagnosis. Peripheral giant cell granuloma has a similar clinical appearance but more blue purple compared to bright red color of pyogenic granuloma. It occurs at younger age group (31-41 years) compared to the present case. Traumatic fibroma presents as a pink sessile nodule similar to present case due to some form of chronic irritation. This was a consideration in present case as patient was a denture wearer. However, in radiographs, resorption of the adjacent interseptal bone is commonly seen in both traumatic fibroma and peripheral giant cell granuloma which was absent in present case. Thus, peripheral giant cell granloma and traumatic fibroma were unlikely diagnoses.

5 **Peripheral ossifying fibroma**. It is a non-neoplastic enlargement of the gingival tissue usually from interdental papilla, usually in incisor-cuspid region. It is most common in teenagers and young adults. Thus this is an unlikely diagnosis in present case considering location and age.

DIAGNOSIS AND MANAGEMENT

History and Clinical evaluation was suggestive of neoplastic disorder in the present case. This was confirmed with incisional biopsy and imaging.

Orthopantomogram (OPG) revealed no abnormality apart from soft tissue shadow of the lesion. An incisional biopsy revealed a tumor characterized by nests, acini and cylindroid formation. Cells had pale acidophilic cytoplasm and rounded stippled nuclei. Mitotic activity was not conspicuous. Stroma was focally hyalinized with myxochondroid change. It infiltrated beneath mucosa. Focal neural invasion was noted. To come to definitive diagnosis, IHC was done. Tumor cells expressed ck7, c5/6, vimentin, s-100protein, p63, SMA, calponin, bcl 2, cd117 and galactin3. They were negative forsmm, cd10, ck19, ttf1, hbme1 andGFAP.MIB1 proliferation

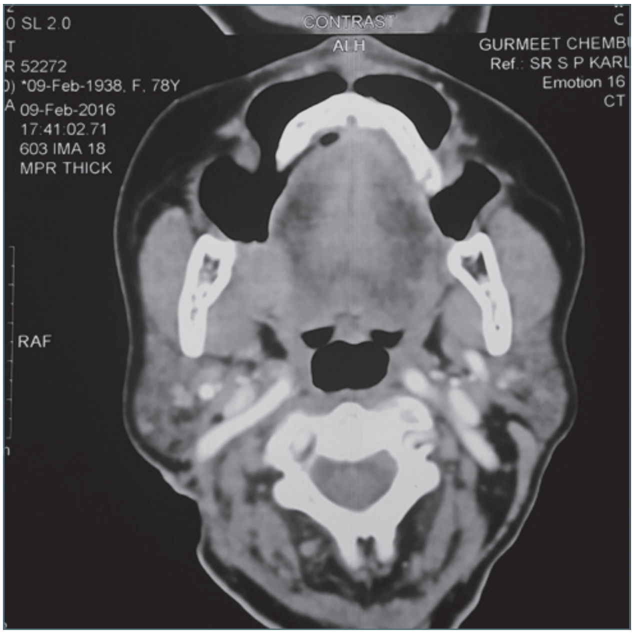

Figure 3. Lesion abuting medial pterygoid.

index was low. Diagnosis of Polymorphous low grade adenocarcinoma (PGLA) was made (Fig. 7), treatment for which is surgical excision.

To access extent and plan surgery CT scan was done which revealed 1.9*1.6*1.8 cm nodular homogenously enhancing lesion in right retromolar trigone. Posteriorly it abutted insertion of medial pterygoid muscle with loss of fat planes (Figs. 3, 4).

Underlying bone, para-pharyngeal space and gingivo-buccal sulci were free. No significant cervical lymhadenopathy was noted.

Owing to her past history of multiple surgeries for thyroid cancer, whole body PET scan was done which revealed similar findings to CT scan and no evidence of distant metastasis (Figs. 5, 6).

TREATMENT

Wide excision of the affected site was done which included lesion, insertion of medial pterygoid muscle (due to involvement on CT scan) and posterior segmental mandibulectomy (clinically tumor fixation to edentulous mandible) (Figs. 8, 9). Subsequently, she underwent external beam radiation to right face (60 Gy/30 fractions) owing to medial pterygoid muscle involvement. (Fig. 10). She is being followed up regularly and free of disease at 2 years (Fig. 11).

The lady did not complain about difficulty in speech and swallowing at the time of follow-up visit. However, due to loss of segment of mandible, she was unable to wear

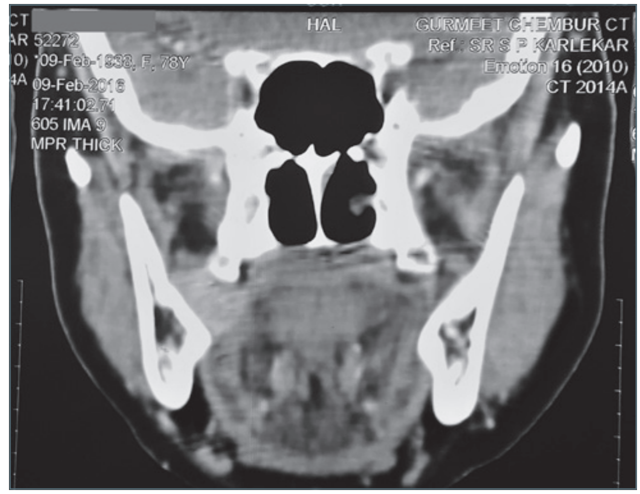

Figure 4. Coronal section of the right retromolar trigone.

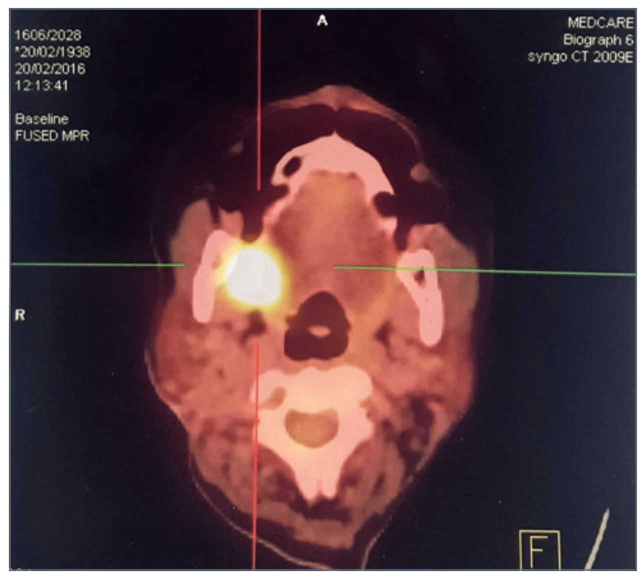

Figure 5. PET scan axial section.

mandibular denture and could only eat soft liquidized food. This was anticipated before operation. It required vascularized bone graft like fibula or ilium to reconstruct lost portion of mandible followed by insertion of titanium dental implants to replace missing teeth. This prolongs operation under general anesthesia to 8-10 hours. In view of her advanced age, this was considered very high anesthetic and surgical risk. The issue was discussed with the patient who opted for removal of tumour and primary closure. Thus her quality of life was affected as far as efficient mastication is concerned.

Histopathology of excisional biopsy specimen confirmed the diagnosis of polymorphous low grade adenocarcinoma (PGLA) made at the time of incisional biopsy (Fig. 12).

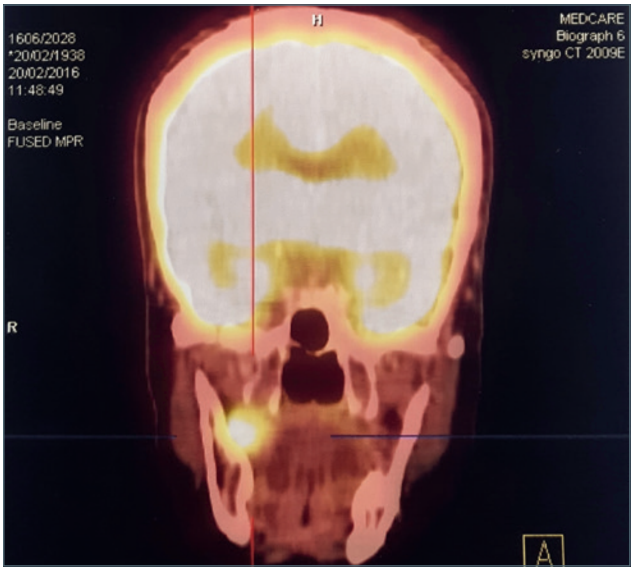

Figure 6. PET scan coronal section.

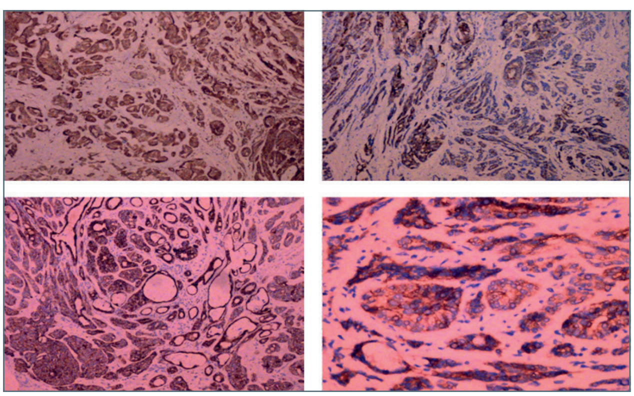

Figure 7. Photomicrograph of the immunohistochemistry (IHC) image of bcl-2 (top left, magnification*10), CD117 (top right, magnification*10), CK7 (bottom left, magnification*10), CD117 (bottom right, magnification*40) in polymorphous low grade adenocarcinoma.

DISCUSSION

Evans and Batsakis in 1984 coined the term PLGA which describes its variable morphological appearances and apparent low-grade behavior [4]. Due to the aggressive clinical behaviour of some of these tumours, the term “low-grade” is omitted but can be used on a case-by case basis [5]. PLGA is a distinct entity due to its architectural diversity, cytological uniformity, and indolent clinical behavior [6 7]. Its clinical behavior is characterized by slow rate of growth, absence of symptoms, less aggressiveness, minimal metastatic potential and good prognosis [8]. The female-to-male ratio is about 2: 1. More than 70% of patients are aged 50-70 years. The most common site for PLGA is palate (60% of cases occur in this region) followed by buccal mucosa, upper lip, retromolar triangle and tongue with retromolar area accounting to only 0.5% of tumours [5-7, 9-11]. This case report describes PLGA in such a rare location.

PLGA is typically submucosal in location and unencapsulated.

Neoplastic cells are small to medium-sized and uniform in shape, with bland, minimally hyperchromatic, oval nuclei and only occasional nucleoli. Mitoses are uncommon and necrosis is seen in high-grade transformation. A salient and prominent feature is the wide variation of morphological configurations within and between tumours. The main microscopic architectural patterns are lobular, trabecular, microcystic or cribriform (as in adenoid cystic carcinoma), solid, and papillary-cystic. An eddy-like pattern can be observed at the peripheral boundaries of tumour. Foci of oncocytic, clear, squamous, or mucous cells can be observed.

Tumour stroma can be mucinous or hyalinized.

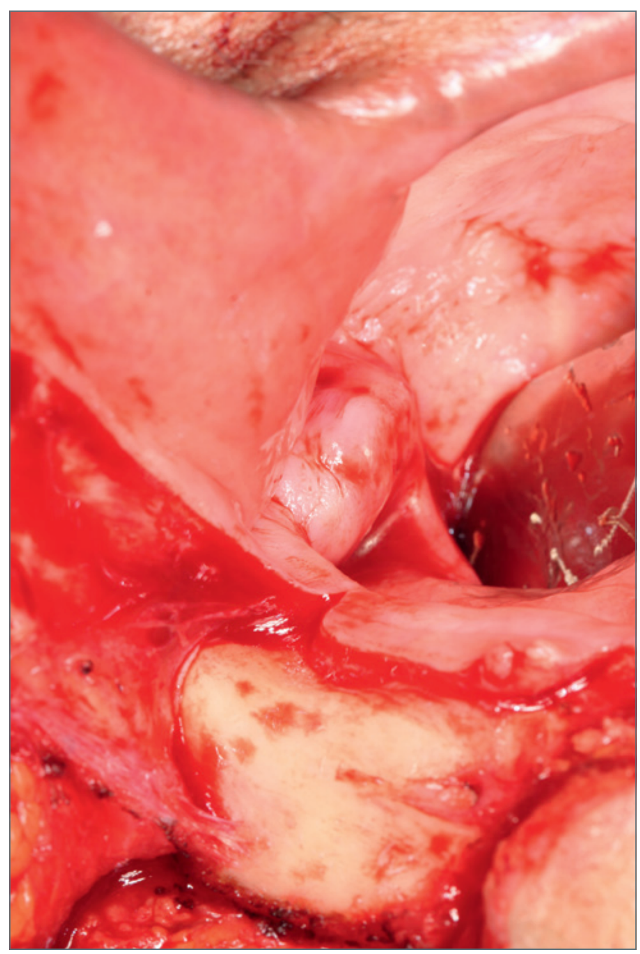

Figure 8. Intra-operative view.

Figure 9. Resected specimen.

Figure 10. Appearance after radiation therapy.

Figure 11. Follow-up picture at 2 years.

Perineural involvement is common Invasion into adjacent bone may be seen in tumours of the palate or mandible [5].

Its propensity for occurrence in the palate and indolent clinical features make confusion with pleomorphic adenoma (PA) or adenoid cystic carcinoma (ACC) even more likely. Seen in entirety, the diversity may establish the diagnosis, but in small incisional biopsies, where only a single pattern may be apparent, the lesion can easily be mistaken for a PA, ACC or a basal cell lesion [12]. Distinguishing ACC from PLGA of the salivary glands is important for their management. IHC is valuable in unclear PLGA cases. Uniformly positive vimentin and CK7 staining, except for the rare two layer ducts, is sufficient for a final PLGA diagnosis. S100 is also positive

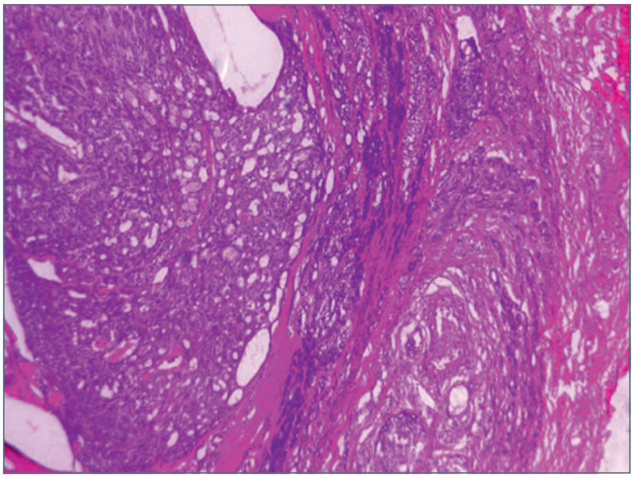

Figure 12. Photomicrograph showing tumour cells arranged in diverse architectural patterns.

in almost all of the cells, but this characteristic is only diagnostically supportive [13]. Wide surgical resection is the mainstay of PLGA treatment and the role of radiation is unclear. Adjuvant radiation therapy is usually given for close and positive margins were present [14]. Overall survival is generally good, reported local recurrence rates range from10-33% (average: 19%). The range of reported regional metastasis rates is 9-1 5%. Distant metastases have seldom been reported. Deaths have occurred after prolonged periods. High- grade transformation of PLGA has been reported and is associated with an unfavorable prognosis [15]. Thus, it is essential to maintain long-term follow up, as local recurrence or metastasis can occur several years later.

Conflict of interest

The authors declare no conflict of interest.

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Screening for atrial fibrillation with electrocardiography: the jury is still out

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Comment to article: Jonas DE, Kahwati LC, Yun JDY, et al. *Screening for atrial fibrillation with electrocardiography: evidence report and systematic review for the US preventive services task force*. JAMA 2018;320:485-98.

Key words: Atrial fibrillation, ECG, Elderly, Screening

Atrial fibrillation (AF) is not uncommon in the elderly. In the Framingham Heart Study, the lifetime risk of this arrhythmia from the age of 55 years onwards has recently been estimated to be as high as 37% [1]. This percentage is remarkably higher than the one calculated from the same cohort a decade ago [2], likely because of a reduction in mortality from competing diseases and intensified medical surveillance, both in general and specifically for AF, as a consequence of increased awareness of this condition.

The most fearsome presentation of AF is systemic embolism and especially ischemic stroke, which becomes particularly threatening at older ages due to higher mortality and probability of long-term sequelae, with functional impairment and ensuing dramatic health care and social costs [3]. The proportion of AF-related strokes among any ischemic stroke is around 10% [4 5] and there is a strong correlation between AF underlying a cerebrovascular event and age or the CHA2DS2-VASc score, which is used to quantify the risk of AF-associated stroke or transient ischemic attack and includes age.

Thus, the elder is prone to AF and its potentially devastating complications. This is a first reason why advocating the search of AF in asymptomatic individuals who are older than a certain threshold age. Second and fundamental, a therapy is available that consistently and noticeably diminishes the risk of cardioembolic cerebral events secondary to AF, and thus provides a strong rationale to screen apparently unaffected subjects for the arrhythmia. Oral anticoagulation (OAC) are highly effective in preventing AF-related stroke, and the new generation of direct OAC (DOAC) is also characterized by more stable pharmacokinetics and more favorable safety profile as compared with vitamin K antagonists [6]. Moreover, these benefits persist among the old and the very old [7]. To give a measure of the impact of OAC treatment on AF outcomes, in England from 2011 to 2016 a 1% increase in OAC use was associated with a 0.8% decrease in the weekly rate of AF-related stroke, while 4068 more strokes would have occurred in 2015/2016 if the use of OAC had remained at 2009 levels [8].

Based on these considerations, screening programs for silent AF have been intensively studied.

Any screening strategy must be low-risk and low-cost to be implemented community-wide. Single-time point or repeated electrocardiography (ECG) may meet these requirements and, thereby, has been proposed to screen for unrecognized AF. Technological advances have led to handheld devices with verifiable ECG traces, which combine accuracy and simplicity of use, rendering the prospect of AF screening even more appealing. For instance, participants in the recent REHEARSE-AF study [9] were provided with a monitor attached to a WiFi-enabled iPod to acquire 30-second single-lead ECGs twice weekly or when

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symptomatic over 12 months and transmit the recordings to a secure server. In the STROKESTOP study [10], ECG were obtained intermittently over two weeks by means of an integrated mobile transmitter, which was activated by placing their thumbs on the device and sent 30-second ECG strip data to a database.

Since the prevalence of AF increases with age, applying these tools to older subjects will make the percentage of cases in which the screening identify AF closer to the total number of positive tests (i.e., the positive predictive value will be higher). Keeping the example of the STROKESTOP study, which recruited 75-76-year-old persons, previously unknown AF was found in 3% of the participants, with 0.5% being diagnosed with AF on the first ECG. By using the same technology with persons in the same age range, but ≥ 2 points at the CHADS2 score, AF was discovered in 7.4% [11]. In REHEARSE-AF, a CHADS-VASc score of ≥ 4 was the strongest predictor of incident AF [9]. Against this background, there has been enthusiasm for AF screening, both in the scientific community and in the lay literature. However, many questions are still open. Is there any harm of systematic screening for AF with ECG? Does it affect health outcomes, such as all-cause mortality and stroke morbidity and mortality? Which are the benefits and harms of OAC for screen-detected AF? (antiplatelet therapy is not recommended for the prevention of AF-related stroke) [12].

These questions have been addressed by a recent systematic review, carried out to inform the US Preventive Service Task Force and specifically focused on studies that enrolled adults of 65 years of age or older without a history of stroke, transient ischemic attack, coronary heart disease or heart failure [13]. In spite of an extensive work of data extraction and analysis, however, the authors could provide almost no definite answer. In fact, the only firm conclusion they reached is that systematic or opportunistic screening of unselected or explicitly asymptomatic adults with ECG leads to the detection of more cases of AF, as compared with no screening. At sharp odds with the promising results of the studies of AF screening individually considered, the effects of ECG screening cannot be precisely gauged. Importantly, this is the case with the risk/benefit ratio of OAC prompted by detection of unknown AF, but also with other aspects that are often overlooked but are actually extremely relevant in evaluating the feasibility of a screening approach, such as anxiety generated by testing or cost-effectiveness.

Inevitably and laconically, the accompanying recommendation statement by the US Preventive Services Task Force concluded that "the current evidence is insufficient to assess the balance of benefits and harms of screening for atrial fibrillation with ECG" [14].

The jury is still out.

Conflict of interest

PA received fees as speaker and member of advisory boards and scientific committees from Boehringer Ingelheim, Bayer, Pfizer and Daiichi-Sankyo, and an investigator-initiated grant from Boehringer Ingelheim.

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CONTENTS

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Special Issue
Sarcopenia: from theoretical approach into clinical practice

Guest Editor
Francesco Landi

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Review

Emerging research on importance of muscle mass and function

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Sarcopenia, the age-related loss of muscle mass and strength with impaired function, is progressively documented as a major issue in geriatric medicine. It is remarkable that the study of this condition has recently extended beyond the borders of geriatrics, highlighting the importance of muscle physiology to the overall health status. Definitely, the assessment of sarcopenia is increasingly raised as an important tool for the risk stratification of patients suffering from different medical conditions, such as cardiovascular and pulmonary diseases, chronic kidney failure, among others. The wide range of negative health-related events to which sarcopenia contributes has activated rigorous research efforts in the attempt to untangle its multifaceted pathophysiology and develop effective specific treatments.

Key words: Sarcopenia, Physical performance, Negative outcomes

Sarcopenia, the age-related loss of muscle mass and strength with impaired function, is progressively documented as a major issue in geriatric medicine. It is remarkable that the study of this condition has recently extended beyond the borders of geriatrics, highlighting the importance of muscle physiology to the overall health status. Definitely, the assessment of sarcopenia is increasingly raised as an important tool for the risk stratification of patients suffering from different medical conditions, such as cardiovascular and pulmonary diseases, chronic kidney failure, among others. The wide range of negative health-related events to which sarcopenia contributes has activated rigorous research efforts in the attempt to untangle its multifaceted pathophysiology and develop effective specific treatments (Fig. 1).

INTRODUCTION

One of the most thoughtful consequences of aging is the onset of sarcopenia, which consists in a progressive decline in skeletal muscle mass and strength [1]. This deterioration accelerates after the age of 50 and in older subjects may hints to functional impairment (e.g., poor endurance, slow gait speed and decreased mobility). Such condition is highly predictive of incident disability, poor quality of life and all-cause mortality in older people [2]. The loss of muscle mass, pooled with the significance lack of strength as an central determinant of aging process, may encourage to the operationalization of a muscle quality definition based on the strength production capacity per unit of muscle mass [3]. Accordingly, an understanding of the influence of aging per se on the skeletal muscle needs particular consideration to modifications in muscle volume but at the same time in muscle quality. This is principally important when pondering the potential effects of treatments, in terms of enhancements not only in muscle mass but also in function and physical performance [4].

SARCOPENIA DEFINITION

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published the first sarcopenia definition with the specific aims to promote

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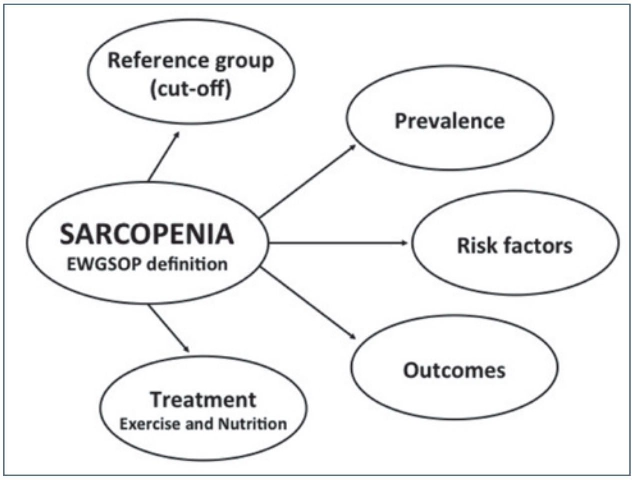

Figure 1. Sarcopenia overview: from definition to treatment.

improvements in identifying and treating for subjects with sarcopenia [5]. In 2018, the same Working Group met again (EWGSOP2) to update the original definition in order to reflect scientific and clinical evidences that have emerged over the last ten years [6].

In this revised and updated consensus paper on sarcopenia, EWGSOP2 "*focuses on low muscle strength as a key characteristic of sarcopenia, uses detection of low muscle quantity and quality to confirm the sarcopenia diagnosis, and identifies poor physical performance as indicative of severe sarcopenia*" [6]. Accordingly, the European group delineated the new clinical algorithm to be used for sarcopenia case-finding, diagnosis and confirmation, and severity determination. Finally, the EWGSOP2 provided the updated cut-off points for measurements of variables that identify and characterize sarcopenia [6].

In this respect, it is important to highlight that methods to assess muscle quantity are available in many but not all clinical settings. As equipment and methods to estimate muscle quality are developed and refined in the future, this factor is estimated to rise in meaning as a defining feature of sarcopenia. Physical performance was previously contemplated as part of the definition of sarcopenia, but sometime this domain has been used as an outcome measure. In the new definition physical performance is considered to categorize the severity of sarcopenia. To use this definition in clinical practice, the EWGSOP2 consensus paper reviewed tests and tools for assessing muscle mass, strength and physical performance, addressing the updated version of a practical algorithm for sarcopenia case-finding, diagnosis and severity determination [6].

REFERENCE GROUP AND CUT-OFF POINTS

The of age-related deterioration, and the age at which declines in muscle mass, muscle strength, and physical performance can first be recognized, have not been widely studied. Recently, we investigated the modification of muscle mass, strength, and physical performance across age in a large and unselected sample of community-dwelling individuals [7]. These findings clearly display that different patterns of muscle mass and physical decline with age are reported for different ages. In particular, muscle mass (measured by calf circumference) slightly decreases with advancing age. Interestingly, for muscle strength (measured by hand grip test) and physical performance (measured by chair stand test) there is stability in the first decades of adulthood, and decrement in the middle years (45 +) and late adulthood. Subjects older than 75 years lose around 60% of their muscle strength and 30% of their physical function. In this study a linear pattern of age-decline has been observed and this pattern is similar in men and women across the entire course of life [7].

In a similar study, we investigated the modifications of muscle mass and strength across ages in a large and unselected sample of Italian and Taiwanese community-dwelling people [8]. As expected, muscle mass and strength decline with advancing age in both ethnic groups. In particular, compared with younger individuals, those aged 80 + show about 10% lower skeletal muscle mass and 20% lower muscle strength. The pattern of age-related decline in both muscle measures is interestingly analogous in men and women across the age groups studied. The overall shape of the curves is similar between the two samples. Nevertheless, muscle mass and muscle strength are significantly greater in Italian participants relative to Taiwanese individuals in all age groups [8].

In light of what has been observed in these population studies, internationally recognized cut-offs have to be found to identify individuals with sarcopenia. These reference values must be specific for age, gender and race.

PREVALENCE OF SARCOPENIA IN DIFFERENT SETTINGS

The prevalence of sarcopenia varies in different studies based on the population studied and the diagnostic criteria adopted. In general, the prevalence and incidence of sarcopenia are very high in older subjects, particularly in institutionalized or hospitalized ones. As expected, sarcopenia is highly prevalent among the population over the age of 65 years and more. However, the prevalence of sarcopenia varies across diverse populations and according to age, gender, and living setting [9]. Based on results from previous studies, the prevalence of sarcopenia ranges between 5% and13% among 60- to 70-year-old subjects and between 11% and 50% in those aged 80 years or older [10], depending on the used definition for such condition.

Using the algorithm proposed by the EWGSOP, of 730 participants enrolled into the InCHIANTI study [11], 122 (16.7%) subjects living in community were identified as affected by pre-sarcopenia and 55 (7.5%) by sarcopenia. Among them, 39 (5.3%) were sarcopenic because of low gait speed (n = 19, 2.6%) or poor grip strength (n = 20, 2.3%), whereas 16 (2.2%) had the concomitant presence of reduced muscle strength and slow gait speed. Prevalence of sarcopenia improved with age, from 2.6 and 1.2% respectively in women and men aged 70-74 years, to 31.6 and 17.4% in women and men older than 80 years [11].

The prevalence of sarcopenia and the association of such condition with functional and clinical status in older people aged 70 years and older living in nursing homes have been estimated [12]. These findings show that sarcopenia-assessed using the EWGSOP algorithm - is highly prevalent in institutionalized older persons (68% among male residents and 21% among female residents) [12].

Among the 770 study participants enrolled in the CRIME study [13] (mean age: 80.8 ± 7 years; 56% women), 214 (28%) met the EWGSOP criteria for the diagnosis of sarcopenia and 556 (72%) did not at the time of admission in the acute care hospital.

In the sample of 655 older hospitalized patients enrolled in the GLISTEN study [14] (mean age 81.0 ± 6.8 years, 51.9% women), mean skeletal muscle index (SMI), evaluated at admission, was 8.16 ± 2.10 kg/m^2. The SMI was greater in men ($p < .0001$), was inversed correlated with age ($p < 0.0001$), and related with handgrip strength ($p < 0.0001$) and walking speed ($p = 0.005$). Adopting the EWGSOP algorithm, 227 (34.7%) patients were diagnosed as affected by sarcopenia; of them, 101 (44.5%) were sarcopenic because of low gait speed (n = 43, 18.9%) or poor grip strength (n = 58, 25.6%), whereas 126 (55.5%) had the concomitant presence of reduced muscle strength and slow gait speed. Of the 169 subjects with walking speed lower than 0.8 m/s at hospital admission, 90 (53.3%) had walking disability and 116 (68.6%) had basic ADL disability in the 2 weeks preceding hospitalization. Finally, prevalence of sarcopenia at the time of hospital admission increased sharply with age, from 11.1% and 30.2% in women and men aged 65-74 years, to 46.7% and 50.7% in women and men older than 85 years, respectively [14].

Among patients without sarcopenia at hospital admission (n = 394), 58 participants (14.7%) met the EWGSOP sarcopenia diagnostic criteria at hospital discharge [15]. More than 50% of those who developed sarcopenia during hospital stay showed over 10% muscle mass loss compared with baseline values. Patients who developed sarcopenia were significantly older than those who did not (82.0 ± 7.2 *vs* 79.2 ± 6.2 years, respectively; $p < 0.01$). Subjects with incident sarcopenia during hospital stay presented significantly lower baseline body mass index compared with participants who did not develop sarcopenia (25.0 ± 3.8 kg/m^2 *vs* 27.6 ± 4.9 kg/m^2, respectively; $p < 0.001$). Likewise, SMI at hospital admission was significantly lower among subjects who developed sarcopenia during hospital stay (8.4 ± 1.5 kg/m^2 *vs* 9.0 ± 1.8 kg/m^2, respectively; $p = 0.01$) [15].

SARCOPENIA RISK FACTORS

The number of risk factors of sarcopenia is high and appears to be rising with recent researches [16]. It is well documented that age and sex vary the prevalence of sarcopenia. The ageing process itself changes muscle turnover, with amplified catabolic stimuli and reduced anabolic stimuli [17]. Subclinical inflammation can play an important role in these modifications [18]. Numerous hormonal deregulations, such as testosterone and the growth hormone, insulin-like growth factor-1 pathways, have been observed during ageing process, as well as changes in neural input. Overall, these modifications have been correlated with the skeletal muscle mass decline and muscle quality changes. Moreover, mitochondrial dysfunction has also been related with muscle mass and ageing [18]. Life style habits, including a decrease of food intake and specifically protein intakes, together with sedentary pattern and/or reduced physical exercise during life course, have all been associated with a higher risk of sarcopenia [18]. Variations in specific living conditions, such as protracted bed rest, immobility and deconditioning, have documented to increase the incident sarcopenia. Finally, a long list of chronic health conditions (comprising cognitive impairment, mood disorders, diabetes and end-stage organ diseases) has also been related with a loss of muscle mass and strength [18].

Even though sarcopenia is related to many potential risk factors, less food intake and/or loss of appetite (defined as anorexia of aging) are the most common risk factor in older subjects. Recently, the association of anorexia with sarcopenia has been extensively studied [19]. These findings show that, in older persons, sarcopenia is correlated with the presence of anorexia, independently of clinical evidence of malnutrition (i.e., weight loss and BMI lower than 20 kg/m^2) [20]. Overall, the results showed that the anorexia is common among community-dwelling older subjects and suggest that among old-old subjects, the presence of anorexia is associated with sarcopenia, as assessed by means of European Consensus [20]. Scientific evidence indicates that a significant number of elderly fail to get proper amount and specific types of food necessary to meet essential energy and nutrient needs. Finally, the identification of particular biomarkers that may help in the development of noninvasive tools for the evaluation and monitoring of the relationship between inflammation and muscle wasting situations has been required for a long time [21]. Recent research efforts on definite "danger molecules" that stimulate inflammation and connect this process with muscular mitochondrial dysfunction could improve the comprehension of muscle pathophysiology. Results from numerous studies show the significant contribution of microbial variations and activity in the gut to the repertoire of inflammatory molecules involved in the milieu describing muscle aging. This is an important matter to be addressed by future studies to untangle the signaling pathways that may act as targets for specific interventions [21].

SARCOPENIA AND NEGATIVE OUTCOMES

Sarcopenia, like all geriatric syndromes, is related to numerous negative outcomes, including increased risk of falling, disability, and mortality [22].

The effect of sarcopenia on the risk of falling during a period of 2 years has been studied in a population of older persons aged 80 years and older living in community [22]. According to these findings, sarcopenia – evaluated using the EWGSOP algorithm – is greatly prevalent among older persons. Also, the rate of such condition does not change across gender. Individuals with sarcopenia are at increased risk of falling regardless of age, gender and other confounding factors [22]. At the population level, sarcopenia seems to be a risk factor for falls. The assessment of muscle mass, muscle strength and physical performance may provide an important benefit for the risk stratification process for primary prevention of falls. A better understanding of the mechanisms underlying the association between sarcopenia and falls may also help the elaboration of valuable interventions across the life course to preserve muscle function and prevent falls [23].

In the same sample (il SIRENTE study), the association between muscle mass (as measured by calf circumference) and frailty, physical performance, and functional status has been evaluated [24]. The results show that in older persons, frailty increases and physical function declines as calf circumference decreases. Specifically, after adjustment for potential confounders, frailty index and physical performance measures (Short Physical Performance Battery score) were directly associated with calf circumference.

The effect of sarcopenia on functional recovery in a population of older persons admitted to an in-hospital rehabilitation unit following hip fracture repair has been recently evaluated [25]. According to these findings, sarcopenia – assessed using the FNIH criteria – is highly prevalent. Sarcopenia was significantly associated with worse overall functional status, as evaluated using the Barthel index total score, both at the time of discharge from the rehabilitation unit and after the 3-month follow-up [25].

The evaluation of the impact of sarcopenia on survival among frail older subjects is an important and intricate issue. In the il SIRENTE study the association between sarcopenia and 7-year mortality has been assessed [26]. Sarcopenia, as identified by the EWGSOP criteria (muscle mass, muscle strength and physical performance), is associated with mortality in older adults living in the community, independently of age and other clinical and functional variables [26].

In the CRIME study, patients with sarcopenia presented a higher mortality rate when compared with those without sarcopenia during hospital stay ($p = 0.007$). During hospital stay, 10 (6%) deaths occurred among patients with sarcopenia and 12 (2%) among those without sarcopenia. The diagnosis of sarcopenia resulted independently associated to mortality during hospital stay either in the unadjusted model (hazard ratio [HR]: 3.19; 95% CI: 1.38-7.38), age- and gender-adjusted model (HR: 3.00; 95% CI: 1.23-7.28), and fully adjusted model (HR: 3.45; 95% CI: 1.35-8.86). Furthermore, patients with sarcopenia presented a higher mortality rate when compared with those without sarcopenia after 12 months from discharge ($p < 0.001$). The diagnosis of sarcopenia resulted independently associated to 1-year mortality in the unadjusted model (HR: 2.12; 95% CI: 1.45-3.10), age- and gender-adjusted model (HR: 1.56; 95% CI: 1.10-2.30), and fully adjusted model (HR: 1.59; 95% CI: 1.10-2.41).

In a study conducted in nursing home, participants with sarcopenia showed the highest risk of death, regardless of age, gender, and other confounding factors [27]. A total of 26 deaths (11 men and 15 women) occurred during the 6-month follow-up. Fifteen (37.5%) participants died among subjects with sarcopenia compared with 11 subjects (13.4%) without sarcopenia ($p < 0.001$). In the unadjusted model, there was a direct association between mortality and sarcopenia. Similarly, this association was consistent both in male (HR 8.28, 95% CI: 0.87-78.25) and female (HR 2.23, 95% CI: 0.75-7.62) subjects. After adjusting for potential confounders, including age, gender, cerebrovascular diseases, osteoarthritis, COPD, ADL impairment, and BMI, such association remained statistically significant although somewhat less strong than that derived from the crude analysis. In the fully adjusted model, participants with sarcopenia had a higher risk of death for all causes compared with non-sarcopenic subjects (HR 2.34, 95% CI: 1.04-5.24) [27].

POTENTIAL TREATMENT FOR SARCOPENIA

Nutrition and physical exercise are the cornerstones of intervention in sarcopenia [27]. Resistance exercise training improves muscle strength and mass and increases protein deposit in skeletal muscles [28]. Aerobic exercise training may also benefit ageing skeletal muscle and improve insulin sensitivity. Improvement of nutritional deficits is also needed. Caloric intake should be increased to cover increased demands posed by exercise. Protein requirements are also increased, with recommended intakes of proteins in sarcopenic patients of > 1.2 g of protein per kilogram of body weight per day, except in patients with significant renal failure [29]. Leucine, β-hydroxy β-methylbutyrate (*HMB*), creatine and some milk-based proteins may have beneficial effects on protein balance in skeletal muscle [30]. Correction of vitamin D deficiencies is needed for proper muscle function, but the role of vitamin D in the presence of normal blood levels is yet to be determined [31]. No drug is currently approved for the treatment of sarcopenia. Studies with anabolic hormones have been disappointing. The next generation of drugs is directed at exploring inhibition of myostatin and manipulation of the neuromuscular junction [32].

Conflict of interest

The authors declare no conflict of interest.

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Original Investigation

Prevalence and clinical correlates of sarcopenia in institutionalized older people: cross-sectional study of a nursing home population

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Background & aims. Sarcopenia is a common condition among institutionalized older people which leads to increased risk of adverse outcomes such as disability and death. We investigated the prevalence and clinical correlates of sarcopenia in older institutionalized adults in Italy, while also evaluating the interchangeability and adequacy of two definitions of sarcopenia (EWGSOP and FNIH) for this geriatric setting.

Methods. Cross-sectional analysis of 97 participants enrolled in a nursing home facility in Italy. Since 97% of the study subjects resulted either unable to walk or "slow walkers", we assessed sarcopenia presence ignoring the walking speed criterion: sarcopenia was assessed as low appendicular skeletal mass index plus low grip strength (EWGSOP criteria) and as weakness plus low lean mass (FNIH criteria). Skeletal muscle mass was estimated using bioimpendance analysis.

Results. In this population of 97 institutionalized older people (age 83.2 ± 9.4 years, women 73.2%), according to both EWGSOP and FNIH criteria 13 participants (13.4%) were identified as affected by sarcopenia; however, only 5 subjects were identified as sarcopenic according to both definitions simultaneously. The prevalence of sarcopenia was directly correlated with male sex and comorbidity level, while being inversely correlated with Body Mass Index.

Conclusions. According to EWGSOP and FNIH criteria, prevalence of sarcopenia is significant among institutionalized older people, and it's strongly related to male sex, BMI and comorbidity level. EWGSOP and FNIH criteria identified as sarcopenic different individuals and therefore cannot be used interchangeably. Assessment of walking speed might be unfeasible in institutionalized older subjects.

Key words: Sarcopenia, Prevalence, Institutionalized older people, Nursing Home

INTRODUCTION

The aging process is associated with the loss of muscle mass, resulting in a loss of muscle strength and function that has been referred to as sarcopenia [1 2]. Sarcopenia as a geriatric syndrome leads to the limitation of physical performance and increases the risk of adverse outcomes including mobility limitation, disability, hospitalization, low quality of life, and death [3 4].

In 2014 the International Sarcopenia Initiative published a systematic review [5] reporting the prevalence of sarcopenia estimated by several studies performed in various geriatric settings: if assessed according to European Working Group on Sarcopenia in Older People (EWGSOP) criteria [4], the prevalence of sarcopenia in community-dwelling populations ranges from 1 to 29%; the prevalence of sarcopenia is even more substantial in institutionalized populations: from 14 to 68% among male subjects and from 14 to 33% among female subjects.

Recently, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project has proposed new

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diagnostic criteria for the assessment of sarcopenia based on the analysis of 9 population studies conducted on a 26625 community-dwelling older adults [6], assessing the role of weakness (defined as low muscle strength) and low muscle mass as key components of the sarcopenia phenotype.
Despite sarcopenia has been found to be an extremely common condition among institutionalized older people [7 8], currently the amount of data regarding this geriatric setting is relatively scarce, due to the difficulties often encountered while analyzing this population [7]: first, institutionalized subjects are often affected by several medical conditions and cognitive impairment, which may hinder the reliability of some diagnostic tests; second, Dual-Energy X-ray Absorptiometry (DXA), which is the reference technique for the assessment of muscular mass, and bioimpendance analysis (BIA), an easily accessible and portable DXA alternative [9], are not usually available in nursing homes.
The estimated prevalence of sarcopenia among different studies performed on institutionalized populations is extremely heterogeneous due to the lack of a common consensus regarding the diagnostic criteria and the methods used to assess sarcopenia criteria (muscle mass, muscle strength and physical performance). The majority of the studies performed on institutionalized populations assessed sarcopenia according to EWGSOP criteria, whereas studies on prevalence of sarcopenia according to the FNIH diagnostic criteria are still lacking in this population.
This study was designed to investigate the prevalence and clinical correlates of sarcopenia in older institutionalized adults in Italy, and to compare the data obtained using two different definitions of sarcopenia, the EWGSOP and FNIH criteria. We investigated the interchangeability and the discrepancies between the two definitions; we also evaluated the adequacy of the current diagnostics criteria when applied to a population with high prevalence of physical limitation and cognitive impairment.

METHODS

Study population

This cross-sectional study was performed on the residents of "Centro Servizi Anziani di Monselice", a structure that is both a Retirement and Nursing Home, located in Monselice, Veneto, Italy.
As of April 2017, the structure hosted a total of 158 older people.
Participants' data were collected through the consultation of the medical records provided by the structure and a standardized dedicated questionnaire including demographic characteristics, functional status, cognitive status, mood assessment, medication use and incident and prevalent medical conditions.
Exclusion criteria were: inability to undergo BIA (leg edema, pacemaker, joint prosthesis, bedridden, refused); inability to perform the grip strength test (joint prosthesis, severe pain to the upper limbs, refused); severe cognitive impairment which precluded the complete cooperation during the questionnaire filling or the tests execution; inability or refusal to grant approval for the inclusion in this study; new entries with inadequate anamnestic and clinical documentation.
Prevalence of sarcopenia and of its clinical correlates was therefore assessed in 97 subjects, 26 males and 71 females.

Assessment of sarcopenia

According to EWGSOP [4] criteria, sarcopenia was defined as presence of low muscle mass plus low muscle strength and/or low walking speed. As requested by FNIH criteria [6,] sarcopenia was defined as "weakness and low lean mass" or "slowness with weakness and low lean mass".
Muscle mass was measured by BIA using a Quantum/S Bioelectrical Body Composition Analyzer (Akern Srl, Florence, Italy). Whole-body BIA measurements were taken between the right wrist and ankle with the subject in a supine position, when possible. Appendicular Lean Mass (ALM) was calculated using the following equation of Scafoglieri and colleagues [10]: $ALM_{HOLOGIC}(kg) = 4,957 + (0,196 X height^2/resistance) + (0.060 X weight) - (2.554 X sex)$, where height is measured in centimeters; resistance is measured in ohms; weight is measured in kilograms; for gender, men = 0 and women = 1. Appendicular lean mass (kg) was converted to appendicular skeletal muscle index (ASMI) standardizing by meters squared (ALM/height^2) and Body Mass Index (ALM/BMI) as requested by EWGSOP and FNIH criteria respectively. As claimed by EWGSOP criteria [4], low appendicular muscle mass was classified as ASMI less than 7.23 kg/m^2 in men and 5.67 kg/m^2 in women; according to FNIH [6], low appendicular muscle mass was classified as a ALM/BMI ratio lower than 0.789 and 0.512 in men and women, respectively.
Muscle strength was assessed by grip strength (GS), measured using a hand-held dynamometer (JAMAR hand dynamometer, Sammons Preston Inc, Bolingbrook, Illinois, USA). Two trials with the dominant hand were performed, when possible, and the highest value was used in the analysis [11]. According to EWGSOP [4 12], Body mass index (BMI) - adjusted values were used as a cutoff point to identify low muscle strength (men: BMI ≤ 24 kg/m^2 GS ≤ 29 kg, BMI 24.1-28 kg/m^2 GS ≤ 30 kg, BMI ≥ 28 kg/m^2 GS ≤ 32 kg;

women: BMI ≤ 23 kg/m^2 GS ≤ 17 kg, BMI 23.1-26 kg/m^2 GS ≤ 17.3 kg, BMI 26.1-29 kg/m^2 GS ≤ 18 kg, BMI ≥ 29 kg/m^2 GS ≤ 21 kg) while, in line with FNIH criteria [6], crude values were used (men: GS < 26 kg; women: GS < 16 kg).

Usual walking speed (m/s) on a 4-m course was used as an objective measure of physical performance; speed lower than 0.8 m/s identified participants with low physical performance ("slow walkers") [4 6]. Thirty-seven subjects did not perform the walking test; since all of them were unable to walk or had an extremely high risk of fall, we included them among those who performed the test and were classified as "slow walkers". Since more than 97% of the subjects (94 out of 97) resulted "slow walkers", we decided to ignore the walking speed criterion included in both sarcopenia definitions; this decision was supported by the result of a previous study [12] suggesting that low walking speed might not be an essential criterion for the diagnosis of sarcopenia.

Covariates

Sociodemographic characteristics. Sociodemographic variables (Age, gender, smoking habit, alcohol consumption, education) were assessed through survey questions.

Functional and mobility status. Functional status in basic activities of daily living (ADLs) and mobility were assessed trough a modified Barthel Index (BI) [13], which has been adapted to be paired with S.Va.M.A score for the evaluation of the elderly in institutionalized settings. Functional status in basic ADL was measured according to the participants' difficulty in performing each of six activities: getting in and out of a bed, bathing, dressing, eating, continence, and using the toilet. The score for functional status ranges between 0 (independent) and 60 (dependent); a score ≥ 15 identified functional disability, whereas a score ≥ 50 identified severe functional disability. Mobility status was measured according to the participants' difficulty in performing each of five tasks: walking, wheelchair use, moving from bed-chair to wheelchair, going up and down stairs. The score for functional status ranges between 0 (independent) and 40 (dependent); a score ≥ 15 identified mobility impairment, whereas a score ≥ 30 identified severe mobility impairment.

Cognitive and mood status. Cognitive functioning was explored using the Mini Mental State Examination (MMSE), with scores less than 24 suggesting cognitive impairment. Mood status was assessed with the 15 item version of the Geriatric Depression Scale (GDS), with scores more than 5 out of 15 suggesting the presence of depressive symptoms [14].

Specific medical conditions and comorbidity. The baseline prevalence of specific medical conditions was established using standardized criteria that utilized information gathered from the structure's clinical records. Comorbidity levels were assessed using the Cumulative Illness Rating Scale (CIRS) calculating for each participants CIRS severity index and CIRS comorbidity index [15].

Statistical analysis

For descriptive purpose, baseline characteristics of the study population were compared according to presence or absence of sarcopenia, using a t-student test for continuous variables with normal distribution, the nonparametric Wilcoxon Mann-Witney test for not normally distributed continuous variables and the Fisher-exact test for categorical variables. To identify factors independently associated with the two sarcopenia phenotype we utilized univariate logistic regression analysis; factors resulted independently related to sarcopenia was then included in multivariate logistic regression models for each sarcopenia definition.

All analyses were performed using Stata 13.0 for Windows (StataCorp, College Station, TX).

RESULTS

General characteristic of 97 participants (mean age 83.2 ± 9.4, 73.2% women) according to the presence of sarcopenia are presented in Table I.

13 (13.4%) participants were identified as sarcopenic using each sarcopenia criteria separately; between them, only 5 subjects were simultaneously identified as sarcopenic according to both definitions (Fig. 1).

Sarcopenic participants were more likely to be male (Fig. 2): 26.9% and 30.8% of the male participants were identified as sarcopenic according to EWGSOP and FNIH criteria respectively, while only 8.5% (EWGSOP) and 7% (FNIH) of the female subjects were identified as sarcopenic. Prevalence of sarcopenia increased in subjects included in the 80-89 years range (18.8% EWGSOP, 21.9% FNIH) compared to younger subjects (13.5% EWGSOP, 8.1% FNIH); lower sarcopenia prevalence was conversely found in subjects 90 years old or older (7.1% EWGSOP, 10.7% FNIH) (data not shown).

No significant difference was found between sarcopenic and not sarcopenic participants, defined by EWGSOP criteria, in both severe functional disability and severe mobility impairment prevalence; conversely we found a substantial although not statistically significant difference in severe functional disability when sarcopenia was defined according to FNIH criteria (46.2% and 23.8% in sarcopenic and not sarcopenic participant respectively).

Figure 3 shows BMI distribution in sarcopenic subjects: the vast majority of sarcopenic subjects, independently by the sarcopenia definition used, were included in the

Table I. Selected general characteristics of study participants according to definition and presence of sarcopenia.

	EWGSOP			FNIH		
	No Sarcopenia	Sarcopenia	P	No sarcopenia	Sarcopenia	P
N	84 (86.6%)	13 (13.4%)	0.612	84 (86.6%)	13 (13.4%)	0.782
Male (%)	22.6	53.8	0.018	21.4	61.5	0.002
Age (years)	83.3 ± 9.9	82 ± 6.1	0.508	83.0 ± 9.7	84.5 ± 7.5	0.597
Education (≥ 5 years, %)	67.9	76.9	0.510	71.4	53.9	0.202
Smokers (%) Never Former/current	 69.1 30.9	 53.9 46.1	0.278	 69.1 30.9	 53.9 46.1	0.278
BMI (kg/m^2)	27.9 ± 4.5	23.1 ± 3.2	0.001	27.2 ± 4.9	27.7 ± 2.2	0.502
Weight loss (≥ 10% in the last 6 months)	16.7	23.1	0.572	16.7	23.1	0.572
ASMI (kg/m^2)	6.7 ± 0.9	6.0 ± 0.7	0.009	6.5 ± 0.9	6.8 ± 0.77	0.424
ALM/BMI	0.6 ± 0.1	0.7 ± 0.1	0.020	0.6 ± 0.1	0.6 ± 0.1	0.723
Grip strength (kg)	22.1 ± 7.8	17.8 ± 4.6	0.009	22.1 ± 7.8	17.7 ± 4.8	0.009
4-m walking speed (n = 60, m/s)	0.5 ± 0.2	0.4 ± 0.1	0.214	0.5 ± 0.2	0.5 ± 0.1	0.623
Severe functional disability (%)	26.2	30.8	0.742	23.8	46.2	0.103
Severe mobility impairment (%)	36.9	30.8	0.765	35.7	38.5	1.000
CIRS severity (median, IQR)	1.3 [1-1.5]	1.4 [1-1.6]	0.391	1.3 [1-1.5]	1.5 [1-1.6]	0.402
CIRS comorbidity (median, IQR)	2 [1-3.5]	4 [1-4]	0.167	2 [1-3.5]	4 [2-4]	0.044
Cognitive impairment (n = 95, %)	60.2	58.3	0.900	57.3	76.9	0.180
Number of medications	6.5 ± 3.0	5.9 ± 2.2	0.232	6.5 ± 3.0	5.8 ± 2.2	0.412

BMI = body mass index; ASMI = appendicular skeletal muscle index; ALM = appendicular lean mass; CIRS = cumulative illness rating scale; IQR = interquartile range. Data are means ± *SD* unless otherwise indicated.

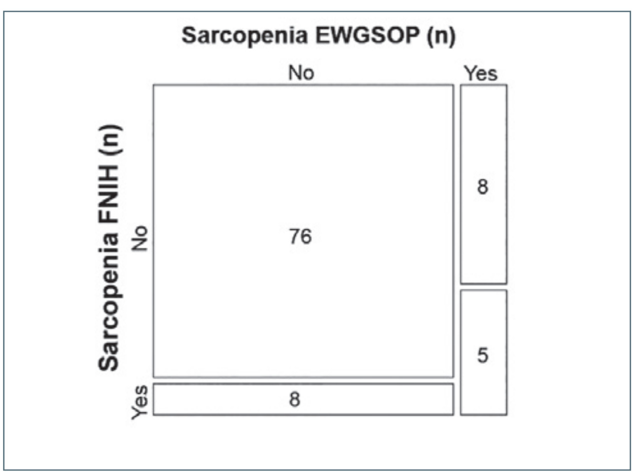

Figure 1. Prevalence of sarcopenia according to sarcopenia definition. Individually, both EWGSOP and FNIH criteria identified 13 participants as sarcopenic; only 5 subjects were identified as sarcopenic according to both definitions simultaneously.

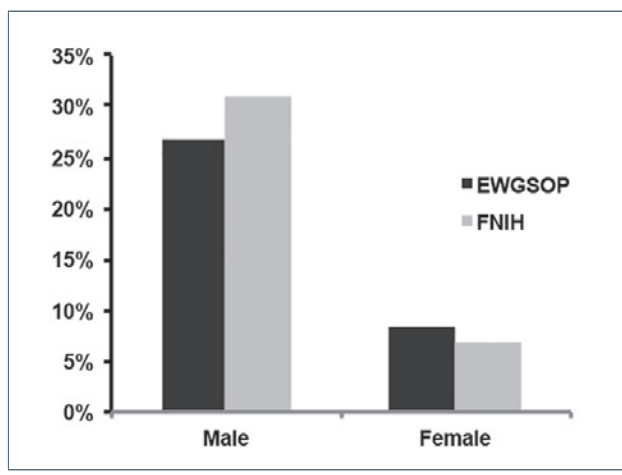

Figure 2. Prevalence of sarcopenia according to sex and definition of sarcopenia. Both EWGSOP and FNIH criteria found the prevalence of sarcopenia to be substantially higher in male subjects compared to female subjects.

21-29kg/m^2 BMI range (84.6% EWGSOP, 92.3% FNIH). Taking into account EWGSOP criteria, 15.4% of the sarcopenic subjects had BMI lower than 21kg/m^2, while none of them could be defined as obese (BMI > 30 kg/m^2); conversely, according to FNIH criteria, none of the sarcopenic subjects had BMI lower than 21kg/m^2, while 7.7% of them had BMI > 30kg/m^2.

No difference was found in prevalence of cognitive impairment between sarcopenic and not sarcopenic subject identified by EWGSOP definition. Conversely,

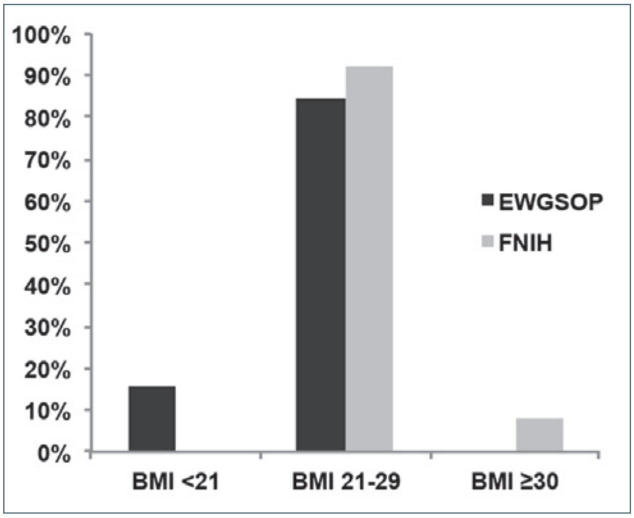

Figure 3. Body Mass Index (BMI) ranges distribution in sarcopenic subjects. Most of the sarcopenic subjects fall into the 21-29 BMI range. None of the subjects identified as sarcopenic by EWGSOP criteria is obese, while none of the subjects identified as sarcopenic by FNIH criteria is malnourished.

according to FNIH criteria cognitive impairment tend to be more common in sarcopenic subject (76.9% and 57.3% for sarcopenic and not sarcopenic participants respectively).

The average number of medications assumed was found to be marginally lower in the sarcopenic subjects compared to not sarcopenic subjects using both definition.

In univariate logistic regression analysis male sex was significantly associated with sarcopenia prevalence using both sarcopenia definition (OR:12.14; 95% CI: 2.31-63.67 for EWGSOP and OR:5.52; 95% CI: 1.54-19.88 for FNIH criteria). Considering EWGSOP criteria, we found a decreased probability of being sarcopenic with increasing BMI (OR: 0.64; 95% CI: 0.50-0.82). According to FNIH definition, subjects with higher CIRS comorbidity score were more likely to be sarcopenic (OR: 1.48; 95% CI: 1.02-2.16). Using the same criteria, an increased probability of being sarcopenic was also found for participants with severe functional disability although this relationship was of borderline statistical significance (OR 2.74; 95% CI: 0.83-9.11) (Tab. II).

Multivariable analysis confirmed an independent and significant association between male sex and sarcopenia defined according to both criteria (OR 95% 12.1; 95%CI 2.3-63.7 for EWGSOP and OR 5.52; 95% CI 1.54-19.9 for FNIH). Inverse association between BMI and probability of being sarcopenic (EWGSOP definition) was also confirmed (OR 0.64; 95% CI 0.50-0.82) as well as an increased risk of being sarcopenic (FNIH definition) with higher CIRS comorbidity score (OR 1.48; 95% CI 1.02-2.16).

DISCUSSION

Our study suggest that, among a population of institutionalized older people, sarcopenia, defined by either EWGSOP or FNIH criteria, is a common condition. Male sex was significantly associated with sarcopenia using both definition; higher BMI was inversely associated with sarcopenia prevalence defined by EWGSOP criteria whereas level of comorbidity was directly associated with sarcopenia defined according to FNIH criteria.

The estimated prevalence of sarcopenia from this study is in line, although somehow lower, with the values reported in the 2014 International Sarcopenia Initiative review [5], according to which the prevalence of sarcopenia in institutionalized older people ranges between 14 and 33%; however, other studies [7 8] reported a significantly higher prevalence of sarcopenia in nursing home settings (as high as 40%). Difference between our data and previous report may be justified by the changes we applied to the diagnostic criteria of sarcopenia. First, we decided to assess muscle mass utilizing the Appendicular Skeletal Muscle Mass Index, as opposed to the Skeletal Muscle Mass Index, since Appendicular Lean Mass has been found to be the more specific in evaluating the skeletal muscle mass of the elderly [6 16]. Second, we ignored the walking speed criterion since 37% of the participants were not able to perform the 4-m walking test because of the inability to walk or co-existing medical conditions that contraindicated the test administration, and 97% of the study subjects resulted "slow walkers", hindering the effectiveness of walking speed as a diagnostic criterion. Our decision was corroborated by the results of a previous study [12] which reported that the assessment of only muscle weakness in addition to low muscle mass provided similar predictive value compared to the original algorithm of the EWGSOP sarcopenia definition in terms of incident disability, risk of hospitalization and mortality, suggesting that low walking speed might not be an essential criterion for the diagnosis of sarcopenia.

In agreement with previous reports in similar settings [7 8], our findings suggest that sarcopenia is significantly more common among men compared to women.

According to EWGSOP criteria, increasing BMI was inversely related to sarcopenia presence and, in our sample, 15% of sarcopenic subjects were malnourished. On the other hand, FNIH criteria led us to opposite findings, since no sarcopenic subject was malnourished, but 7.7% of them were obese. This significant gap can be justified by the different method used to assess low muscle mass by the two definitions of sarcopenia: EWGSOP suggests to standardize ALM by meters squared while FNIH suggests to standardize ALM by Body Mass Index. As reported by Dam et al. [6] sarcopenic subjects identified by

Table II. Univariate and multivariate logistic regression analyses for the likelihood of being sarcopenic according to sarcopenia definition.

	EWGSOP				FNIH			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex (male)	3.99 (1.20-23.31)	0.024	12.1 (2.3-63-7)	0.003	5.9 (1.71-20.13)	0.005	5.52 (1.54-19.9)	0.009
Age (years)	0.99 (0.93-1.05)	0.631			1.02 (0.95-1.09)	0.593		
Education (≥ 5 years)	1.58 (0.40-6.21)	0.513			0.47 (0.14-1.53)	0.209		
Smokers	1.91 (0.58-6.25)	0.283			1.91 (0.58-6.25)	0.283		
BMI (kg/m^2)	0.72 (0.60-0.88)	0.001	0.64 (0.50-0.82)	< 0.001	1.03 (0.91-1.16)	0.689		
Weight loss (last 6 months)	1.50 (0.37-6.16)	0.574			1.50 (0.37-6.16)	0.574		
Severe Functional Disability (%)	1.25 (0.35-4.48)	0.729			2.74 (0.83-9.11)	0.099		
Severe Mobility Impairment (%)	0.76 (0.22-2.67)	0.669			1.13 (0.34-3.75)	0.848		
CIRS severity	1.79 (0.43-7.48)	0.421			1.71 (0.41-7.08)	0.458		
CIRS comorbidity	1.31 (0.93-1.85)	0.127			1.54 (1.07-2.21)	0.019	1.48 (1.02-2.16)	0.039
Cognitive impairment (n = 95, %)	0.92 (0.27-3.16)	0.900			2.48 (0.64-9.69)	0.191		
Number of medications	0.92 (0.75-1.14)	0.461			0.91 (0.73-1.14)	0.408		

OR = odds ratio; CI = confidence interval; BMI = body mass index; CIRS = cumulative illness rating scale.

EWGSOP criteria have lower obesity prevalence compared to those identified with FNIH criteria; furthermore the FNIH criteria identified participants that, despite having higher lean mass and higher BMI, are functionally more impaired. These data suggest that the use of lean mass adjusted by body mass seems to be the best choice to capture subjects that are unable to generate enough muscular strength or to achieve an adequate physical performance relative to their body mass and that ALM/BMI may be a good measure for low muscle quality or efficiency [6 17].

These results suggest that the EGWOSP and FNIH criteria identify as sarcopenic different individuals and therefore the two definitions cannot be used interchangeably. Since more than one out of five subjects of this study were found to be obese, we can assume that the results obtained according to FNIH sarcopenia definition may offer a better representation of the actual sarcopenia prevalence in this population. Furthermore, FNIH definition seems to identify a sarcopenia phenotype with higher comorbidity level and functional disability. Nevertheless, longitudinal studies should be performed to directly compare the predictive value in term of clinical outcomes of the two diagnostic algorithm.

In interpreting our findings, some limitations should be considered. First, the setting limited generalization of our findings: the high prevalence of functional impairment along the low cooperation offered from subjects with cognitive impairment may have partially compromised the usefulness of the result obtained from the gait speed and grip strength tests, as stated before in literature with similar population [7]. Second, of the 158 residents, only 97 were included in this study; the majority of the excluded residents presented health-related conditions: healthy selection bias has to be taken into account and therefore our analyses might have underestimated the true prevalence of sarcopenia. Third, the cross-sectional design of the study did not allow us to clarify any temporal or cause-effect relationship between sarcopenia and its associated factors. Fourth, the low number of subject defined as sarcopenic (13 according to both definitions) might have limited the statistical significance of the multivariate analyses. Finally, the use of BIA for muscle mass assessment presents some drawbacks mainly due to the hydration problems usually observed in older persons, that may result in an underestimation of the body fat and an overestimation of fat-free mass. On the other hand, BIA is inexpensive, easy to use, readily reproducible, and appropriate for both ambulatory and bedridden patients, considered as a portable alternative to dual-energy X-ray absorptiometry [9], and its standardized use may favor a widespread assessment of body composition in everyday clinical practice and in nursing home residency.

In summary, in this sample of Italian institutionalized older people, both EWGSOP and FNIH criteria identify sarcopenia as a common condition, strongly related to male sex, BMI and comorbidity level. Our results suggest that the EGWOSP and FNIH criteria cannot be used interchangeably, since both definition identified as sarcopenic different individuals. Finally, this study reinforce the notion that walking speed assessment might not be feasible in most of the patients admitted in nursing home facilities.

Conflict of interest

The authors declare no conflict of interest.

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Review

Assessment of sarcopenia: from clinical practice to research

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Sarcopenia is the loss of muscle mass and function that occurs in aging. Multiple factors are involved in the pathogenesis of sarcopenia, such as mitochondrial dysfunction, protein synthesis alteration, and poor exercise. Both European (EWGSOP) and American (FNIH) diagnostic criteria are currently available. Sarcopenia could represent the biological substrate of physical frailty. In every older patient presenting compatible clinical features, the presence of sarcopenia should be screened with validated questionnaires such as SARC-F. The DXA evaluation is considered the current gold standard technique both in research and in clinical practice for the assessment of muscle mass. In clinical practice, the measurement of muscle strength by handgrip strength is recommended, while physical performance should be primarily assessed by SPPB test. In this review, we report current strategies to counteract sarcopenia, which consist of adequate protein intake and physical exercise.

Key words: Muscle strength, Muscle mass, Physical performance

INTRODUCTION

The aging process is characterized by alterations of various organs and systems that affect the total homeostatic capacity of the human body. As described for the first time by Irwin Rosenberg in 1989 in Albuquerque (New Mexico, USA), "from a structural and functional point of view, no decline is more dramatic than the one that muscle mass undergoes during the various decades of life", and proposed the term "sarcopenia" to define the loss of muscle mass and function that occurs in aging [1]. The muscle mass and functional decline described by Rosenberg 30 years ago has been clearly documented with large observational studies. Recent findings show that different patterns of muscle mass and physical decline with age are observed for different ages [2]. In general, muscle mass slightly decreased with advancing age. Interestingly, for muscle strength (as measured by hand grip test) and physical performance (as measured by chair stand test) there is stability in the first decades of adulthood, and decrements in the middle years (45+) and late adulthood. In particular, individuals older than 75 years lose approximately 60% of their muscle strength and 30% of their physical function. The linear pattern of age-decline is surprisingly similar in men and women across the entire course of life, and is independent by different race [2].

Biological substrates of sarcopenia

Multiple factors are involved in the pathogenesis of sarcopenia [1] (Fig. 1): (a) constitutional factors, such as male sex, low birth weight, genetic susceptibility; (b) modifications related to the aging process itself. The latter factors can be schematized as follows:

- *muscle cell alterations*: including decreased type II cells – involved in rapid muscle power contraction and with a predominantly glycolytic metabolism -a size reduction of residual muscle cells, loss and disorganization of myofilaments, accumulation of lipofuscin pigments;
- age-dependent decline level of *hormones:* androgens (testosterone and DHEA), estrogen, growth hormone (GH), and decline of insulin sensitivity;

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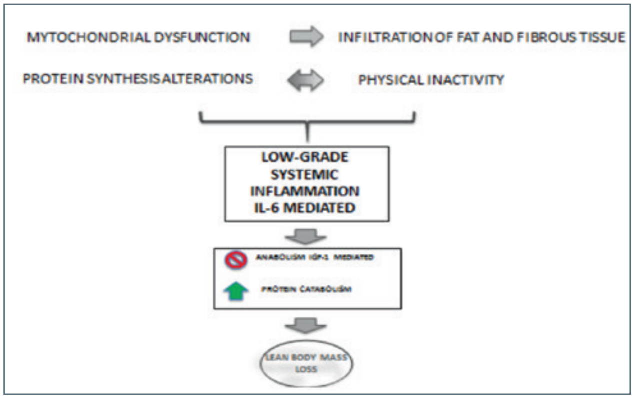

Figure 1. Biological substrates of sarcopenia.

- degeneration of spinal *moto-neurons*, probably due to a "retrograde effect": the muscle, through largely unknown mechanisms, sends negative "remodeling" information to the motor terminal;
- *Mitochondrial dysfunction*: in the muscles of sarcopenic subjects, a significant deletion of the mitochondrial genome has been found caused by errors in DNA replication. The shorter genome replicates faster and induces the formation of malfunctioning or completely inactive mitochondria [3]. This causes a cell energy deficit and the loss of the fiber itself, which is replaced by infiltration of connective and fatty tissue;
- increased *protein turnover*: since an adequate availability of nutrients, there is an imbalance between the ability of the fibers to complete a correct protein synthesis and the rate of degradation [4];
- *poor exercise and/or sedentary lifestyle*: in this connection, current evidence clearly shows that physical exercise may exert a positive impact on muscular physiology through systemic and local effects [7].

Finally, a long list of chronic diseases (such as cognitive decline, mood disorders, diabetes mellitus, heart failure, liver failure, renal failure, respiratory failure, chronic pain, obesity) is related to sarcopenia, being the systemic inflammation a common pathologic pathway.

Functional aspects

Among the diagnostic criteria of sarcopenia currently available, two are the most used: those developed in 2010 during the European consensus on sarcopenia (EWGSOP) [8], and the more recent ones published in 2014 by the group "FNIH Sarcopenia Project" [9]. Both consensuses underline the importance of functional criteria in addition to the structural ones. The first criteria are based on the detection of decreased muscle mass associated with strength or physical performance decline. The reference values for the diagnosis of sarcopenia developed by the EWGSOP are [10]:

- muscle mass: SMI (skeletal mass index) < 8.87 kg/m^2 for male; < 6.42 kg/m^2 for female;
- pretension force < 30 kg for male; < 20 kg for female;
- physical performance < 0.8 m/s at the 4-meter walking test.

In 2014, as part of the "FNIH Sarcopenia Project" [9], analyzing data produced by 9 studies conducted on populations belonging to the community (for a total of 26,625 participants), a further conceptual step was carried out, with the aim of identifying clinically relevant thresholds of muscle mass and function. As a conceptual assumption, there was a clinical paradigm according to which, starting from a patient with poor physical performance, you can identify in the differential diagnosis "weakness" as the causative agent of this and, subsequently, a reduction of the muscle mass at the base of the weakness itself.

The identification of subjects in whom reduced muscle mass is the main cause of weakness is crucial because they are able to gain significant benefit from the addressed interventions. The reference values for the diagnosis of sarcopenia developed by FNIH are [9]:

- weakness: grip strength < 26 kg for male and < 16 kg for female; alternative grip strength adjusted for BMI < 1.0 for male and < 0.56 for female.
- pppendicular lean body mass (ALM): ALM adjusted for BMI < 0.789 for male and < 0.512 for female; alternative ALM < 19.75 kg for male and < 15.02 kg for female.

The threshold values of the lean mass identified by the "FNIH Sarcopenia Project" as "clinically relevant" are associated with impairment of mobility. In a subsequent research, Studensky also demonstrated that these cut-offs were not only clinically relevant, but also highly predictive of incident disability and mortality [11]. Thus sarcopenia, and not multimorbidity, is strongly associated with adverse outcomes. This fundamental evidence revolutionizes the conceptual terms of the syndrome framework, especially considering that it represents a potentially reversible condition. Hence, it is important to refer to a clear and universal accepted operational definition, in order to develop adequate therapeutic interventions to prevent disability. Interventions will not target a pathology, but functionality, revolutionizing the paradigm so far adopted towards patients in clinical practice.

The updated EWGSOP2 recommendations indicate low muscle strength as the primary parameter of sarcopenia, since this is the most reliable measure of muscle function, similarly to FNIH criteria. The diagnosis has to be confirmed by the detection of low muscle mass. The key conceptual step is represented by the fact that sarcopenia may be the biological substrate of physical frailty and the pathway through which it develops [12].

Sarcopenia may be envisioned as the "organ failure" underlying the clinical manifestations of physical frailty [13]. Therefore, the implementation of this theoretic model will feasibly encourage important advancements over the traditional approaches to this syndrome by enabling the accurate operationalization of the disorder, a clear identification of the affected population, and the rapid translation of findings to the clinical setting. It is important that such a conceptualization renders sarcopenia comparable to other common geriatric conditions, with the great benefit of making the syndrome easily acceptable by health care professionals, public health authorities, and regulatory bodies [14].

According to this conceptual model, sarcopenia relies on a biological substrate at the muscle level (low muscle mass and quality). The clinical manifestations of sarcopenia, such as slow gait speed, impaired balance, and weakness, are also objectively measurable with specific assessment scales [15]. This set of measurable biological substrate, clinical manifestations, and functional performance is similar to the diagnostic path that is usually performed for other common age-related degenerative conditions, such as congestive heart failure, chronic obstructive pulmonary disease, and peripheral artery disease [15]. This implies that older persons with sarcopenia can be easily identified as those with target organ damage (muscle mass), specific clinical phenotype, and impaired physical performance [16].

We present currently available tools for measuring muscle mass and physical function in order to better understand their advantages and limits, and their appropriate use in clinical setting.

SCREENING OF SARCOPENIA IN CLINICAL PRACTICE

In every older patient presenting with weight loss, weakness, fatigue, frequent falls, and difficulties in activities of daily living, the presence of sarcopenia should be evaluated. In this regard, the *SARC-F questionnaire* is a simple validated questionnaire should be administered during general medical examination to quickly identify subjects at risk of sarcopenia [17]. It includes 5 questions about difficulties to lift and carry 5 kg, walking across a room, transferring from a chair or bed, climbing 10 stairs, and numbers of falls in the previous year. Despite an uncertain sensitivity, a score ≥ 4/10 is reported to be predictive of sarcopenia and its negative outcomes [18]. This screening test is considered as the first step in the identifications of sarcopenia by the revised version of 2EWGSOP [8].

Other recent studies tested different ways to predict sarcopenia in primary setting, such as probability tables based on low muscle mass by age and BMI, or predictive score charts including variables such as age, handgrip strength, and calf circumference, but these need to be validated [17].

ASSESSMENT OF SARCOPENIA

It follows the list of methods for measuring muscle mass, useful in clinical practice or in research settings.

Assessment of muscle mass

Anthropometric measures – calf circumference, mid-arm muscle circumference

Mid-arm muscle circumference (MAMC = mid-arm circumference – (3.14 X triceps skinfold thickness) and calf circumference have been show to reflect both health and nutritional status, and to predict performance and survival in older people, and have been shown to be correlated with ALM [19]. The WHO Expert Committee considers a calf circumference smaller than 31 cm indicative of low muscle mass [20]. Anthropometry represents the most portable, easy to use, inexpensive tool, therefore it seems to be suitable for screening in primary care.

<u>DXA – Dual energy X-ray absorptiometry</u>

DXA is the most popular technique to estimate body composition, in particular appendicular skeletal lean mass [21]. Based on the attenuation capacity of X-rays in proportion to the composition and thickness of a composite material, DXA is able to measure the body content of soft tissue, fat mass and total body (appendicular and trunk) skeletal mass. Allowing measurement of the three body compartments and the estimation of appendicular skeletal lean mass (ALM) as the sum of the non-bone and non-fat mass of the four limbs (which is used both in EWGSOP and FNIH Sarcopenia project diagnostic criteria), DXA is considered the current reference technique both in research and clinical practice for the assessment of muscle mass [21]. The ALM is demonstrated to be strongly correlated with both MRI and CT measures of skeletal muscle volume. The main advantages of this tool are non-invasiveness (for the small doses of radiation: < 1 μSv for whole body scans) [22], cheapness, rapidity, and low rate of errors (1,2%). Weaknesses include that DXA is not portable, it is unable to assess intramuscular adipose tissue and consequently muscle quality; furthermore, its results could be affected by diseases associated with water retention (e.g. heart, kidney or liver failure), or with extracellular fluid accumulation, due to its inability to differentiate between water and bone-free lean tissue. Finally, the DXA machine usually does not support very tall or very obese people [21].

Magnetic resonance imaging (MRI)

MRI gives high accuracy information about muscle quantity and quality: different tissues have different magnetic properties (such as density of hydrogen atoms and relaxation time), so variations in the radio frequency pulse sequence allow to differentiate adipose tissue and fat-free mass. Its use in clinical practice is limited by difficult access, high costs, long execution time, the need of high trained staff; it is suitable for small-scale research studies [23].

Computed tomography (CT)

CT produces images as maps of pixels which reflect different tissue attenuation (related to electron density): bone, skeletal muscle and adipose tissue have specific range, and this allow their identification in the cross-sectional images. Strengths and weaknesses are very similar to MRI, except for radiation exposure and a shorter time for image acquisition [23].

Bioeletric impedance analysis (BIA)

BIA allows to quantify body compartments based on their different electrical conductivity: water rich tissue, such as skeletal muscle, are less resistant to the passage of an electrical current than lipid-rich adipose tissue [21]. Whole-body bioelectrical impedance measurement, in particular the resistance caused by the total water across the body, is taken between the right wrist and ankle with the subject in a supine position. The muscle mass is calculated through the Janssen equation (Skeletal muscle mass (kg) = [(height 2/BIA resistance X0.401) + (gender X 3.825) + (age X-0.071)] + 5.102).

Although BIA is a portable, easy to use, non-invasive, unexpensive tool, there is a poor correlation between BIA and DXA measurements (36), probability due to the fact that BIA measurements are very sensitive to subjects' conditions such as hydration, recent activity and time being supine, body temperature, intra and inter-instrumental variability, and electrode positioning.

Thus, BIA is suitable for screening of sarcopenia in community dwellers and bedridden patients [23].

Muscle ultrasonography (US)

The US beam propagates through and is reflected back to the transducer by tissues, according to their acoustic impedance; therefore, US allows the determination of thickness and cross-sectional areas of superficial muscle, and estimates muscle architecture parameters such as muscle volume, fascicle length, and pennation angle (which represents the angle of the muscle fibres relative to the force-generating axis, directly affecting both the force production and the muscle excursion) [24]. Although the major issue that must be taken into consideration is the impact on the measurements result of the applied pressure on the probe, an excellent intra and inter rater reliability for US measurements of quadriceps muscle layer thickness has recently been reported. In addition, US is portable and radiation-free, being promising for muscle mass assessment in clinical and research settings [24].

Other approaches to estimate muscle mass

Neutron activation (NAA). A stationery neutron beam passes over the subject lying on bed. A gamma detection system capturs gamma rays emitted by excited atomic nuclei, in turn excited by interaction with neutrons. Although very accurate in estimating muscle mass, this technique is not recommended for its high costs and radiation exposure [21].

Electrical impedance miography (EIM). It is based on the interpretation of muscle as a set of resistances and capacitances [21]. Resistances, determined by intra and extracellular matrices, increase when muscle cross sectional area reduces; capacitances, constituted by cell lipid bilayer membranes, also increase in case of muscle loss. These quantitative parameters are measured by applying, through separated electrodes, a high-frequency/low-intensity electrical current. EIM is a non-invasive, painless tool to measure muscle mass, but it requires high trained personnel. Hence, is not applicable in daily clinical practice [21].

Serum and urinary creatinine. Creatine is a widely present amino acid in skeletal muscle [21]. Creatine is non-enzymatically converted in creatinine at a relatively constant rate per day (about 2%) and excreted in urine. So, serum creatinine or 24-h creatinine excretion could be assumed to be proportional to the absolute amount of muscle mass [21]. Measurement could be affected by many factors such as renal failure. Some Authors suggested that, in the presence of stable renal function, it could be considered a reliable indicator of muscle mass, meat intake (accurate assessment would require a meat-free diet for about 1-2 weeks), inaccurate 24-h urine collection, conversion rate influenced by pH and temperature. Although predictive equations of creatinine excretion taking into account sex, weight, race and age have been developed, the absence of a normal range of reference does not make this technique currently applicable.

Deuterated creatinine (D3-creatine) dilution method. According to the non-enzymatic transformation just described above, urine excretion of D3 creatinine can be quantified after an ingestion of oral dose of deuterated creatine, considering it an indirect measure of skeletal muscle mass [21]. Although it is a complex technique that can only be used for research purposes, the estimation of muscle mass with this method showed excellent concordance with MRI measurements of muscle mass in rats and humans. Some researchers have tested the possibility of using muscle turnover circulating products (such as those of collagen types II and IV), as muscle mass biomarkers, but further studies are needed.

Assessment of muscle strength

Hand grip strength

The measurement of muscle strength by handgrip strength is currently recommended in clinical practice. For this aim, the gold standard is the use of a Jamar dynamometer, an isometric instrument composed of a hydraulic gauge, an adjustable handle and a display that indicates (in kg) the peak of strength reached during the test [25]. The standard exam is performed with the subject seated, and the grip size is adjusted for the first test hand. The examiner has to explain the test: the patient has to squeeze the hand grip as hard as he can with the forearm at the thigh level, taking a breath in before starting, and blowing out the air during the performance. Six measures should be taken (3 per each arm) and the highest reading must be reported as the final result. This test presents some limitations in relation to the presence of arthritis, tendonitis, carpal tunnel syndrome, and surgery on hand or wrists in the previous three months. In these cases, physicians can use a pneumatic dynamometer to assess muscle strength.
In the case that sarcopenia could be viewed as a clinical biomarker to identify persons with a high risk of disability and negative-related outcomes, hand grip strength, absolute or adjusted for BMI, assumes fundamental importance because it "*can be considered a composite measure of muscle mass and muscle function and, at the same time, as an important discriminator of mobility limitation*" [8]. Considering this and the fact that it is portable, inexpensive and easy to perform, there is an urgent need to standardize reference values stratified for age, gender and ethnicity.

Leg extension strength

It is another test that measures lower body muscle isometric strength. The participant sits with its lower legs hanging down (knee angle 90°). A resistance is fastened around the right lower leg of the participant, who must try to extend this leg with maximum strength and hold that position for 3 seconds. The score is given in kilograms of force. After one practice trial, the best score of three trials is recorded. The main disadvantage consists in the need of an adequate equipment and trained staff.

Assessment of physical performance

Short Physical Performance battery (SPPB)

Physical performance should primarily be assessed by Short Physical Performance Battery (SPPB) test. It estimates the lower body function and is highly correlated with disability and negative outcomes such as hospitalization, institutionalization and mortality, because it "*provides an accurate picture of the biological age of an older person. At the same time, the SPPB is strongly related with the quantity and quality of skeletal muscle, and is therefore able to capture the core of Physical Frailty and Sarcopenia*" [13].
The SPPB test includes balance tests, gait speed test, and chair stand test. In the balance tests, the participant first tries to stand for about 10 seconds with his feet together side by side, then with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds, and finally with the heel of one foot in front of and touching the toes of the other foot for about 10 seconds. During the three tests, the patient could extend arms or move the body to maintain the balance, but not move the feet. The second test measures the 4 meters gait speed. The patient could use a cane and has two tries. The final test is the "chair stand test": the subject stands up straight as quickly as he can five times without stopping in between, keeping arms folded across the chest. The performance is considered good if chair stand time is $\leq$ 11.19 seconds. A total score < 9 is indicative of poor physical performance.

Time up and go test (TUG)

The patient is seated in a chair. When the examiner says "go" the patient must get up, walk three meters (appropriately marked on the floor) at its usual gait, go back and sit again. The patient can use a walking aid if necessary. Time is recorded. Time $\geq$ 12 seconds to complete the TUG is considered an indication of poor physical performance.

Six minutes meters walking test

The patient must walk for 6 minutes along a corridor with a flat surface. The corridor must be at least 30 meters long. Before and after the test, heart rate and blood pressure should be monitored. The six-minute walk distance in healthy adults has been reported to range from 400 m to 700 m. Age and sex-specific reference standards are available to identify individuals with poor physical function.

400 meters walking test

The test is performed by asking the patient to walk for 400 meters along a corridor having a flat surface [13]. The patient could use a walking aid if necessary; the patient could stop at most 10 times. Each stop can last a maximum of 60 seconds, otherwise the test is interrupted. At the beginning and at the end of the test it is necessary to record the heart rate and the arterial pressure. At the end of the test, the examiner must also investigate the perception of fatigue and the severity of the breathlessness with the Borg scale. A time ≥ 15 minute to complete the 400-m walking test is considered an indicator of poor physical performance.

CONCLUSIONS

In clinical practice, EWGSOP2 new guidelines recommend the use of the SARC-F questionnaire for screening. If it is positive, muscle strength should be measured by grip strength and chair stand test. The evidence of low muscle strength (probable sarcopenia) is enough to search the causes and start intervention. Low muscle quality or quantity should be detected to confirm the presence of sarcopenia; in this regard EWGSOP2 advise the use of DXA and BIA methods in usual clinical care, and DXA, MRI or CT in research. The measures of physical performance (SPPB, TUG and 400-m walk tests) should be used to assess severity of sarcopenia.

Conflict of interest

The author declare no conflict of interest.

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Review

Impact of physical activity on the management of sarcopenia

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The maintenance of muscle function in old age prevents the development of negative health outcomes.
Physical inactivity is the primary risk factor for muscle loss and weakness and is one of the leading causes of various chronic diseases. Conversely, regular physical activity, modifies the age-related pattern of decline of muscle mass and strength and represents the most effective strategy against sarcopenia. This evidence has urged the World Health Organization to recommend regular physical activity throughout the course of the life. Resistance exercise improves muscle mass and strength while endurance training increases maximum aerobic power. Recommendations for adult and older people include combined endurance and resistance exercises, based on a regular program (at least 3 days a week).
This narrative review presents the available evidence on the beneficial effects of exercise on physical frailty and sarcopenia. We also describe the exercise protocol adopted in the "Sarcopenia and Physical fRailty IN older people: multicomponenT Treatment strategies" (SPRINTT) project. The SPRINTT clinical trial will provide evidence of physical activity and nutritional supplementations in preventing several adverse outcomes associated with sarcopenia and physical frailty in older adults.

Key words: Exercise, Skeletal muscle, Physical performance

INTRODUCTION

The aging process is accompanied by progressive decline in skeletal muscle mass that may lead to decrease strength and physical performance associated with an increased risk of disability. This condition, referred to as sarcopenia, is increasingly recognized as a major risk factor for adverse outcome in frail older people [1]. Several factors seem to play a role in progression of sarcopenia; however, its physiopathology is still unclear. Without any available pharmacological intervention to sarcopenia, physical activity and specific nutritional supplementations represent the only strategies currently available for the management of sarcopenia [2].
Physical activity is defined as all body movements produced by skeletal muscles that require energy expenditure [3]. The four main types of physical activity are: baseline activity, leisure-time physical activity, moderate-intensity physical activity and exercise. Exercise, is a subcategory of physical activity that is planned, structured and repetitive. There are different forms of exercise: aerobic (endurance), resistance (strength), combination of aerobic and resistance exercises, stretching and balance exercises.
Aerobic exercise involves performing continuous movements with large muscle groups for 20 minutes or more. Biking, swimming, walking or jogging are forms of aerobic exercise. Aerobic activity depends primarily on oxygen consumption and improves cardiovascular function. Resistance exercise is a form of exercise that causes muscle contractions against an external resistance with the expectation of increases in strength, tone and mass and requires the use of

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weight machines, dumbbells, and barbells as resistance sources for improving muscle strength [4]. In older persons, resistance training has a greater impact on improving mass and strength than aerobic training [5]. Several studies have demonstrated that specific programs of physical activity (combination of aerobic and resistance exercises) can improve muscle mass and muscle strength and reduce the risk of physical disability.

THE EFFECTS OF PHYSICAL ACTIVITY ON MUSCLE: MECHANISM OF ACTION

There are different supposed mechanisms by which physical activity acts against sarcopenia. The recruitment and activation of muscle satellite cells represent a major adaptation to physical exercise. The incorporation of new nuclei from satellite cells into parent cells increases the fiber cross-sectional area [6]. Satellite cell activation is influenced by many factors, including age, nutritional status, type and intensity of physical exercise. In particular, during physical exercise, active muscles release hormones and inflammatory mediators that are satellite cell stimulants [7].

Among the different types of training, aerobic exercise increases energy production by mitochondria and capillary density. The increased muscle capillary allows matching the enhanced requirements of oxygen flux by muscle mitochondrial. During endurance exercise the muscle mitochondrial compartment (mitochondrial biogenesis and function) can be expanded. Instead, this type of training marginally affects the muscle fiber cross. Resistance exercise program impacts mainly on muscle mass and function (strength and power), by increasing the size and number of fast-twitch fibers (type II A and II X) [8].

In response to physical activity/exercise, muscle cells modulate the expression of specific proteins related to mitochondrial biogenesis and function, such as peroxisome proliferator-activated receptor γ co-activator 1α (*PGC-1*α) and muscle fatty acid binding protein (*mFABP*) [9]. In particular, *PGC-1*α activates the transcription of mitochondrial genes, while *mFABP* is involved in the utilization of fatty acid for mitochondrial energy production.

The down regulation of inflammation is another mechanism by which exercise acts against muscle mas and strength loss. Different studies have shown a decrease of levels of C-reactive protein (*CRP*) and interleukin-6 (*IL-6)* in older adults engaged in regular physical activity program. Finally, available evidence suggested that regular physical activity impacts positively muscle physiology through local and systemic effects.

THE ROLE OF EXERCISE IN PREVENTING DISABILITY

A sedentary lifestyle is the main modifiable risk factor for sarcopenia and is a well-known risk factor for several chronic diseases and disability in older adults. Conversely, physical activity improves mobility and decreases the risk of disability. In this field, the largest and longest study is the Lifestyle Intervention and Independence for Elders (LIFE), a multicenter randomized controlled trial conducted in the United States designed to compared a moderate-intensity physical activity program with a successful aging health education program on the incidence of major mobility disability (expressed by inability to walk 400 m) in more than 1600 sedentary and functionally limited older persons followed for 3 years. The major inclusion criterion was the presence of functional limitations (Short Physical Performance Battery [SPPB] score $\leq$ 9) [10]. The physical activity program (intervention group) consisted of a combination of walking at moderate intensity, balance, resistance exercise, stretching and behavioral counseling. Preliminary result from the LIFE pilot study (conducted on a sub-group of participants) showed the decrease of the incidence of disability and the increase of SPPB score in the intervention group over 1 year of follow up. The LIFE full study extended the promising results of the pilot study by showing that this specific exercises protocol reduce the risk of disability by 18% compared to the control group especially in participants who were frailer at baseline (SPPB < 8). In conclusion, these results show that a specific physical activity program (combination of endurance and resistance exercises) improves the frail status in older adults at risk of disability and prevent mobility disability.

EXERCISE AND SARCOPENIA

Sarcopenia is a major component of the frailty syndrome and is also a strong predictor of disability, morbidity, and mortality in older persons. The term sarcopenia identifies a condition characterized by loss of lean body mass and decreased strength and functionality. Several studies have explored the benefits of exercise in improving muscle mass and function and in preventing disability. Fielding and colleagues compared two different exercise programs (high-velocity and low-velocity resistance training) in frail, community-dwelling older women with self-reported physical disability. This study revealed that high-velocity resistance training has a greater effect on lower extremity muscle power than low-velocity training, despite the high-intensity arm is equally as efficacious as low-intensity arm for improving muscle strength [11].

Table I. Physical activity: guidelines.

General recommendations
• Start slowly • Warm-up and cool down
Recommendations for endurance training
• 30-60 minutes of moderate-intensity physical activity/day or at least 20-30 minutes of vigorous intensity/day • Exercise sessions should last a minumum of 10 minutes for intermittent aerobic activity • At least a total energy expenditure of 150/250 kcal for each session
Recommendations for endurance training
• Set of 8-10 exercise on two or more non consecutive days/week using the major muscolar groups • 8-12 repetitions of each exercise resulting in volitional fatigue • Flexibility exercise at least two days /week and 10 minutes/day involving areas of neck, shoulder, wrist, hip, knee and ankle

Goodpaster and colleagues evaluated the effects of a specific physical activity program (aerobic, strength, flexibility and balance training) on strength and skeletal muscle fat infiltration in sedentary, community–dwellers, older persons over a follow-up of 12 months. This trial demonstrated a clear effect of exercises program to prevent progressive loss of muscle strength in older adults. Furthermore, the significant age-associated increase in muscle fat infiltration was prevented with increased physical activity [12].
Marques and colleagues evaluated the effects of a multicomponent training with weight-bearing exercises on muscle strength, balance, agility, and bone mineral density in older women and demonstrated that this training is effective at increasing bone mineral density, muscle strength, and distinct functional fitness skills, which are associated with aging and increased risk of falling and fracture [13].
Based on this evidence, recommendations for frail older people should include a specific activity program with endurance training and resistance training at least 3 days a week (Tab. I).

EXERCISE AND NUTRITIONAL INTERVENTIONS ON MUSCLE HEALTH

Muscle composition and function are regulated by muscle protein turnover rate. Protein intake and physical activity are the main anabolic stimuli for muscle protein synthesis. An adequate dietary protein intake is necessary for muscle health because it provides the essential amino acids needed to replace those lost from catabolism and stimulates muscle protein synthesis and growth. Low protein intake is associated with increased muscle loss in older adults. Leucine is the essential amino acid that can directly activate the mechanistic target of rapamycin (*mTOR*) signaling pathway in skeletal muscle stimulating protein synthesis [14]. It is recommended that older persons consume food with higher proportion of essential amino acid (high quality protein), such as lean meat and leucine-rich foods (soybeans, peanuts, cowpea and lentils). Because of metabolic changes, older persons may produce less muscle protein than younger person from the same protein intake. Therefore, the current recommended dietary allowance for protein (RDA:0.8 g/kg/day), although sufficient for young people, fails to prevent muscle and strength loss with aging. The minimal amount required to maintain muscle function is 1.0 g/kg/day. It is recommended that older persons consume between 1.0 and 1.5 g of protein/kg/die. In addition, a balance caloric supplement should be considered to prevent sarcopenia. Foods are used to provide energy for organ function and muscle activity. If caloric intake is not enough to meet needs, muscle are catabolized to provide energy. Therefore, an adeguate total caloric intake is mandatory for maintenance of muscle health.
The time of protein ingestion and the synergistic effect of protein intake with physical activity are important factors to improve muscle mass. In old age, the ingestion of large quantities of proteins in a single meal may be difficult to maintain over the long term, therefore, the quantity of proteins introduced should be distributed equally throughout the day (25-30 g of high-quality protein at each meal) in order to ensure a greater 24-hour anabolic response [15 16].
The absorption kinetics and the amino acid composition of dietary proteins are also relevant factors that must be considered to prevent muscle and strength loss. The speed of absorption of dietary amino acids by the gut influences postprandial protein synthesis, breakdown, and deposition [17] and has contributed to the development of the fast *versus* slow protein concept which may have significant involvements on the management of sarcopenia. In young individuals, slowly digested proteins (e.g., casein) produce greater protein retention than those that are rapidly digested (e.g., whey). An opposite pattern has been observed in elderly individuals [18]. Pennings et al. have demonstrated that the ingestion of whey proteins stimulates postprandial muscle protein deposition in older men more efficiently than casein.
Muscle protein synthesis is influenced by several factors including timing of protein intake and functional and training status [20]. In this context, an optimal time window for protein ingestion in relation to physical activity is still a matter to be solved. Generally, it is assumed

that muscle is responsive to amino acids ingestion for up three hours after physical activity [21]. Older persons practicing physical activity may also be recommended to ingest fast proteins (e.g., whey) or amino acids (e.g., leucine-enriched balanced EAA mix) immediately before or 2-3 hours after the training session to enhance exercise-induced muscle hypertrophy [22 23]. However, inconsistent results in timing of protein ingestion have been reported in older persons involved in physical activity programs [24]. In this respect, larger clinical trials are needed to identify the optimal timing of protein intake during the day and in relation to physical activity.

PHYSICAL ACTIVITY FOR OLDER ADULTS: GENERAL RECOMMENDATIONS

Sedentary behavior enhances with aging and has been shown to increase risk of chronic diseases, particularly diabetes and cardiovascular disease. Participation in a regular exercise program is an effective intervention to reduce a number of functional declines associated with aging. Recommendations for physical activity in older adults comprises a specific exercise program including combination of endurance and strength exercises at least three times a week. Endurance training can help maintain and improve various aspects of cardiovascular function and contribute to an increase in life expectancy. Strength training helps offset the loss in muscle mass and strength typically associated with normal aging. Additional benefits from regular exercise include improved bone health with reduction in risk for osteoporosis; improved postural stability reducing the risk of falling and increased flexibility. The regular physical activity can also produce a number of psychological benefits related to preserved cognitive function and alleviation of depression symptoms.
The activity should be initiated with low intensity to gradually increase in order to minimize the risk of injury. Each session is preceded by a brief warm-up and followed by a brief cool-down. These exercises allow to gradually modifying the individual's heart rate and/or breathing. The aerobic physical activity should be performed for 30-60 minute of moderate-intensity per day or at least 20-30 minutes per day of vigorous intensity and the resistance training should be performed two or more non consecutive day with gradual increase (from moderate to vigorous).

EXERCISE PROTOCOL IN THE SPRINTT CLINICAL TRIAL

The "*Sarcopenia and Physical fRailty IN older people: multicomponenT Treatment strategies*" (SPRINTT) is a multi-center randomized clinical trial designed to evaluate the efficacy of a multicomponent intervention (MCI) program compared with a healthy aging lifestyle education (HALE) program on mobility disability, in community-dwelling older people with physical frailty and sarcopenia.
The MCI consists of a combination of structured physical activity, nutritional counseling/dietary intervention and information and communication technology intervention (ICT) and is designed to help older persons improve their physical function to prevent disability. In the ICT, actimetry data are collected through a dedicate device to monitor adherence to physical activity [25]. The HALE program consists of a series of workshops aimed at increasing awareness of important health issues relevant to older persons.
The physical activity intervention has been designed based on the exercise protocol adopted in the "Lifestyle Interventions and Independence for Elders" (LIFE) study which has been shown to be safe and effective at preventing mobility disability and improving physical frailty status [26]. Physical activity includes aerobic, strength, flexibility, and balance training. Walking is the primary mode of aerobic physical activity and should be performed for 150 min per week at moderate intensity. The physical activity intensity will be gradually regulated on the basis of perceived exertion, according to the Borg's scale. Each session is preceded by a brief warm-up (5 minutes) consisting of low intensity walking and followed by a brief cool-down period (3 minutes) in which the walking speed is gradually reduced. Strength exercises based on five lower extremities exercise using adjustable ankle weights. This is followed by a brief lower extremity stretching routine. Balance training is introduced during the initial phase of the program as a complement to the aerobic and strength components. Upper body exercises are included at the end of the session.
This exercise program is designed to be performed both at the center and at home. During the intervention, participants train at the center twice a week. In order to optimize participant compliance to the intervention, the total amount of physical activity is monitored by actimetry devices which allows to provide personalized feedback to the participant.
Finally, the nutritional component of the MCI has been designed to maximize the benefits of physical activity. Indeed, the combination of nutritional interventions and physical activity appears to be the most effective strategy presently available for improving sarcopenia and preventing disability.

CONCLUSIONS

Physical inactivity is a major risk factor for muscle loss and weakness, which results in increased fatigability. The regular exercise is effective at improving aerobic capacity, muscle mass, strength and endurance in adult and older persons. Engagement in regular physical activity brings many health benefits in young and old person. Indeed, the World Health Organization recommends people of all ages being as physically active as possible and including a minimum of 30 minutes of moderate-intensity physical activity on most, if not all, days of the week. In older persons, regular exercise provides the same beneficial effects as in younger individuals. The combination of regular physical activity with appropriate nutritional support seems to be the most effective strategy to improve physical function and prevent disability. High-quality clinical trials are needed to identify the type ad duration of multicomponent intervention (exercise and nutrition) that maximizes the health benefits in older persons [27].

The SPRINTT trial will provide evidence of combining long-term moderate-intensity physical activity and nutritional supplementations in preventing several adverse outcomes in older adults and its finding are expected to promote significant advancements in the management of sarcopenia.

Conflict of interest

The authors declare no conflict of interest.

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Review

Nutritional approach to sarcopenia

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To maintain a good balance of skeletal muscle mass, it is important to consume high amount of proteins and specific amino acids. In fact, the main nutritional stimulus for protein synthesis is represented by amino acids derived from food protein; in particular, leucine is the main dietary regulator of muscle protein anabolism. It is also important to select the quality of proteins taken up with the diet. Proteins show specific absorption rates based on amino acid composition and are distinguished into "fast" or "slow" absorption proteins. Research has shown that proteins, essential amino acids, leucine, hydroxymethylbutyrate (HMB) and vitamin D play a role in the metabolism of skeletal muscle and are valid nutritional supplements. Being sarcopenia a complex geriatric syndrome, the most effective approach for its prevention and management is represented by multimodal interventions that mainly include physical exercise and nutritional intervention. The important role of nutrition in both prevention and management of sarcopenia is proven by the remarkable evidence linking nutrition with muscle mass and function. Therefore, the best strategy to prevent and treat sarcopenia in older people is to combine a specific exercise protocol and adequate amino acid intake, as expected in the multi-center European clinical trail "Sarcopenia and Physics fRailty IN elderly: multi-component treatment strategies" (SPRINTT).

Key words: Skeletal muscle, Diet, Protein

INTRODUCTION

Malnutrition is one of the main causes of the onset of sarcopenia and frailty. Research showed that specific dietary interventions can prevent or treat the loss of muscle mass and strength related to age. Anorexia of aging consists in loss of appetite and/or reduction in food intake with serious consequences for the individual. This condition can in fact lead to muscle wasting, decreased immune-competence, depression, and an increase in the rate of complications of diseases. In particular, a reduction in food intake along with low levels of physical activity leads to significant loss of muscle mass and strength. Anorexia is strongly associated with a higher risk of quantitative malnutrition due to a reduced caloric intake, and especially in early stages can be related to a high risk of low qualitative intake of individual nutrients, particularly proteins and vitamins. In fact, sarcopenia can be correlated with the onset of selective malnutrition, for example, in terms of lack of individual macro or micronutrients.

Sarcopenia is characterized by a progressive atrophy of type II skeletal muscle fibers, which are mainly involved in the production of power. The turnover of muscle proteins is responsible for the composition and function of the muscle. A reduced synthesis of muscle proteins can be due to many factors, including an inadequate nutritional intake, and a deficit in protein synthesis after absorption because of incorrect response to nutrients, especially amino acids. Between 40 and 70 years a 25% average drop in energy requirement occurs and, consequently with increasing age, there is a progressive reduction in food intake secondary to physiological, psychological and social factors that influence appetite

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and food consumption. The changes that occur during the aging process include loss of taste, smell and vision, changes in secretion and peripheral action of the appetite hormones, effects on gastrointestinal motility, difficulty in chewing and swallowing. These modifications are often associated with functional limitations that negatively impact on the ability to access and prepare food, on depression and dementia, as well as on social problems (many elderly people live alone) [1].

The economic estimate of malnutrition related to the disease is high. Sarcopenia frequently coexists with malnutrition in older patients [2], and poor nutritional status is associated with the onset of frailty. During the International Conference on Frailty and Sarcopenia Research Task Force, in February 2018, the current state of research on nutritional interventions for sarcopenia was discussed; the effective efficacy of the combination of nutritional supplements with physical activity, and the role of nutritional intervention in sarcopenia obese individuals were evaluated. The Task Force concluded that nutritional supplementation should be integrated with pharmacotherapy and physical activity in order to have a substantial impact on individual patients and on the prevalence of sarcopenia [3].

ENERGY AND DIETARY PROTEIN INTAKE

The amount of food intake and the energy consumed are of fundamental importance to maintain muscle mass and physical performance. In fact, the lack of energy derived from the food consumed, associated with the lack of some nutrients, can determine the onset of sarcopenia. An inadequate nutrient and energy intake triggers a catabolic process that involves both body fat and muscle. Older subjects present with a reduced energy intake, derived from multiple causes including a reduction of appetite (anorexia of aging) [4]. For example, in the InCHIANTI study, which enrolled 802 people aged 65 or over, frailty was found to be associated with an energy intake < 21 kcal/kg [5]. These data were confirmed by further studies, such as the Third National Health and Nutrition Examination Survey involving 4731 US participants over the age of 60, and it was inferred that daily energy intake was lower in people who were frail, followed by the pre-frail ones. On the other hand, subjects who were not frail presented a higher daily intake of energy [6]. The Fourth Korea National Health and Nutrition Examination Survey for sarcopenia reported that energy intake was significantly lower in sarcopenic participants [7]. So, in elderly and frail subjects, protein-energy malnutrition is one of the main risk factors for the development of sarcopenia and its association with adverse clinical outcomes [8].

Effect of protein metabolism on muscle cells

Skeletal muscle mass is regulated by the balance between protein synthesis and breakdown, and most of the metabolism of muscle proteins depends on the intake of adequate amounts of proteins and amino acids with the diet. In fact, the consumption of high amounts of dietary proteins and/or specific amino acids promotes the synthesis of muscle proteins and inhibits protein degradation. Amino acids derived from food proteins greatly influence the muscle anabolic process, since essential amino acids are the main nutritional stimulus for protein synthesis. In particular, leucine is the main dietary regulator of muscle protein anabolism, because it is able to activate the mammalian target pattern of rapamycin and to inhibit the proteasome [9].

In older subjects, there is a reduction in the anabolic response at low doses of essential amino acids (EAA), whereas the administration of high doses of EAA (eg 10-15 g with at least 3 g of leucine) can stimulate protein synthesis similarly to what happens in adults [9]. Anabolic resistance is defined as the inability of skeletal muscle to stimulate protein synthesis in order to maintain protein mass, and this occurs in case of physical inactivity and muscle disuse. There are also many other mechanisms that can influence muscle metabolism including smoking, alcohol intake, the skin structure, and the presence of chronic inflammatory diseases [10]. Finally, insulin plays a very important role in protein metabolism stimulating, together with amino acids, muscle anabolism.

Protein sources

For the maintenance of a proper muscle metabolism, it is important to select the quality of proteins taken up with the diet [11]. Various protein sources are characterized by specific anabolic properties according to the amino acid profile, digestibility and bioavailability. Proteins show specific absorption rates based on the amino acid composition, which characterizes "fast" or "slow" absorption proteins. The absorption rapidity of dietary amino acids by the gut is of fundamental importance, because it influences the rate of postprandial protein synthesis. Compared to fast absorption proteins (whey), slow-absorption proteins (casein) stimulate a greater post-prandial accumulation of proteins in the muscle of young individuals. An opposite model has been documented in older individuals. As a result, some authors have shown that whey protein intake stimulates post-prandial accumulation of muscle protein in older subjects more efficiently than casein or hydrolyzed casein [12]. There are few studies that considered the different effect of animal-derived proteins with respect to those of plant origin on skeletal muscle. However, it is known that plant-derived proteins generally contain smaller amounts of EAA and are less digestible than those derived from animal proteins, since they include lower amounts of lysine, methionine and/or leucine. Recent studies conducted in older populations indicate that consumption of large amounts of plant-based proteins, as a strategy to improve muscle protein synthesis, might not be as effective as expected. Amino acids derived from soy protein are poorly involved in *de novo* muscle protein synthesis compared to amino acids derived from whey. It is therefore recommended to choose meat as a source of high-quality proteins, since it contains essential amino acids that are of fundamental importance for optimal muscle growth and bone development. Therefore, a nutritional intervention aimed at the prevention of sarcopenia should include the consumption of meat 3-4 times a week (white meat twice a week, lean red meat less than twice a week, and processed meat no more than twice a week).

The importance of animal protein intake for the prevention of sarcopenia was also confirmed by the VIP (Very Important Protein) study, conducted during the 2015 Expo in Milan, Italy. A population survey was conducted to evaluate main health parameters with particular attention to the relationship between protein intake derived from animals, muscle mass through the circumference of the calf and the mid-arm muscle circumference, and muscle strength of the upper and lower limbs assessed by means of a resistance test to the handle and repeated test of the support of the chair, respectively. Participants in the highest tertile of protein consumption showed better performance both in terms of grip strength and chair support test compared to the lowest tertile. The same results were found for calf circumference (CC) and mid-arm muscle circumference (MAMC). The results of the VIP survey suggest the presence of a synergistic effect on muscle parameters given by the intake of proteins derived from animals and carrying out physical activity [13].

Dietary protein requirements

The amount of dietary protein required to meet nutritional needs and maintain the nitrogenous balance is defined as protein requirement. This quantity is widely variable, and is fundamental for the maintenance of muscular homeostasis. Most of the studies conducted on protein metabolism focused on the anabolic response to protein ingestion or individual amino acids, and on the calculation of the adequate daily-recommended dose of high-quality proteins. The European Geriatric Medicine Society, in collaboration with other scientific organizations, launched the PROT-AGE Study Group [14] with the aim of developing updated and evidence-based recommendations that regulate the daily protein needs of elderly subjects. Overall, the current recommendations for protein intake for men and women aged 19 or over indicate 0.8 grams per kg of body weight per day [15]. Recent research suggests a protein intake of 1.0-1.2 g/kg/day for the maintenance of muscle health during the aging process. Older subjects with acute or chronic diseases are recommended to take up 1,2-1,5 g/kg/day of proteins. A further increase in protein requirements occurs in older people with serious illness or malnutrition, for which a contribution of 2.0 g/kg/day of protein is recommended.

Recently, it has been shown that nutritional deficit including low protein intake can aggravate muscular atrophy in individuals with sarcopenia, increasing the rate of adverse events such as hip fractures [16]. A study conducted among older subjects hospitalized for hip fracture due to accidental falls at the Emergency Department of the Teaching Hospital "Agostino Gemelli", Catholic University of the Sacred Heart (Rome, Italy) explored the relationship between food intake and muscle mass, calculated using bioelectrical analysis. Dietary assessment conducted on these patients showed that over 75% of the participants consumed less than 1.0 g kg-1 day of protein. This study showed that in older subjects with hip fracture there is a significant association between protein-calorie malnutrition and the presence of sarcopenia.

Optimal timing of protein intake

To improve muscle health, it is important to consider the timing of protein intake, in particular in relation to the performance of physical activity. Most researchers agree that proteins should be introduced homogeneously during the day to ensure a more sustained 24-hour anabolic response. Thus, older people should eat a suitable portion (for example, 25-35 g) of high-quality protein sources at each meal [17], to take between 1.0 and 1.2 g/kg per body weight per day of proteins. To increase the anabolism of muscle proteins, it is important to optimize the timing of protein intake and to coordinate it with the exercise timing. Some data suggest that resistance and aerobic exercise offer the greatest benefit to muscle function when combined with protein intake. Training with resistance exercises determines a transient increase in skeletal muscle protein synthesis by activation of AMP protein kinase, and reduced phosphorylation of 4E-binding protein 1E and other key specific regulators of the initiation of translation. However, studies shown that the highest level of protein synthesis is observed 60 minutes after exercise, since the maximal synthesis rate of muscle proteins is restored and theoretically amplified by the activation of protein kinase B, mTOR, ribosomal protein S6 kinase beta-1, and eukaryotic elongation factor 2 [18]. Therefore, improving the availability of amino acids during this period could offer the greatest anabolic advantage, and it is also important to maintain the appropriate dietary protein in the post-exercise period to facilitate adaptive muscle response.

ORAL NUTRITIONAL SUPPLEMENTATION

Nutritional supplementation plays an important role in the prevention of sarcopenia and the treatment of protein-caloric malnutrition. Protein, essential amino acids, leucine, hydroxymethylbutyrate (HMB) and vitamin D are important factors in the management of sarcopenia. Table I summarizes the effects of the main metabolic treatments on the skeletal muscle.

Essential amino acid

Several studies focusing on muscular anabolic responses following oral or intravenous intake of amino acid mixtures in adults and older people observed a large increase in muscle protein synthesis with an associated reduction in the rate of protein turnover, regardless of the type of mixture. These results suggest the importance of the amino acid intake; in fact, low doses of proteins do not stimulate muscle protein synthesis, since there is a threshold value of the amino acid quantity capable of stimulating protein synthesis. Furthermore, this threshold increases during the aging process and in the presence of inflammation.

Many protein supplementations containing essential amino acids demonstrated their effectiveness in randomized controlled trials, leading to an improved muscle-genesis. The essential amino acids can not be synthesized by the body and are necessary dietary components. A small study comparing a supplement containing only essential amino acids against a supplement containing a balance of essential and non-essential amino acids, suggests that the essential amino acids are responsible for stimulating amino acid-induced muscle protein synthesis [19].

Randomized controlled trials were conducted in Italy to test the efficacy of Aminotrofic®, a supplement composed of essential amino acids. The researchers reported that a dose of 4 grams of this supplement given twice a day between meals resulted in a significant increase in grip strength in the elderly and significant increases in lean mass among sarcopenic individuals. Recent studies have shown that protein-enriched amino acid sources such as leucine play a beneficial and protective role in muscle mass and function in older people; such effects occur at a set minimum dosage [20].

Table I. Effects of metabolic treatments on skeletal muscle.

Metabolic treatments	Effects on skeletal muscle	Validated treatment
Leucine	• Activation of mTOR signal pathway • Stimulation of protein synthesis/attenuate protein degradation • Nitrogen donor for the synthesis of muscle alanine and glutamine	Yes
HMB	• Activation mTOR signal pathway • Substrate for cholesterol synthesis • Stabilization of muscle cell membrane • Stimulation of protein synthesis/inhibition of protein degradation • Inhibition of caspase 8	Yes
Vitamin D	• Muscle fibers type effects – increased number type II fibers – increased size type II fibers • Metabolic effects – increased gene expression of protein – increased metabolism of calcium • Anabolic effects – increased protein synthesis – increased muscle cell growth • Anti-inflammatory effects – reduced cytokine other inflammatory effects	Yes
Other possible metabolic approches:		
Omega 3	Mediators and regulators of inflammation Action on the synthesis of muscle proteins through effects on mTOR signaling.	No
Gut microbiota manipulation	Regulation of inflammatory and redox status Deposition of fat mass Sensitivity to insulin	No

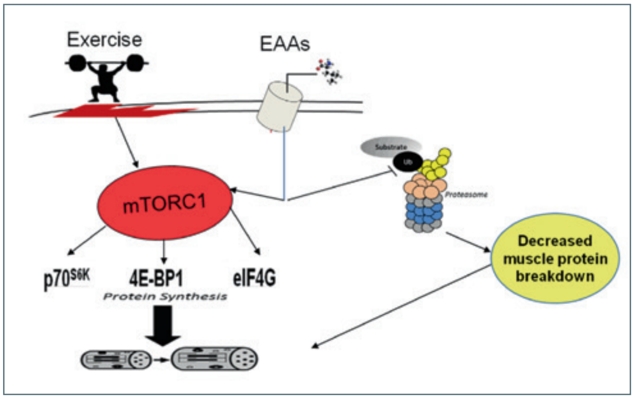

Figure 1. Protein ingestion combined with physical exercise stimulates initiation of protein translation via the mammalian target of ripamycin complex 1 (mTORC1). mTORC1 promotes protein synthesis by phosphorylating its substrates eIF4E, binding protein 1 (4E-BP1) and p70 rpS6 kinase (p70S6K). The inhibition of the proteasome by essential amino acids, in particular leucine, reduces muscle protein breakdown.

A study designed to evaluate the effects of a mixture of 6,7 g of essential amino acids enriched with leucine on the metabolism of muscle proteins in elderly and young individuals, showed that a higher percentage of leucine resulted in greater stimulation of the speed of muscle protein synthesis by essential amino acids in the elderly [21].

Oral nutritional supplement with leucine

At present, the only definitive test is currently limited to the integration of proteins and/or single amino acids. Essential amino acids stimulate myofibrillar protein synthesis, and several animal studies have shown that leucine, a branched-chain essential amino acid, independently stimulates muscle protein synthesis by activating components of the mammalian rapamycin target (mTOR) cascade. Activation of mTOR leads to increased phosphorylation of ribosomal protein S6 kinase 1 (S6K1) and eukaryotic 4E-binding protein initiator factor, thereby increasing muscle protein synthesis rates. Leucine is also an important insulin secretagogue, and it has been suggested as an effective active ingredient for the prevention and treatment of sarcopenia and type-2 diabetes. Leucine stimulates insulin secretion because the intracellular catabolism of amino acids in the pancreatic beta cells increases the intracellular relationship of ATP/ADP, which leads to the activation of insulin. Leucine has been shown to be a nitrogen contributor for the synthesis of muscle alanine and glutamine, and it is able to interact with proteolytic degradation attenuating skeletal muscular atrophy [22]. All these effects have been shown to depend on the dose. Many studies examined muscular anabolic responses following oral or intravenous intake of amino acid mixtures in adults and older people [23].

The PROVIDE study showed that stimulation of the rate of muscle protein synthesis by essential amino acids can be achieved in older subjects taking sufficient quantities of enriched essential amino acids, regardless of physical exercise [24]. This study showed that a targeted nutritional supplement containing whey protein, enriched with leucine and vitamin D in a timely amount of bolus, induced muscle protein growth and muscle strength improvement regardless of exercise among non-malnourished sarcopenic older people at high risk of disability.

Oral nutritional supplement with HMB

Leucine acts as the main diet regulator for the muscle cell, and it has been recently shown that HMB, a leucine metabolite, is able to stimulate protein synthesis and to improve muscle strength and body composition in the elderly. Therefore, nutritional supplementation with HMB could protect or restore muscle mass in the elderly who have a reduced lean mass. After its absorption, the dietary leucine is converted to α-ketoisocaproate, which is further metabolized to isovaleryl-CoA or HMB. In normal conditions, most KICs are converted to isovaleryl-CoA, while only about 5% of leucine is metabolized to HMB. Therefore, to reach pharmacological levels of HMB, this compound should be administered directly, rather than by increasing the leucine dosage. HMB promotes muscle cell membrane stabilization, modulates protein degradation by selectively inhibiting intracellular inflammation, inhibits caspase-8 activation on the cell membrane, increases protein synthesis directly through mTOR activation, and its effects are enhanced by IGF-1. The results of a recent study have suggested that age-related decline in endogenous HMB plasma concentration was positively correlated with lean appendicular mass and muscle strength in young and old [25].

Recently, several clinical studies have been conducted to determine the importance of HMB supplementation as a contributor to the preservation of muscle mass in older subjects. This supplementation can be useful in preventing muscle atrophy induced by bed rest or other factors. Daily administration of a nutritional mixture comprising HMB (2 g), arginine (5 g), and lysine (1.5 g) for 12 weeks, to elderly women who did not exercise was shown to improve physical performance, muscle strength, lean mass and protein synthesis.

In a multicenter, randomized, placebo-controlled, double blind trial, Deutz and colleagues demonstrated that early administration (within 72 hours of admission) of a oral supplement containing high concentrations of protein and HMB in malnourished older subjects was

associated with decreased post-discharge mortality and improvement of nutritional status [26]. A further study was conducted to determine whether HMB was able to attenuate muscle decline in healthy older adults during full bed rest, and the results showed that supplementation with HMB preserved muscle mass [27]. Furthermore, a meta-analysis of seven randomized controlled trials of HMB supplementation in the elderly showed that there is a greater gain of muscle mass in the intervention groups, compared to the control groups [28].
A recent study evaluated the effects of 24-week intake of 2 high-quality oral nutritional supplements (ONS), different for the amount and type of key nutrients in older adult men and women. These supplements had a high caloric quantity (330 kcal): Control ONS (C ONS, 14 g of proteins, 147 IU of vitamin D3) against experimental ONS (E ONS, 20 g of proteins, 499 IU of vitamin D3, 1,5 g CaHMB) taken twice a day. Participants were assessed at baseline, 12 and 24 weeks for gait speed, gripping force, and muscle mass of left and right leg by dual energy X-ray absorptiometry. Both ONS groups (E ONS and C ONS) improved leg strength, grip strength, and gait speed from baseline, without treatment differences. Based on the results, the participants were classified into two groups: those with severe sarcopenia, and those with mild-moderate sarcopenia. High quality oral nutritional supplements improved strength results and leg muscle quality in malnourished elderly adults with mild-to-moderate, but not severe, sarcopenia [28]. These results suggest that CaHMB can improve resistance parameters associated with loss of function and performance.
In conclusion, HMB is emerging as a promising candidate for nutritional interventions against sarcopenia, but further extensive studies are needed to establish the precise effects of HMB on muscle strength and physical function in the elderly, the optimal dosage and possible side effects resulting from chronic supplementation.

Other possible nutritional supplementation

Vitamin D

Vitamin D deficiency often occurs in elderly patients with reduced muscle mass and predisposes individuals to falls. For example, more than a decade ago, Visser and colleagues showed that older people enrolled in the Longitudinal Aging Study Amsterdam study who had serum 25 (OH) D concentrations below 25 nmol/L were twice as likely to be sarcopenic [29]. The action of vitamin D is mediated by the vitamin D receptor expressed in muscle tissue, and it has been shown that the number of VDRs present in human muscle tissue tends to decrease with age. However, recent studies have shown that the expression of VDR can be modified by vitamin D supplementation. A 4-month RCT demonstrated that women with reduced mobility administered with 4000 IU of vitamin D3 showed a greater variation in the concentration of intra-nuclear VDR than the placebo group [30].
In muscle tissue, vitamin D modulates the expression of the IGF-1 factor-binding protein-3 gene, and the calcium channels of the muscle membrane fibers, together with a neuro-trophic effect on nerve conduction. Therefore, vitamin D deficiency is associated with muscle atrophy, reduced muscle strength and power, reduced balance ability, and consequently increased risk of falls and recurrent fractures.
Factors influencing vitamin D deficiency are reduced sun exposure, decreased renal absorption, and reduced expression of vitamin D receptors. Furthermore, vitamin D exerts an important anti-inflammatory effect, as demonstrated for example in the InCHIANTI study, which showed an inverse association between serum concentration of 25 (OH) D and the proinflammatory cytokine IL-6 in the elderly [31]. Vitamin D deficiency is associated with a lower limb strength deficit, preferentially affecting type II muscle fibers. Since vitamin D deficiency is common in many older subjects, much attention has been focused on the potential therapeutic benefits of such supplementation. A meta-analysis consisting of about 29 vitamin D supplementation studies confirmed a small positive effect on muscle strength [32]. To date, ten meta-analyses of falls prevention studies have been published and, except for one meta-analysis which did not show the benefits of supplementation [33], the remaining studies described a reduction in fall rates from 37% to 12% after vitamin D supplementation. Moreover, considering the strong role played by both vitamin D and physical activity on muscle mass and strength, their combination use can represent an ideal strategy for the treatment of sarcopenia.
Clinical studies showed that muscle strength can improve as a result of vitamin D supplementation. 800 IU of vitamin D significantly improved lower limb strength or 4-11% function after 2-12 months of treatment in individuals aged 65 and over. In conclusion, it is recommended to measure the plasma value of vitamin D in frail older people, particularly in those who live in nursing homes, and to carry out vitamin D supplementation to patients with a plasma level below 40 nmol/L [34]. In order to increase serum vitamin D levels to the optimal value of 75-100 nmol/L, the recommended daily dose (between 400 and 600 IU) may not be sufficient. In contrast, intake between 700 and 1,000 IU per day could facilitate the achievement of satisfactory plasma levels of vitamin D.

Omega 3

Essential fatty acids are involved in muscle metabolism.

Since eicosanoids derive from polyunsaturated fatty acids with 20 carbon atoms, fatty acids are among the mediators and regulators of inflammation, which act on the synthesis of muscle proteins through mTOR signaling.
These evidences raise the possibility that dietary intakes of long-chain polyunsaturated n-3 and n-6 acids and their balance in the diet may be important. Omega-3 fatty acids, including linolenic acid and its metabolic products, such as eicosapentaenoic acid and docosahexaenoic acid present in fish oil, promote muscle anabolism, while a high ratio of omega-6/omega-3 may cause higher IL-6 levels, which interfere with IGF-1 mediated processes by blocking the p70s60k protein phosphorylation, necessary for protein synthesis activation [35]. A recent study conducted on 3,000 elderly adults reported that increased consumption of fish oil is associated with increased gripping force [36]. In particular, the long-chain n-3 polyunsaturated fatty acids may be powerful anti-inflammatory agents and may exert direct effects on the synthesis of muscle proteins via mTOR signaling. Therefore, supplementation of n-3 fatty acids could increase muscle mass in older subjects. In a randomized controlled study, the supplementation with n-3 long-chain polyunsaturated fatty acids in elderly patients resulted in an increase of rate of muscle protein synthesis. In a muscle strengthening trial, the use of fish oil supplements (2 g/day) led to greater improvement in muscle strength and functional capabilities compared to a strength training program.
Integration with LCPUFA n-3 (1.86 g of eicosapentaenoic acid, 1.50 g of docosahexaenoic acid acid) in subjects aged between 60 and 85 years old was associated with increased muscular volume of the thigh over the 6-month follow-up period, as compared with subjects that were given corn oil. Muscle strength at follow-up was also higher in the integrated group [37]. These data offer the promise of a simple and low-cost approach to guarantee the prevention and treatment of muscle mass reduction and muscular functions in old age. However, not all tests have confirmed the efficacy of treatment with essential fatty acids in sarcopenia.

Gut microbiota manipulation

The interaction between the human host and its symbiotic microbial inhabitants plays an essential role in defining the health status of the host [38]. The gastrointestinal tract hosts more than 1,000 distinct bacterial species, with important implications for the bioavailability of nutrients, glucose and lipid metabolism, conditioning the immune system response, protection against pathogens, metabolism and drug toxicity. Some diseases such as obesity, type 1 and 2 diabetes mellitus, cardiovascular disease, inflammatory bowel disease, colorectal cancer, fatty liver disease, multiple sclerosis, and autism, have been hypothesized to result from an imbalance between the host and the microbial species caused by changes in the function of the gastrointestinal tract and other age-related events. This human-microbial imbalance can lead to chronic low-grade inflammation, increased susceptibility to systemic infections, malnutrition, drug side effects and possibly accelerated progression of chronic diseases, fragility, and sarcopenia. In view of these observations, appropriate manipulation of the intestinal microbiota could be exploited to achieve therapeutic gain in old age.
A better understanding of the symbiotic relationship between the aging human host and the intestinal microbiota is also of utmost importance in sarcopenia, since this microbial ecosystem is involved in the regulation of inflammatory and redox status, in the splanchnic extraction of nutrients, in the deposition of fat mass, and in insulin sensitivity. Furthermore, the intestinal microbiota can influence (and can be influenced by) the bioavailability and bioactivity of most of the proposed nutritional factors as remedies against sarcopenia.
Three main approaches are currently available to manipulate the composition and function of intestinal microbiota: probiotics, prebiotics and symbiotics. Probiotics are defined as "live microorganisms which, when administered in adequate quantities, confer benefits to the host". Prebiotics are "non-digestible food ingredients that positively affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already residing in the colon" (eg. galacto-oligosaccharides, fruit- oligosaccharides, inulin and lactitol). Finally, symbiotics are food supplements that combine probiotics and prebiotics, the administration of which produces health benefits deriving from the synergistic actions of the two components. These three approaches can improve intestinal function, modulate the function of the immune system, and improve the bioavailability of nutrients. However, no study has yet specifically analyzed the effects of these interventions on muscle aging. Therefore, further research is justified to explore the potential application of its manipulation for the management of sarcopenia.

NUTRITIONAL INTERVENTIONS AGANIST SARCOPENIA IN CLINICAL STUDIES

Being sarcopenia and frailty complex geriatric syndromes, multimodal strategies that include exercise and nutritional intervention seem to be the most sensitive approach for the prevention and improvement of these conditions. The "Sarcopenia and Physics fRailty IN elderly: multi-componenT Treatment strategies "(SPRINTT) is an ambitious multi-center European trial that attempts to demonstrate the effect of multimodal interventions in frail and sarcopenic older subjects. This study was launched by the Joint Initiative for Innovative Medicines Initiative (IMIJU 11561) in 2014 and has recently completed the registration of 1500 participants residing in communities aged 70 or over who are at high risk for developing disability [39]. Eighty researchers from 11 countries conduct the randomized controlled phase III trial, which is aimed at preventing disability mobility with a multi-component intervention (MCI) consisting of a long-term structured physical activity program, personalized nutritional counseling. The control group will receive a healthy lifestyle education program (HALE).

The SPRINTT clinical trial includes an intervention that can support the nutritional program of the planned physical activity; this intervention consists of two phases. In the first phase, all the participants (MCI and HALE) are subjected to a nutritional screening through the Mini-Nutritional Assessment – Short Form (MNA-SF); in the second phase, the participants randomized to the MCI group will receive personalized nutritional recommendations and will be followed for the entire duration of the clinical trial by the nutritionist/dietician, with the support of the study physician and the participant's general practitioner. The nutritionist/dietician must keep in mind various problems that may be present, including oral/dental problems, difficulty swallowing, gastrointestinal problems, poly-pharmacy, chronic pain, depression, any allergies or intolerances, unfavorable social and financial conditions.

Participants of the SPRINTT study receive a personalized diet program from a dietician/nutritionist who elaborates this plan based on anthropometric data, blood chemistry tests, and concomitant clinical problems. The food preferences of the subjects are also considered. Participants in the MCI group complete a three-day dietary record at baseline and at each annual clinical visit, and based on this registration, the dietician/nutritionist determinate the macro and micronutrient to elaborate the diet plan. The nutritional objectives to be achieved are: a total daily energy intake between 25 and 30 kcal/kg, and a daily protein intake between 1.0 and 1.2 g/kg. These objectives can be customized based on the participant's current nutritional status, and on comorbidities (severe kidney dysfunction, obesity, diabetes). In patients with obesity, the total energy requirements should be calculated based on the correct body weight and not on the actual body weight.

In patients with mild chronic kidney disease it is not necessary to reduce the protein intake provided by the SPRINTT protocol. In patients with moderate CKD it is possible to prescribe a protein intake as foreseen in the protocol, but it is necessary to check the creatine values twice a year. In patients with severe CDK, the daily protein intake should not exceed 0.8 g/kg per day. In patients with diabetes mellitus, it is necessary that the dietician finds strategies to increase the protein intake without altering the glycemic compensation.

In case of further situations that require specific dietary measures, for example patients suffering from hypertension that must follow a low sodium diet, it is necessary that the nutritionist/dietician formulate the dietary strategies to obtain the nutritional target foreseen by the study. Finally, the dietician/nutritionist will provide recommendations on how to improve the intake of vitamin D with the diet.

CONCLUSIONS

Nutrition plays an important role both in the prevention and in the management of sarcopenia due to the remarkable evidence linking nutrition with muscle mass and function. However, further high-quality studies are needed to allow an understanding of the dose and duration effects of individual nutrients, to clarify the mechanical connections, and to define optimal profiles and nutrient intake schemes for the elderly. In older populations, wider efforts should be made to promote a quality diet alongside a physically active lifestyle, with the aim of preventing disability. Therefore, the best strategy to prevent and treat sarcopenia in older people is to combine a specific exercise protocol and an adequate intake of amino acids. Moreover, although several promising pharmacological approaches are currently under investigation, these are not yet available to treat sarcopenia in frail older people. HMB supplements showed promising effects in muscle improvement mass and function parameters. Protein supplements did not show consistent benefits on muscle mass and function. For the prevention and treatment of sarcopenia, a balanced diet can be proposed: it is advisable to adhere to the Mediterranean diet and to improve physical activity to obtain a significantly lower risk of sarcopenia and frailty.

Conflict of interest

The authors have no conflict of interest to declare.

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Original Investigation

Daily meat consumption and variation with aging in community-dwellers: results from longevity check-up 7 + project

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Background & aims. Behavioral factors, including protein intake, influence the quantity and quality of skeletal muscle. The aim of this study was to provide a better insight into the comprehension of aging-related changes of daily meat consumption throughout an individual's life span (from 18 to 98 years).

Methods. For the present study, the database Longevity Check-up 7 + (Look-up 7 +) is used. A brief questionnaire exploring lifestyle habits, dietary preferences and the consumption of selected foods was administered. A frequency questionnaire was administered to collect information on how often in a week participants consumed a standardized portion size of meat (beef, pork, chicken or turkey).

Results. The mean age of the 8,144 participants was 55.4 ± 15.1 years (range: 18-98 years), with 4624 (56.8%) women. As compared with participants in the first tertile of daily meat intake, those in the third tertile were younger and showed slightly higher BMI. Systolic and diastolic blood pressure, as well as blood cholesterol level, was similar across different tertiles. Daily meat protein intake (as measured by the daily portion of meat) declined significantly during the young and adult age, both in men and women. Overall, among old subjects the meat-derived protein intake was less than 3.5 grams per day.

Conclusions. The results of the Look-up 7 + survey suggest a significant decline in daily meat-derived protein intake with advancing age. Our findings also indicate that the higher meat consumption does not correlate with higher prevalence of cardiovascular risk factors, such as blood pressure and cholesterol and glucose levels.

Key words: Daily meat intake, Protein quality, Recommended dietary allowance (RDA), Cardiovascular risk factors

INTRODUCTION

The World Health Organization identified the healthy ageing of the global population as an important public health challenge in the 21st century [1]. In addition to providing medical management, healthcare professionals can advise patients about how to maintain wellness and quality of life. This can be achieved by encouraging patients to preserve physical activities, and by providing dietary recommendations and nutrition services to ensure they eat well and their nutrient needs are met [2]. An adequate intake of dietary protein is vital to muscle health as it ensures the provision of essential amino acids (EAAs), which in turn stimulate muscle anabolism [3]. The recommended protein intake, referred to as recommended dietary allowance (RDA) for protein, is based on the results of nitrogen balance studies as meta-analyzed by Rand et al. [4]. Accordingly, a daily intake of ~ 0.8 g of good-quality proteins per kg of body weight is currently promoted by the World Health Organization as the amount that is sufficient to satisfy the metabolic demand and to achieve nitrogen equilibrium in 97.5% of the adult population [5]. Besides quantity, protein quality has a relevant influence on the health status. Protein quality is mainly determined

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by the amino acid profile (in particular, EAA content), digestibility, and absorption kinetics [6]. In this context, it is important to highlight that the consumption of a moderate amount of lean meat-based high-quality protein maximally stimulated muscle protein synthesis both in young and old people [7]. Notably, animal-derived protein was reported to stimulate protein synthesis to a greater extent than vegetable protein in older subjects both at rest and post-exercise [8]. Furthermore, greater protein consumption, especially of animal origin, has recently been associated with higher levels of physical performance in community-dwelling older adults [9]. These findings emphasize the relevance of ingesting adequate amounts of high-quality protein to promote muscle health and physical function across different age groups. The present study was, therefore, undertaken to provide a better insight into the comprehension of aging-related changes of daily meat consumption throughout an individual's life span (from 18 to 98 years), using an unselected sample of subjects assessed during the Longevity Check-up 7 + project.

MATERIALS AND METHODS

For the present study, the database Longevity Check-up 7 + (Look-up 7 +) is used. The Look-up 7 + study protocol has been previously described in detail elsewhere [10 11]. Briefly, this project is an ongoing initiative developed by the Geriatric Medicine Department of Catholic University of Rome planned with the aim to improve healthy lifestyles in the general population [11]. Subjects entering public environments (i.e., exhibitions, shopping centers, sport events) or subjects participating in prevention campaigns have been screened using a specific questionnaire on lifestyle and had a brief check-up, specifically assembled on the basis of the ideal cardiovascular health metrics indicated by the American Heart Association [12]. Participants are selected as eligible if they are at least 18 years of age and provide written informed consent. The exclusion criteria are: self-reported pregnancy, incapacity to perform the physical performance tests, denial of blood capillary check, and the refusal to give written informed consent. The Catholic University of Sacred Heart Ethical Committee ratified the study protocol [13].

Study sample

Between June 1st, 2015 and October 30th, 2017, we enrolled 8242 subjects. Recruitment took place in several Italian cities adhering to the Look-up 7 + project: Milan EXPO 2015 (Milan, June-October 2015), Mese del Cuore (Rome, September-October 2016), La Romanina (Rome, December 2017), Mese del Cuore (Milan, March-April 2017), Ministry of Health Women's Day (Rome, April 2017), CamBio Vita (Catania, May 2017), COOP shopping centers (Bologna, Modena, Genoa, Rimini, Grosseto, May-June 2017), Mese del Cuore (Rome, September-October 2017), Tennis&Friends (Rome, October 2017), CONAD shopping centers (Terni, Perugia, Viterbo, Anzio, Caserta, November 2017) and Longevity Run (Rome, April 2018). For the present study, 98 subjects were excluded for missing values in the variables of interest; as a consequence, a sample of 8144 subjects was considered.

Data collection

Seven parameters indicated as the most important cardiovascular risk factors [13 14], were assessed through closed questions and direct measurements. Smoking habit was categorized as current or never/former smoker. Sedentariness was considered as the lack of involvement in any kind of physical activity. Body weight was assessed by an analogue medical scale, while a standard stadiometer was used to measure body height. The body mass index (BMI) was then calculated as the weight (kg) divided by the square of height (m). Healthy diet was considered as the consumption of at least three portions of fruit and/or vegetables per day. Cholesterol was measured from capillary blood samples using disposable electrode strips based on a reflectometric system with a portable device (MultiCare-In, Biomedical Systems International srl, Florence Italy) [15]. Blood glucose was measured from capillary blood samples using disposable electrode strips based on an amperometric system with a MultiCare-In portable device [15]. Blood pressure was measured – in the sample Milan EXPO 2015 – with a clinically validated Omron M6 electronic sphygmomanometer (Omron, Kyoto, Japan), and in all other samples with a manual sphygmomanometer according to recommendations from international guidelines [16].

Dietary assessment

A frequency questionnaire was administered to collect information on how often in a week participants consumed a standardized portion size of meat (beef, pork, chicken or turkey). For the present study, the mean daily intake of meat-derived protein was calculated by multiplying the consumption frequency of meat by the mean protein content of its standard portion, then dividing by seven (the days of a week). The daily meat-derived protein intake was calculated considering the average amount of 25.0 grams of protein for each portion of any meat.

Statistical analyses

Data are expressed as proportions (%) or mean ± standard deviation (SD). For analytical purposes, three groups of daily meat-derived protein intake were created based on the tertiles of this variable: first tertile (5.85.2 g/day;

n = 2183), second tertile (> 5.85 and < 8.78 g/day; *n* = 2617), and third tertile (8.78 g/day; *n* = 3344).
The characteristics of the study sample are presented according to the tertiles of meat-derived protein intake. Differences in proportions or means of covariates among tertiles were assessed using Fisher's Exact Test and ANCOVA, respectively.
All analyses were performed using the SPSS software package (version 11.0, SPSS Inc., Chicago, IL).

RESULTS

The mean age of the 8,144 participants was 55.4 15.1 years (range: 18-98 years), with 4624 (56.8%) women. The main characteristics of the study sample according to the tertiles of meat protein consumption are presented in Table I. As compared with participants in the first tertile, those in the third tertile were younger, had a higher prevalence of smoking habit, and showed slightly higher BMI. Conversely, participants in the third tertile were characterized by a marginally lower prevalence of healthy diet compared with the other participants. Systolic and diastolic blood pressure, as well as blood cholesterol level, were similar across different tertiles. Finally, serum glucose level was significantly lower among participants in higher tertile group of meat consumption compared with subjects with lower daily meat intake.
Figure 1 shows the mean and standard deviation of daily meat-derived protein intake across age groups. Meat protein intake (as measured by the daily portion of meat) declined significantly during the young and adult age, both in men and women. In particular, among men, daily meat protein intake decreased significantly from 18 years (11.1 grams) to 50-54 years (7.4 grams); after 55 years of age a further slightly decline is observed with a loss of 4.4 grams per day in the group of oldest subjects (11.1 grams *vs* 6.7 grams, respectively; $p < 0.001$). Similarly to men, a linear meat protein intake decline was detected in women, with about a 2.4 grams difference between the youngest group and the oldest group (8.9 grams *vs* 6.5 grams, respectively; $p < 0.001$).

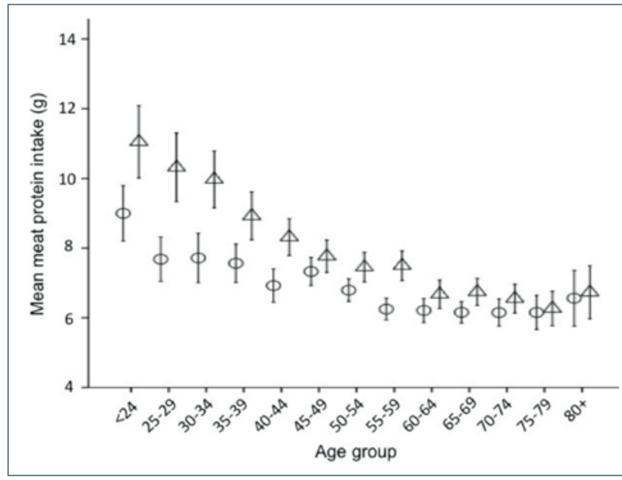

Figure 1. Meat protein intake (mean and SD) according to age group and gender (triangle for men, circle for women).

DISCUSSION

In the present study, we explored the association between habitual consumption of meat-derived protein and age in a large sample of unselected community-dwelling adults. Our findings show that the mean daily meat-derived protein intake significantly decreased with advancing age. In particular, people over 50 years old showed a meat intake of about half of that they eat at

Table I. Characteristics of study population according to the daily meat-derived protein intake tertiles*.

Characteristic	Total sample (*n* = 8144), protein intake tertiles			
	I (*n* = 2183)	II (*n* = 2617)	III (*n* = 3344)	P for trend
Age, years	58.5 ± 13.8	56.6 ± 14.4	52.4 ± 15.7	< 0.001
Gender (female)	1361 (62.3)	1504 (57.5)	1759 (52.6)	< 0.001
Smokers	351 (16.1)	410 (15.7)	616 (18.4)	0.01
Regular physical activity	1251 (57.6)	1479 (57.0)	1735 (52.4)	0.51
Healthy diet	1601 (73.4)	1902 (72.7)	2263 (67.7)	0.03
Body Mass Index (kg/m^2)	25.3 ± 4.3	25.5 ± 4.0	25.9 ± 4.5	< 0.01
Systolic blood pressure (mmHg)	125.9 ± 16.9	125.7 ± 17.0	125.3 ± 16.8	0.37
Diastolic blood pressure (mmHg)	75.8 ± 10.1	75.8 ± 9.9	75.6 ± 10.0	0.66
Cholesterol (mg/dl)	209.6 ± 33.9	211.5 ± 33.6	210.4 ± 34.6	0.16
Blood glucose (mg/dl)	104.9 ± 23.6	103.0 ± 23.0	102.6 ± 23.4	< 0.01
Daily meat protein intake (g)	2.1 ± 1.2	5.8 ± 0.9	11.2 ± 3.3	< 0.001

*Data are given as number (percent) for gender, smoking, physical activity, healthy diet; for all the other variables, means ± SD are reported.
Regular physical activity: physical exercise at least twice a week.
Healthy diet: consumption of at least three portions of fruit and/or vegetables per day.

a young age. Furthermore, it is important to underline that the greater consumption of meat was higher in men, but overall it was not associated with the higher levels of blood pressure or serum cholesterol levels. On the contrary, subjects who consumed more portions of meat per week showed lower blood glucose levels.

Recent evidence suggests that an adequate protein intake is required for the preservation of lean body mass and muscle function across different life stages [17 18]. This is particularly relevant considering that, for muscle strength (as measured by hand grip test) and physical performance (as measured by chair stand test), there is stability in the first decades of adulthood, and decrements in the middle years (45 +) and late adulthood. In particular, individuals of more than 75 years lose about 60% of their muscle strength and 30% of their physical function. We previously observed a linear pattern of age-decline that was surprisingly similar in men and women, and in different race, across the entire course of life [19 20]. Loss of muscle mass and function has a multifactorial origin; however, lifestyle factors, including poor nutrition and sedentary behavior, seem to play a major role [21]. Indeed, the combination of nutritional interventions and physical activity is to date the most effective strategy to counteract muscle aging [22].

Meat contains a large quantity of essential amino acids and nutritional factors of high quality and availability, including minerals like iron and zinc, and a variety of vitamins, especially B group vitamins, and even a modest intake can improve muscle protein synthesis in older subjects. Nevertheless, several studies indicate that the consumption of different meats, with high intake of processed meats, may enhance the risk of negative health-related events, including cardiovascular disease, metabolic syndrome, type-2 diabetes, cancer, and death [23]. However, risks for fresh white and red meat are significantly less, and moderate consumption is encouraged as part of a healthy diet plan for older population to guarantee an adequate protein intake. Other nutritional strategies of importance for lean body mass loss include fortifying the nutrient value of meats. Some studies on muscle cells and animal models recognized the potential effects of the amino acid, for example glycine, to downgrade inflammation, reduce muscle mass loss, and improve muscle cells anabolic stimuli. Notably, greater consumptions of animal-derived proteins have recently been associated with lower insulin resistance, inflammation, arterial stiffness, blood pressure, and adiposity-related metabolites in adult twins, independent of genetics [2 24 25].

Although reporting potentially relevant findings, our study presents limitations that need to be discussed. First, due to the particular setting in which the investigation was conducted, we could not administer a comprehensive dietary questionnaire. Second, the study setting may have influenced the assessment of some health metrics. Indeed, random cholesterol and glucose determinations could overestimate both parameters. Furthermore, cholesterol and glucose levels were determined in capillary blood samples. Even though this procedure was previously validated [10], the standard error of portable devices is higher than the standard equipment. Third, although anthropometric measures are frequently adopted for estimating lean body mass, they do not represent the gold standard for the quantification of muscle mass. Finally, although blood pressure was measured according to international guidelines, it is likely that the particular settings where the study sample has been enrolled may have influenced the measurement outcome.

In conclusion, the results of the Look-up 7 + survey suggest a significant decline in daily meat-derived protein intake with advancing age. Our findings also indicate that the higher meat consumption does not correlate with higher prevalence of cardiovascular risk factors, such as blood pressure, cholesterol and glucose levels. These results form the basis for future investigations aimed at establishing the possible strategies to increase protein intake among old subjects. Some studies addressed the potential diet for preventing sarcopenia that proposes eating meat 3-5 times a week (including white meat twice per week, lean red meat less than twice per week, and processed meat less than once per week) [26]. In the context of sarcopenia, where reduced protein intake has significant health implications for older people, particular attention should be focused on increasing protein through meats, fish and vegetable sources, and through supplements and fortified foods [6 27 28].

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Author contributions

All of the authors participated in the conceiving, design and writing of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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