Table 1 Characteristics of long-term care elderly and healthy elderly controls

	LTC elderly	Controls	*P*
No. participants	105	17	
Age (years)	86.5 ± 6.0 (75–100)	86.3 ± 9.1 (75–103)	0.311
Sex, male (%)	29 (27.6)	6 (35.3)	0.999
Body mass index	19.5 ± 3.3	22.0 ± 3.5	0.009
Cardiovascular risk factors, *n* (%)			
Hypertension	57 (54.3)	11 (64.7)	0.590
Diabetes mellitus	13 (12.4)	2 (11.8)	0.999
Hyperlipidemia	14 (13.3)	3 (17.6)	0.921
Chronic heart failure	12 (11.4)	1 (5.9)	0.792
Ischemic heart disease	15 (14.3)	1 (5.9)	0.572
Physical function			
FIM	46 ± 26	116 ± 24	<0.001
Barthel Index	30 ± 31	92 ± 16	<0.001
Blood nutritional data			
Albumin (g/dL)	3.5 ± 0.5	3.9 ± 0.3	<0.001
Hemoglobin (g/dL)	12.0 ± 1.8	12.4 ± 2.2	0.188
Total cholesterol (mg/dL)	177 ± 40	175 ± 34	0.892
Heart rate variability indices			
SDANN	85.0 ± 34.3	112.1 ± 27.2	0.001
Heart rate (b.p.m.)	73.1 ± 12.1	71.5 ± 7.4	0.878
LF (ms^2)	36.1 ± 25.3	42.4 ± 37.5	0.274
HF (ms^2)	65.9 ± 56.3	60.7 ± 52.3	0.813
LF/HF	0.69 ± 0.27†	0.87 ± 0.31	0.023

Values are mean ± standard deviation. †After adjusted for age, sex, cardiovascular risk factors and Function Independent Measure (FIM), low frequency/high frequency (LF/HF) were significantly lower in long-term care elderly than healthy controls ($P = 0.049$). HF, high frequency; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Results

We registered 105 elderly in LTC, and assessed HRV from 24-h Holter monitoring. The underlying diseases of older adults in LTC for rehabilitation were cerebrovascular disease ($n = 59$, 56.2%), disuse syndrome ($n = 26$, 24.8%), fracture ($n = 19$, 18.1%) and dementia ($n = 1$, 1.0%). The proportions of underlying diseases were similar to those reported in Japanese older adults in LTC.[3]

The background data of the present study are shown in Table 1. In LTC elderly, mean age was 86.5 ± 6.0 years, blood nutritional data including albumin, hemoglobin and total cholesterol were at the lower limit of the normal range, and physical function represented by FIM and Barthel Index was significantly lower (46 ± 26 and 30 ± 31, respectively) than that in elderly controls (116 ± 24 and 92 ± 16, respectively). Scores for each FIM item were as follow: eating 3.7 ± 2.2, grooming 2.6 ± 1.8, bathing 1.5 ± 1.1, upper body dressing 2.5 ± 1.7, lower body dressing 2.2 ± 1.6, toileting 2.7 ± 2.0, bladder management 2.6 ± 2.1, bowel management 2.4 ± 2.0, bed to chair transfer 3.0 ± 1.9, toilet transfer 2.4 ± 1.7, shower transfer 1.5 ± 1.4, locomotion (ambulatory or wheelchair level) 2.0 ± 1.8, stairs 1.2 ± 0.8, cognitive comprehension 3.6 ± 2.2, expression 3.6 ± 2.2, social interaction 3.2 ± 2.2, problem solving 2.8 ± 1.9 and memory 2.8 ± 1.9. These score showed that the overall participants required moderate care supporting physical and cognitive function. In addition, BMI, albumin, SDANN and LF/HF were significantly decreased in LTC elderly compared with elderly controls. After adjustment for covariance, of all HRV indices, only LF/HF was significantly lower in LTC elderly (Table 1). Data of HRV indices were obtained every 5 min, and averaged every 3 h to examine the circadian rhythm in both LTC elderly and healthy controls. A significant decrease of LF/HF was observed in the night-time in healthy controls, whereas there was a loss of circadian rhythm in LTC elderly (Fig. 1).

Multiple regression analysis showed that the associations between heart rate, SDANN and physical function (Barthel Index and FIM) were independent of age, sex, and CVD. Furthermore, albumin and hemoglobin were also correlated with heart rate and SDANN. In contrast, LF, HF and LF/HF were not significantly correlated with physical function and blood nutritional data (Table 2).

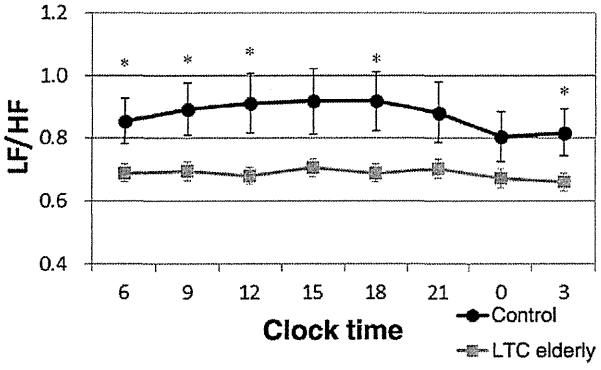

Figure 1 The activity of low frequency/high frequency (LF/HF) in long-term care (LTC) elderly and controls. The RR interval data were measured every 5 min, and averaged every 3 h. $*P < 0.05$, mean ± SEM.

Next, we followed the survival of LTC elderly, and 23 people died among 105 LTC elderly during a mean follow-up period of 8.9 months. The major cause of death was pneumonia ($n = 12$). There was no sign of stroke among the study participants, and one participant with acute myocardial infarction was observed during the follow-up period. Mortality according to HRV indices divided by the average is shown in Table 3. After adjustment for covariates, of all HRV indices, only LF/HF was associated with mortality. Kaplan–Meier survival curves also showed an association between decreased LF/HF and high mortality (Fig. 2). In addition to adjusted covariates, BMI, Barthel Index, and blood nutritional data were not different between the high LF/HF group and low LF/HF group (data not shown).

Discussion

In the present study, we investigated the relationship between physical function, mortality and sympathetic nervous activity measured by HRV in Japanese LTC elderly, and it was shown that LF/HF was significantly decreased in LTC elderly after adjustment for age, sex, CVD risk factors and FIM compared with elderly controls. In addition, the circadian rhythm of LF/HF was lost in LTC elderly, and low LF/HF was associated with overall mortality.

In a previous study, low LF/HF was associated with both frailty and mortality in community-dwelling people of whom one-third were frail elderly,[9] and these associations were consistent with the present data. Additionally, low LF/HF was also shown in LTC elderly, and was independent of physical function.

Elevated heart rate or low SDANN leads to cardiovascular disease and low physical function,[17,18] and the same relationship was also observed in LTC elderly. Furthermore, low albumin and low hemoglobin were observed in the high heart rate group, and limited physical function was observed in LTC elderly. These results are supported by a previous report.[19] So it might be possible to improve the physical function of LTC elderly by maintaining their nutritional state. The high LF/HF group has been reported to show high physical function and muscle mass,[4,20] whereas the present data did not show this association. One of the reasons for this discrepancy is thought to be the effect of aging. Aging generally attenuates LF/HF, and the patients in the present study were older than those in other studies.[9,14] Another reason might be autonomic nervous system disturbance. In particular, the circadian rhythm of LF/HF was impaired in LTC elderly.

Circadian imbalance of LF/HF has been shown in some disorders, such as Parkinson's disease, type 2 diabetes mellitus (T2DM) and ischemic stroke;[21–23] and furthermore, physical activity also influences HRV indices.[24,25] In the present study, LTC elderly with Parkinson's disease were excluded, and CVD risk factors including T2DM were matched between LTC elderly and healthy controls, as stroke and physical activity might affect LF/HF. However, the influence of both conditions on LF/HF is controversial. High physical activity and good posture led to high LF/HF activity,[26] whereas it was also suggested that LF/HF was not affected by physical activity.[13] The effect of LF/HF on stroke is also controversial.[23,27,28] In ischemic stroke patients, LF/HF was higher than healthy controls in some studies,[27,28] whereas another study suggested that LF/HF was lower in patients.[23] So the mechanism of LF/HF circadian rhythm disturbance is not clear, though its recovery might be important to increase physical function in LTC elderly. Other reasons why LF/HF and physical function did not show a correlation in LTC elderly might to be the effects of stroke, insufficient exposure to daylight and posture at daytime. All participants were aged over 75 years in the present study, and there is a possibility that asymptomatic lacunar infarction might be observed. It has also been suggested that lacunar infarction disturbs the autonomic nervous system, leading to a decrease in LF/HF and the related value of the autonomic nervous system, resulting in a disappearance of the correlation between physical activity and LF/HF. In addition, exposure to daylight was known to be one of the most powerful rhythmic regulators in the environment.[29] All participants in the present study spent their time indoors for rehabilitation and care. Furthermore, it is known that the supine position increases HF and decreases LF/HF,[30] and LTC elderly participants who were at rehabilitation units or health service facilities might spend more time in bed compared with outpatient controls, leading to low LF/HF and disappearance of the correlation between LF/HF and physical activity in the present study.

Table 2 Multiple regression analysis of heart rate variability indices with physical function and blood nutritional data after adjusted for age, sex and cardiovascular risk factors

	HR	SDANN	LF	HF	LF/HF
FIM	−0.25*	0.28*	0.19	0.15	−0.08
Barthel Index	−0.27*	0.29*	0.08	0.04	0.00
Body mass index	−0.05	0.05	0.00	−0.08	0.19
Albumin	−0.21*	0.25*	0.05	−0.02	0.11
Hemoglobin	−0.20*	0.27*	0.12	0.12	0.05
Total cholesterol	−0.01	−0.05	−0.13	−0.17	0.03

*$P < 0.05$, analyzed in 105 long-term care elderly. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Table 3 Proportional hazards regression analysis of the impact of heart rate variability measure on overall mortality

	Hazard ratio†	95% Confidence interval	*P*
Unadjusted			
SDANN (ms)	1.84	0.77–4.38	0.171
LF (ms^2)	1.61	0.59–4.38	0.353
HF (ms^2)	2.14	0.72–6.34	0.169
LF/HF	4.73	1.59–14.06	0.005
Age, sex and cardiovascular risk factors adjusted for association with mortality			
SDANN (ms)	1.53	0.60–3.86	0.372
LF (ms^2)	1.65	0.57–4.78	0.357
HF (ms^2)	2.60	0.82–8.22	0.105
LF/HF	3.37	1.02–11.07	0.046
Age, sex, FIM and cardiovascular risk factors adjusted for association with mortality			
SDANN (ms)	1.19	0.44–3.17	0.736
LF (ms^2)	1.49	0.50–4.41	0.475
HF (ms^2)	2.85	0.83–9.83	0.097
LF/HF	3.61	1.08–12.10	0.038

Based on 23 deaths among 105 participants. Mean values of heart rate variability measure are in Table 1. †Hazard ratio of death rates of participants whose heart rate variability were less than average. FIM, function independent measure; HF, high frequency; HR, heart rate; LF, low frequency; SDANN, standard deviations of the all NN intervals in all 5-min segments of the entire recording.

Recent studies showed that decreased HRV indices including LF, HF and LF/HF were associated with CVD risk factors, and decreased LF was an independent predictor of death in elderly people.[31,32] However, the present findings showed that, of all HRV indices, only LF/HF was associated with mortality. This result is supported by a previous study in which, of HRV indices, LF/HF was associated with both frailty and mortality.[9] The major difference between the present study and other studies is whether or not the participants included frail LTC elderly. All participants were LTC elderly in the present study and WHAS-I, which was reported by Varadhan *et al.* and consisted of one-third frail elderly, whereas in other studies the participants were community-dwelling older adults with intact ADL, and they did not consider physical function.[14,32,33] These results suggest that the significance of LF/HF might differ between LTC elderly and elderly with intact ADL and physical function.

There is a discrepancy in the results derived from studies of LTC elderly and studies of elderly with intact physical function regarding sympathetic nervous activity. Exercise activates the sympathetic nervous system, leading to an increase in blood pressure, muscle blood

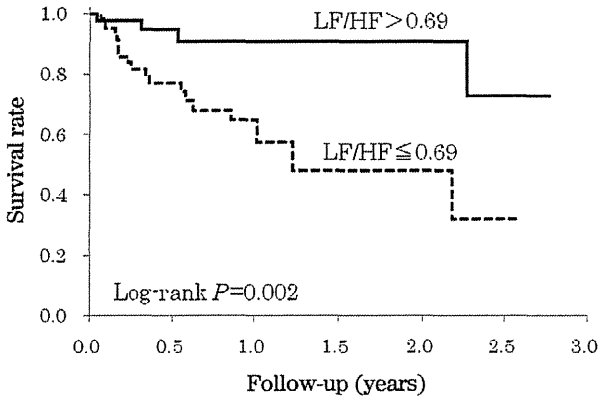

Figure 2 Kaplan–Meyer survival curves for death according to low frequency/high frequency (LF/HF). Mortality was significantly higher for patients with low LF/HF than for patients with high LF/HF. The mean follow-up period was 8.9 months.

flow and muscle strength by inducing muscle protein synthesis,[34–37] suggesting that low sympathetic nervous activity is related to not only physical dysfunction, but also the inability to maintain muscle strength, leading to a worse outcome in LTC elderly. Appropriate activation of the sympathetic nervous system might prevent muscle wasting and improve overall mortality in LTC elderly.

Activation of the sympathetic nervous system has been applied to aging or sarcopenic model rats. The β2-adrenergic agonists, clenbuterol and formoterol, improved muscle mass and muscle strength, and prevented muscle aging in aging, disuse and sarcopenia[38–44] model rats. In contrast, inhibition of sympathetic nervous activity with β-blockers was associated with a worse outcome in older adults.[45] These findings also suggest the importance of preventing a sympathetic nervous activity decline in LTC elderly.

There were several study limitations. First, this was an observational study, and could not provide direct evidence of causality. So it will be necessary to carry out randomized controlled trials to show whether high sympathetic nervous activity leads to a good outcome or not. Second, excessive sympathetic nervous activity is associated with cardiovascular risk factors, such as hypertension, left ventricular myocardial hypertrophy and old cerebrovascular disease.[46,47] In addition, the number of control subjects was relatively small in the present study. Based on these results, it might be hard to apply the findings in the present study to the oldest old population in general. However, some studies, particularly in the elderly, showed that decreased sympathetic nervous activity was associated with a worse outcome.[9] In addition to low physical activity, poor handgrip strength and frailty are known to be important risk factors predicting death older adults,[2,48–50] and few reports have focused on LTC elderly. Therefore, the present study has the possibility of providing evidence to improve physical function and mortality in LTC elderly by means of maintaining or increasing LF/HF.

In summary, the present study showed that LF/HF is a factor that distinguishes LTC elderly from elderly controls independent of physical function. In addition, the circadian rhythm of LF/HF was lost in LTC elderly. Furthermore, low LF/HF was associated with high mortality. For LTC elderly aged 75 years or over, LF/HF might be a predictive biomarker of physical function and mortality.

Disclosure statement

There is no financial support or relationship that might pose conflicts of interest.

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サルコペニアの定義と診断法

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サルコペニアは“加齢に伴う筋肉量の減少”という意味であるため，一義的には筋肉量減少を中心として考えるべきであるが，EWGSOPやSSCWDでは同時に発生する歩行機能や握力などの身体機能の低下と関連づけて定義されている．我が国のデータによれば，身体機能の低下は必ずしも筋肉量減少と並行して起こるわけではないので，今後我が国独自で移動能力の低下，転倒，ADL・QOLの低下，要介護状態の招来，施設入所，入院など臨床的意義と関連づけてサルコペニアを定義する必要がある．

サルコペニアの概念

- サルコペニアの本来の概念は“加齢に伴う筋肉量の減少”である
- EWGSOPではサルコペニアを筋肉量低下，筋力低下，身体機能の低下の3つの要因で捉えている

サルコペニアの一般的な概念は“加齢に伴う筋肉量の減少”であり，これと相俟って高齢者では筋力，身体機能が低下する．サルコペニアの定義として，European Working Group on Sarcopenia in Older People（EWGSOP）が2010年8月にEuropean consensusを発表した．それによるとサルコペニアを，筋肉量低下（low muscle mass），筋力低下（low muscle strength），身体機能の低下（low physical performance）の3つの要因に分けて考え，筋肉量低下を必須の要因として，これに筋力低下，身体機能の低下が加わることでサルコペニアの段階が上がっていくよう提唱している（図1）[1]．

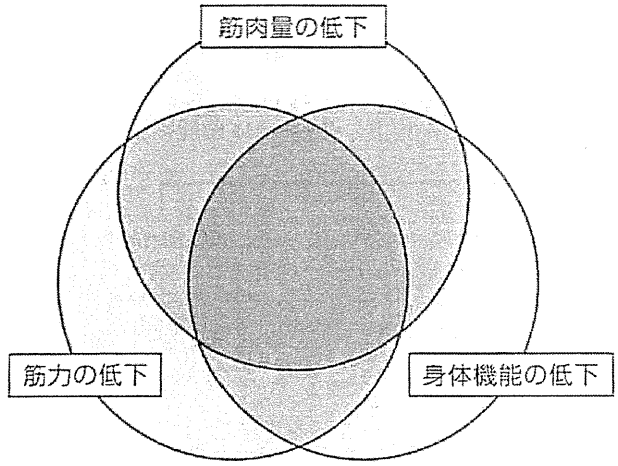
サルコペニアの分類

- サルコペニアは原因によって一次性と二次性に分類される

サルコペニアは原因によって二次性と一次性に分けることができる．

二次性は，①活動能力の低下によるもの，②悪性腫瘍や慢性閉塞性肺疾患（chronic obstructive pulmonary disease；COPD），重症心不全などの器質性疾患によるもの，③栄養状態の低下によるもの，に分けられている．

一次性は加齢以外に原因が明らかでない場合である．



前サルコペニア　：筋肉量の低下
サルコペニア　：筋肉量の低下＋筋力の低下または身体機能の低下
重度のサルコペニア：筋肉量の低下＋筋力の低下＋身体機能の低下

図1　サルコペニアの3つの要因

（文献[1]より改変）

サルコペニアは“加齢性筋肉減少症”と訳されているので，加齢が原因であることが圧倒的に多いが，二次性の場合，高齢者でなくともサルコペニアの状態になることがある．また，一次性の場合であっても実際には二次性の要因が重なって起こることも多い．

サルコペニアの定義

- EWGSOPコンセンサスレポートでは歩行速度（0.8m/秒以下），握力，筋肉量を測定し，フローチャートに従ってサルコペニアを診断する
- SSCWDでは歩行速度（1m/秒以下）または6分間歩行距離（400m未満）と筋肉量減少（YAM－2SD未満）を移動能力の低下したサルコペニアの定義としている

(1) EWGSOPの定義

EWGSOPのコンセンサスレポートではサルコペニアの診断の流れを示しており，図2に示すようにまず身体機能として歩行速度を測定し，0.8m/秒以下であれば，次に筋肉量を測定し，低値であればサルコペニア，正常であれば“サルコペニアではない”と診断する．一方，歩行速度が0.8m/秒超であった場合，筋力として握力を測定し，低値であった場合，筋肉量の測定に合流するという流れになっている．あくまでも筋肉量の低下がサルコペニアの診断に必須であることが分かる．

(2) SSCWDの定義

EWGSOPが筋肉量の低下を必須と定めているのに対して，Society on Sarcopenia, Cachexia and Wasting Disorders（SSCWD）では歩行機能の低下を前提とした筋肉量の低下をサルコペニアと呼ぶよう定義している[2]．

具体的には図3に示すように歩行速度1m/秒以下もしくは6分間歩行距離が400m未満であって，かつ筋肉量が若年者の平均の2SD未満であった場合“移動能力の低下したサルコペニア”と呼ぶ．

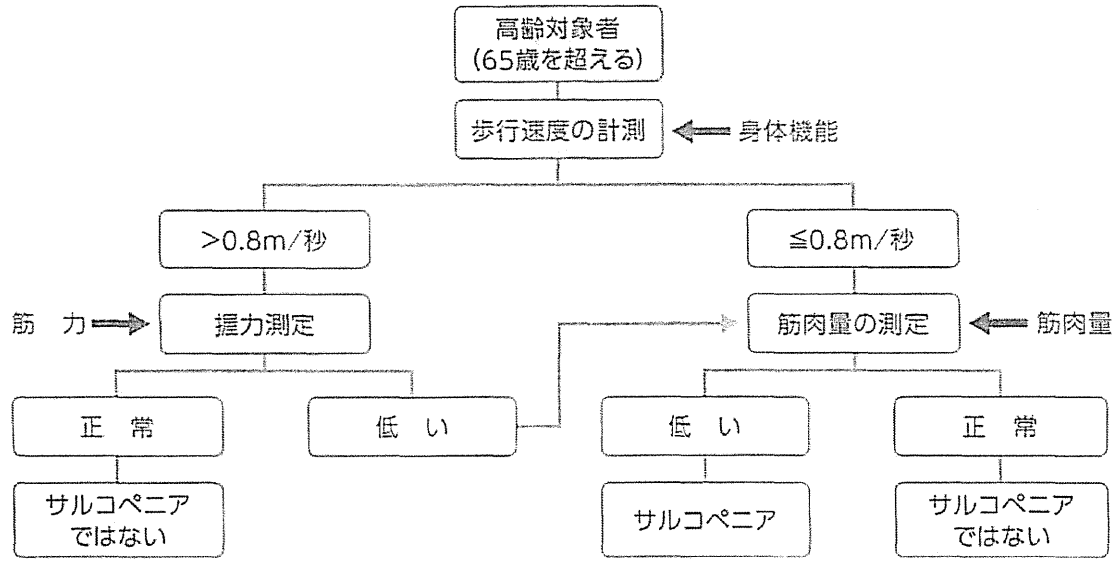


図2　高齢者におけるサルコペニア診断の流れ

(文献[1]より改変)

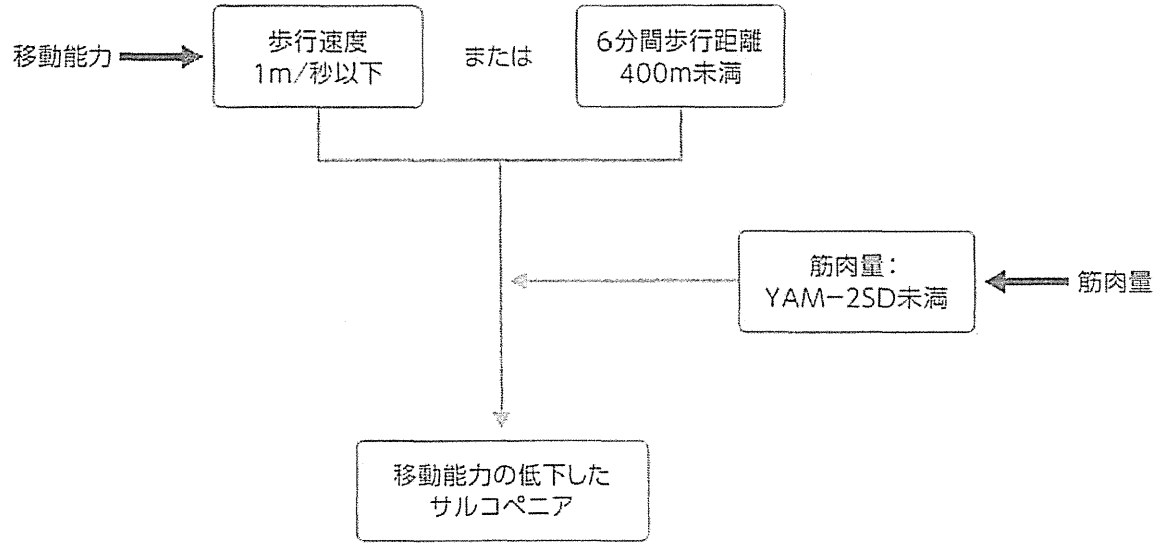


図3　移動能力の低下したサルコペニアの診断手順

YAM：若年成人平均値 (young adult mean)

(文献[2]を基に作成)

サルコペニアの診断の実際

- 握力は男性30kg未満，女性20kg未満が1つの基準になる
- 筋肉量はDXAでのYAM－2SD(男性6.87kg/m^2, 女性5.46kg/m^2) が基準になる

EWGSOPでは歩行速度，握力，筋肉量で診断するが，握力，筋肉量については基準値が設定されておらず，また，歩行速度0.8m/秒は遅すぎるのではないか（基準値設定の根拠が不十分），という問題点が指摘されている．歩行速度に関しては，日本の横断歩道を渡るために必要な1m/秒のほうがよいとの意見が多い．下方らの一般地域住民の長期

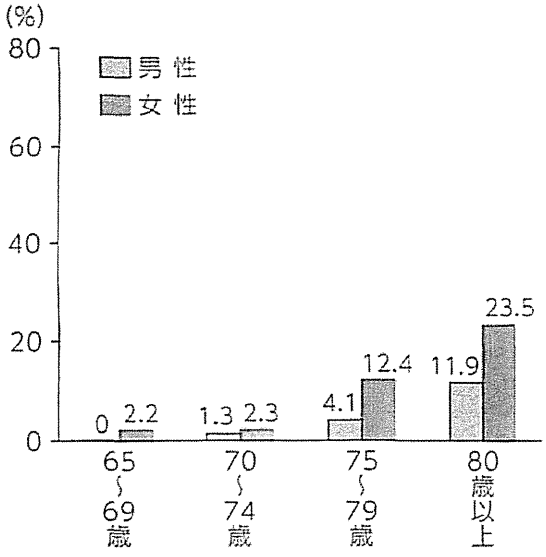


図4 性・年代別に見た歩行速度低下者（1m/秒以下）の頻度

（文献[3]より引用）

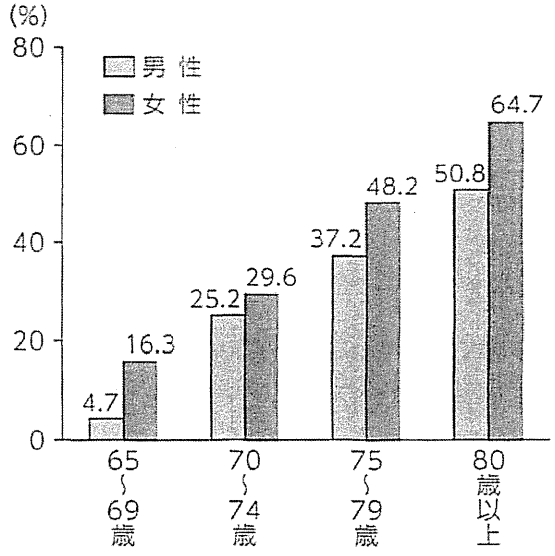


図5 性・年代別に見た握力低下者（男性31kg未満，女性20kg未満）の頻度

（文献[3]より引用）

縦断疫学研究（National Institute for Longevity Sciences-Longitudinal Study of Aging；NILS-LSA）では，通常歩行速度が1m/秒以下の男女の頻度は図4に示すように，加齢に伴って増加することが報告されている[3]．

握力の基準としては介護予防に用いられている男性30kg未満，女性20kg未満が1つの基準になると思われる．同じくNILS-LSAのデータでは，男性31kg未満，女性20kg未満の対象者の頻度は80歳以上で男性50.8%，女性64.7%となっている（図5）[3]．

筋肉量については，二重エネルギーX線吸収測定法（dual-energy X-ray absorptiometry；DXA）による筋肉量測定で，補正四肢筋量（四肢の筋肉量の総和を身長の二乗で補正した数値）が若年成人平均値（young adult mean；YAM）の2標準偏差（YAM－2SD）未満がgold standardとされ[4]，我が国ではSanadaらの基準値である男性6.87kg/m^2，女性5.46kg/m^{2}が用いられている[5]．同数値を基準値として用いたNILS-LSAのデータでは，80歳以上の筋量減少の頻度は男性

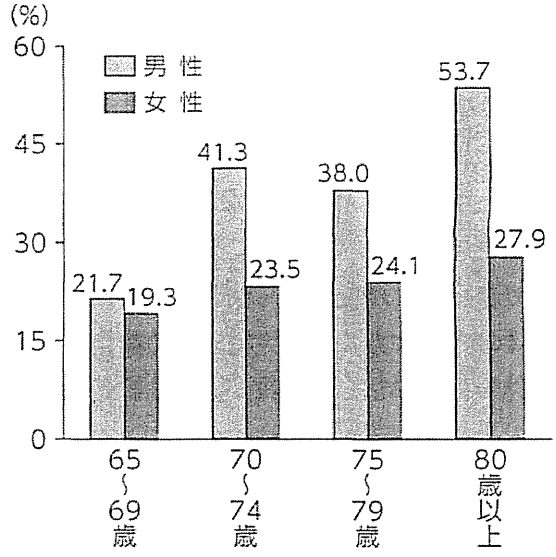


図6 性・年代別に見た筋肉量低下者（YAM－2SD）の頻度

（文献[3]より引用）

53.7%，女性27.9%となっている（図6）．

筆者が勤務する杏林大学医学部付属病院高齢診療科ともの忘れセンターで，外来通院患者を対象としてEWGSOPのアルゴリズムに基づいて，高齢サルコペニア患者の実態を調査した．

歩行速度は0.8m/秒，握力は男性30kg，女性20kgを用い，DXAでの筋肉量は男性6.87kg/m^2，女性5.46kg/m^{2}に相応するインピーダンス法での値，すなわち男性8.87kg/m^2，女性7.0kg/m^{2}を用いた．その結果，男性52名のうち35名（67%），女性85名のうち42名（49%）がサルコペニアの範疇に入ることが分かった．厳密に比較できる対照がないが，この数値は一般高齢者に比べて非常に高いと考えられる．

サルコペニアの診断の課題

- DXAに代わる筋肉量測定法の導入が必要である
- 我が国でのサルコペニア診断基準の開発が必要である
- その際，筋肉量減少だけでなく，移動能力の低下，転倒，ADL・QOLの低下，要介護状態の招来，施設入所，入院など臨床的問題点と関連づけることが必要である

サルコペニアは日常臨床の中で診断されるべきものである．しかるに，筋肉量の測定は現在DXAの使用がgold standardとなっている．汎用性を考えればDXAに代わる信頼性の高い筋肉量測定法が，サルコペニア診断に導入される必要がある．

もう1つの重要な課題は，サルコペニアの診断は世界的にも我が国でも統一されていないことである．そのような状況では各地域，各国でのサルコペニアの実態を比較することはできない．今後，何らかの統一的な基準を設ける必要があるが，人種による体格差は大きいので，少なくとも我が国で診断基準を定める必要がある．その際，サルコペニア（加齢性筋肉減少症）という言葉にとらわれすぎるのは適切ではないと考えられる．SSCWDがそうであるように，筋肉量減少を歩行などの身体機能の低下と関連づけて考える必要がある．

実際，加齢に伴う筋肉量の減少は女性では男性ほど顕著ではないが（図6），歩行速度（図4）も，握力（図5）も女性は男性と同等かそれ以上に低下する．すなわち，女性の場合，筋肉量の減少と機能の低下は必ずしも並行するわけではなさそうである．

サルコペニアが臨床的に問題になるのは移動能力の低下や転倒など，ADL（activities of daily living）やQOL（quality of life）の低下が生じることであり，ひいては要介護状態の招来や介護施設や病院への入所・入院につながる危険がある．したがって，このような臨床的問題点と関連づけて，今後サルコペニアを定義する必要がある．

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Chronic lung disease was found to have a strong association with being underweight. It was one of the chronic wasting diseases with systemic inflammation and protein degradation, and the prevalence was higher in the underweight population with greater disease-specific mortality.[9] Sarcopenia was considered the possible pathophysiological mechanism behind the obesity paradox.

The RAP trigger for nutrition was not a good indicator of underweight or obesity. Most MDS items for nutrition were not found to be good indicators of protein or calorie malnutrition.[10] Other tools with better detection sensitivity and specificity, such as bioelectrical impedance analysis for sarcopenia, should be employed in assessment of nutritional risk for nursing home residents.

There are several limitations of this study. First, BMI was not necessarily correlated with measures of body composition, such as visceral adiposity and sarcopenia. Second, the dynamic change in BMI, RAP triggers, and disease diagnosis could not be fully presented in this cohort study. Weight loss, new RAP triggers, and new disease diagnoses were all considered important risk factors for mortality and morbidity. Third, all participants were male, so the results should not be generalized to women.

In conclusion, being underweight was associated with greater risk of mortality after adjustment for age and comorbidities. Chronic lung disease was significantly associated with being underweight. Other than the intervention program for malnutrition, a multidimensional approach for all associated factors would prevent further adverse health outcomes in the elderly population.

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ACKNOWLEDGMENTS

We thank Hsiao-Ling Lin, Kai-Chun Chang, and Heng-Liang Yeh who made great efforts on longitudinal data collection during the study period.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Chen, Peng, Liu: study concept, design, analysis, data interpretation, manuscript writing; Lin, Chen: data verification and analysis. Chen, Lan, Chang: critical suggestions and review before manuscript submission.

Sponsor's Role: None.

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WEIGHT LOSS AND HOMEOSTATIC IMBALANCE OF LEPTIN AND GHRELIN LEVELS IN LEAN OLDER ADULTS

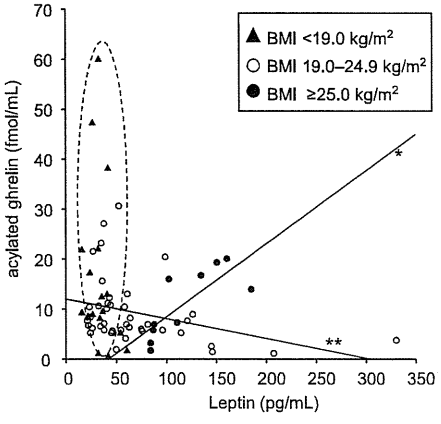
To the Editor: Appetite and food intake decline with age in elderly adults, and their decline results in unintended weight loss, which leads to frailty, morbidity, and mortality.[1] One reason why this anorexic state prevents elderly people from returning to their original weight is impaired regulation of food intake, which makes them likely to be

less hungry and to become rapidly satiated.[2] An imbalance between leptin and ghrelin, two peripheral hormones that signal changes in energy balance to the central nervous system (CNS) and act reciprocally to maintain body weight, may cause predisposition to impaired regulation of food intake.[3]

Sixty-eight elderly adults aged 65 and older (mean age 80.5 ± 5.8 years; female:male ratio 48:20) who were making regular visits to the geriatric outpatient clinic of Kyorin University Hospital were examined. Their diseases were well controlled. Fasting plasma leptin and acylated ghrelin levels were measured using enzyme-linked immunosorbent assay. Because of the potential effects of instrumental activities of daily living (IADLs) on daily energy needs and appetite, they were evaluated by scoring them on the Lawton IADL scale.[4]

The results of a simple regression analysis showed a positive correlation between subjects' plasma leptin levels and their body mass index (BMI; correlation coefficient (r) = 0.54, P<.001), although there was no correlation between their BMI and ghrelin level (r = −0.23, P = .06), age (r = 0.12, P = .31), or sex (r = 0.08, P = .54). After adjustment for age and sex, the results of multiple regression analysis showed significant correlations between BMI and leptin (partial regression coefficient [prc] = 0.29, P = .02), ghrelin (prc = −0.41, P<.001), leptin–ghrelin interaction (prc = 0.41, P<.001), and IADL scores (prc = 0.26, P = .04). When the subjects were stratified into three groups according to BMI (high, ≥25.0 kg/m^2; normal, 19.0–24.9 kg/m^2; and low, <19.0 kg/m^2), there was a significant positive correlation between leptin and ghrelin levels in the high BMI group (r = 0.79, P = .008) and a significant inverse correlation in the normal BMI group (r = −0.33, P = .03), but no significant correlation was not observed between the two peptides in the low BMI group (r = 0.22, P = .39) (Figure 1).

Leptin is a peptide and the product of the *OB* gene, which is expressed primarily in adipocytes, and it signals



*r=0.79, p=.008 for BMI ≥25.0 kg/m²
**r=−0.33, p=.03 for BMI 19.0–24.9 kg/m²

Figure 1. Relationship between plasma leptin and acylated ghrelin levels of elderly adults attending a geriatrics clinic according to body mass index (BMI). Solid lines represent the statistically significant linear regressions of the data.

the CNS about the quantity of stored fat, whereas ghrelin is an acylated peptide produced in the stomach that relays hunger signals to the CNS. Thus, both peptides mutually act to maintain body weight. The results of the present study confirmed the existence of a strong positive correlation between plasma leptin levels and BMI in elderly adults,[5] as well as a tendency for higher ghrelin levels to be associated with lower BMI,[6] although the results provide preliminary evidence that the feedback control of leptin and ghrelin is limited to a small body weight range.

In the high BMI group, the relationship between the two peptides shifted to a positive correlation with increasing BMI. Regardless of the potential role of leptin in ghrelin regulation, insulin may be an important peripheral peptide in regulating energy balance in obese people. A previous study found that the plasma ghrelin levels of obese subjects depended on whether they had insulin resistance, because the obese insulin-sensitive subjects in their study had higher ghrelin levels, suggesting that compensatory hyperinsulinemia mediated the relationship between obesity and ghrelin.[7] Attenuated postprandial ghrelin suppression in obese subjects may also contribute to impaired satiety signaling and persistent hunger feelings.[8]

The data obtained data in the current study showed that all three subjects with the highest ghrelin levels were in the low BMI group. This is consistent with previous observations that plasma ghrelin levels increase under conditions associated with negative energy balance, such as body weight loss or anorexia, reflecting the ghrelin compensatory response to undernutrition. However, some individuals in the low BMI group had low ghrelin levels, which may reflect aging[9] or atrophic changes in the gastric mucosa, and their low ghrelin levels may have caused delayed gastric emptying that in turn suppressed food intake. A sedentary lifestyle and psychological and social factors may also underlie anorexia in elderly adults because the results of the current study showed that higher IADL scores were associated with higher BMI.

Further study will be needed to determine whether treating lean elderly adults with ghrelin would increased their food intake, although a comprehensive approach to lifestyle factors is now the best conceivable approach to preventing low body weight and sarcopenia in elderly adults.[10]

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ACKNOWLEDGMENTS

Conflict of Interest: The authors have no conflicts of interest to report in regard to this letter. This work was supported by the Research Grant for Comprehensive Research

on Aging and Health from the Ministry of Health, Labor and Welfare.

Author Contributions: Conception and design: Kozaki, Tanaka. Analysis and interpretation of data: Tanaka, Nagai, Matsui. Drafting of the article: Tanaka, Matsui. Critical revision of the article for important intellectual content: Kozaki, Sudo. Final approval of the article: Sudo, Kozaki. Statistical expertise: Matsui, Nagai. Collection and assembly of data: Tanaka, Obara, Nagai, Koshiba.

Sponsor's Role: None.

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ARE GERIATRIC SYNDROMES ASSOCIATED WITH RELUCTANCE TO INITIATE ORAL ANTICOAGULATION THERAPY IN ELDERLY ADULTS WITH NONVALVULAR ATRIAL FIBRILLATION?

To the Editor: Age is associated with risk of atrial fibrillation (AF) and its consequences, including stroke. In turn, stroke has been associated with mortality, disability, and health-related quality of life.[1] The American Association of Chest Physicians states that anticoagulation therapy (AT) must be initiated in individuals with nonvalvular AF in moderate- and high-risk categories for the development of stroke (according to congestive heart failure, hypertension, aged ≥75, diabetes mellitus, stroke, vascular disease, aged 65–74, sex (CHA_2DS_2VASc) score),[2,3] whereas a variety of major bleeding prediction scores, such as the hypertension, abnormal (renal/liver function), stroke, bleeding tendency, labile international normalized ratio, elderly, drugs (HAS-BLED) have been developed to aid in the decision-making process in relationship to prescribing AT.[4] Nevertheless, recent work has shown that the net clinical benefit favors the initiation of AT over the risk of major bleeding, even in individuals at high risk of bleeding.[5]

Bleeding risk in elderly adults with AF is frequently overestimated, whereas thrombotic risk is underestimated.[1,6] Thus, AT is underused in this context. It is likely that age-related factors such as functional status, falls, and cognitive impairment influence the decision to anticoagulate these individuals, although an association between the presence of geriatric syndromes (GSs) and the reluctance to initiate AT in elderly adults with nonvalvular

Table 1. Multivariate Logistic Regression of the Absence of Oral Anticoagulation Therapy

	Univariate Analyses, n = 137	Model 1, n = 136	Model 2, n = 129	Model 3, n = 128	Model 4, n = 128
Characteristic	**Odds Ratio (95% Confidence Interval)**				
Age	1.03 (0.97–1.08)	1.02 (0.96–1.08)	—	1.03 (0.96–1.11)	1.04 (0.96–1.12)
Female	0.70 (0.35–1.37)	0.61 (0.29–1.27)	—	0.55 (0.21–1.42)	0.58 (0.22–1.55)
Lives alone	0.67 (0.20–2.22)	0.82 (0.24–2.82)	—	1.03 (0.23–4.65)	0.94 (0.20–4.35)
Education, years	0.96 (0.90–1.02)	0.94 (0.88–1.01)	—	0.95 (0.88–1.48)	0.97 (0.89–1.06)
Hearing impairment	1.66 (0.84–3.27)	—	1.57 (0.66–3.73)	—	—
Visual impairment	2.09 (0.97–4.53)	—	2.45 (0.89–6.78)	2.84 (0.99–8.16)	—
≥3 falls/years	2.37 (1.01–5.53)[a]	—	1.61 (0.53–4.86)	—	—
IADLs disability	0.64 (0.26–1.56)	—	0.81 (0.26–2.56)	—	—
ADLs disability	0.49 (0.25–0.97)[a]	—	1.43 (0.58–3.55)	—	—
Depressive symptoms	5.12 (2.19–11.99)[b]	—	4.59 (1.73–12.12)[a]	4.94 (1.81–13.52)[a]	5.14 (1.84–14.34)[a]
Cognitive impairment	7.97 (3.62–17.53)[b]	—	7.32 (2.98–17.99)[b]	6.79 (2.73–16.87)[b]	6.27 (2.54–15.46)[b]
CHA_2DS_2VASc stroke risk score	1.03 (0.06–16.80)	—	—	—	1.02 (0.04–22.71)
HAS-BLED	2.58 (1.27–5.23)[a]	—	—	—	2.52 (1.03–6.16)[a]

Model 1 included age, sex, living situation, and educational level; Model 2 included hearing impairment, visual impairment, falls, instrumental activities of daily living (IADLs) and activities of daily living (ADLs) disability, depressive symptoms, and cognitive impairment; Model 3 included age, sex, living situation, educational level, visual impairment, depressive symptoms, and cognitive impairment; Model 4 included depressive symptoms and cognitive impairment and was adjusted for age; sex; living situation; educational level; congestive heart failure, hypertension, aged ≥75, diabetes mellitus, stroke, vascular disease, aged 65–74, sex (CHA_2DS_2VASc) stroke risk score; and hypertension, abnormal (renal/liver function), stroke, bleeding tendency, labile international normalized ratio, elderly, drugs (HAS-BLED) major bleeding risk score. Depressive symptoms = Geriatric Depression Scale (GDS) >5; Cognitive impairment = Mini-Mental State Examination (MMSE) ≤ 23.

$P <$ [a].05, [b].001.

サルコペニアと転倒―老年医学の立場から

Sarcopenia and fall – From geriatric perspective

神﨑 恒一*
Kozaki Koichi

抄録▶転倒は多要因によって発生し，それがもとで要介護状態に至る点で注目すべき老年症候群の１つである．そして，サルコペニアは転倒の重要な一因である．2010 年に発表された EWGSOP のコンセンサスレポートで，サルコペニアの診断アルゴリズムが示されたが，これによるサルコペニア高齢者は非サルコペニア高齢者に比べて約３倍転倒リスクが高いことが報告され，EWGSOP の基準の妥当性が示された．

Key Words 転倒，要介護，老年症候群，EWGSOP，FRI

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転倒，サルコペニアと要介護

高齢者は転倒しやすく，屋内外さまざまな場所で転倒する．諸報告によれば高齢者の転倒率は20～40％といわれている．転倒は大腿骨近位部などを骨折することによって直接要介護状態になることもあれば，骨折や重篤な外傷を免れたとしても，再度転倒することに対する不安から外出する意欲を失い家に閉じこもることで廃用が進み，やがて要介護状態に至ることもある．いずれの場合も転倒は要介護状態を招来する大きな要因である．

一方，要介護の原因からみた場合，高齢になるに従って，衰弱や認知症，転倒・骨折の占める割合が大きくなる(図1)．“衰弱”の具体的な病態は明らかでないが，“加齢に伴う身体ならびに認知・精神機能の低下”と考えられ，この中にサルコペニア(加齢性筋肉減少症)が含まれるものと思われる．そして，サルコペニアは転倒の重要な要因である．

転倒，サルコペニアの老年医学的問題点

転倒，ならびに歩行障害の原因は多岐にわたり，筋力やバランス保持能力の低下(サルコペニアに起因)のほか，骨粗鬆症や関節疾患，認知機能低下に伴う注意力の障害，白内障に伴う視力障害，薬物の影響，屋内外の障害物などさまざまある(図2)．このように，転倒は複数の要因が関わって起こるため治療介入が容易でない．このような多臓器・器官の機能低下に伴って起こる高齢者の症候は“老年症候群”と呼ばれ，老年医学的に重要な概念である．老年症候群の代表は歩行障害・転倒のほか，摂食嚥下障害，認知機能障害，失禁などがあり，これらの症候が長く続くとQOLやADLが低下し，やがて要介護状態に陥ってしまう．

サルコペニアは本来加齢に伴う“筋肉量”の減少を意味する造語であるが，サルコペニアが臨床的に問題になるのは，“筋肉量”が減少する結果，筋力や歩行能力が低下することである．なぜなら，それによって歩行障害やその他の機能

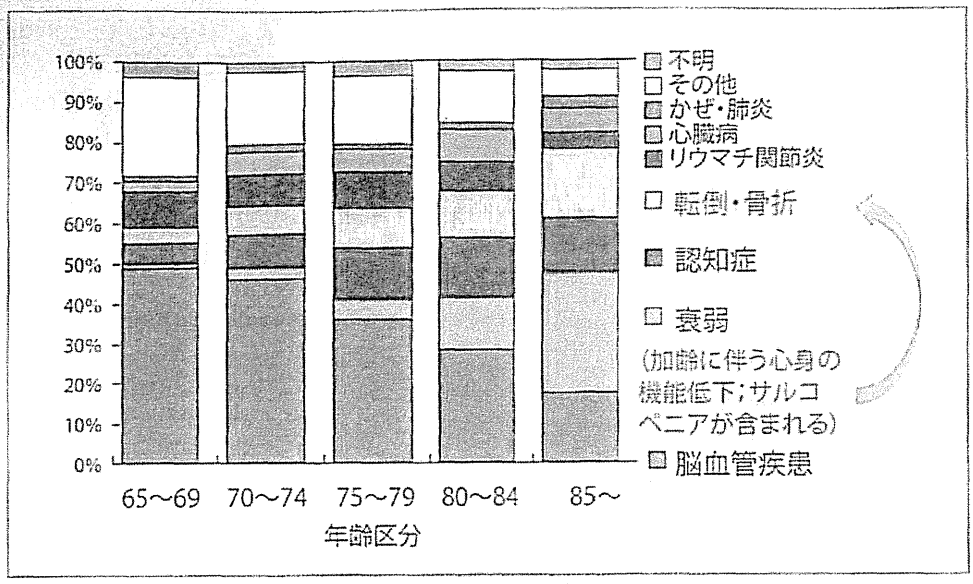

図1　要介護に至る原因

(平成10年厚労省国民生活基礎調査の概況より作図)

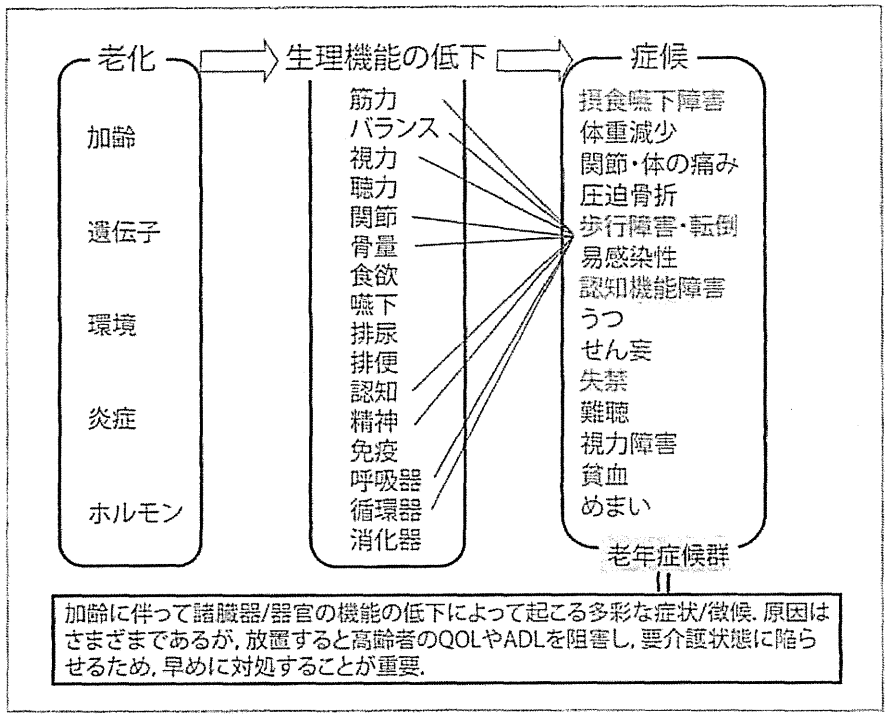

図2

障害が生じ，疾病の発生や要介護状態に陥るからである．

サルコペニアの定義

サルコペニアは明確な定義がなく，これまでBaumgartnerらが報告した"DXAによる筋肉量測定で，補正四肢筋量(四肢の筋肉量の総和を身長の2乗で補正した数値)が若年成人平均値(young adult mean; YAM)の2標準偏差未満(YAM-2SD)"が長くgold standardとして用いられてきた[1]．この基準に従えば白人では男性7.26 kg/m^2，女性5.45 kg/m^{2}未満がサルコペニア(筋量の低下)のカットオフとなる．わが国では同様に，SanadaらがYAM-2SDの基準値として男性6.87 kg/m^2，女性5.46 kg/m^{2}を提唱している[2]．そのような流れの中，2010年にEuropean

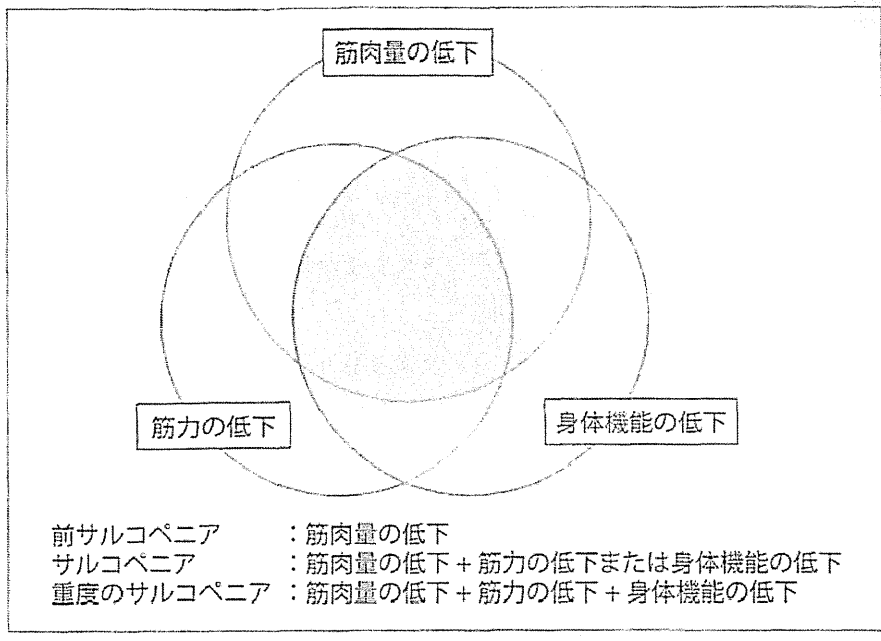

図3　サルコペニアの段階

(2010年European Working Group on Sarcopenia in Older Peopleコンセンサスレポートより)

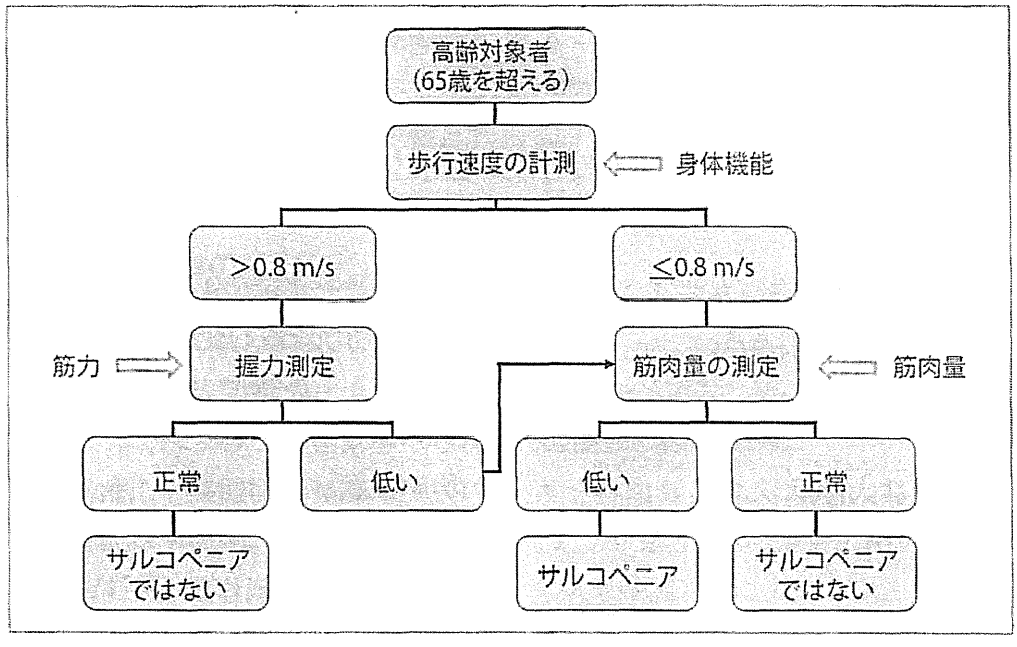

図4　高齢者におけるサルコペニアの発見のためのアルゴリズム

(2010年European Working Group on Sarcopenia in Older Peopleコンセンサスレポートより)

Working Group on Sarcopenia in Older People (EWGSOP)がサルコペニアに関するコンセンサスレポート[3]を発表した．その中で，サルコペニアを筋肉量の低下，筋力の低下，身体機能の低下の3つの要因でとらえ，筋肉量の低下を必須要因とし，筋力の低下または身体機能の低下がある場合にサルコペニアと呼ぶよう提唱した(図3)．さらに，診断のためのアルゴリズムを作成し，図4のように，歩行速度0.8 m/sec未満で筋肉量が低下している場合，もしくは歩行速度は0.8 m/sec以上であるが，握力と筋肉量が低下している場合サルコペニアと判断するよう提唱した．しかしながら，このアルゴリズムでは握力と筋肉量のカットオフ値が示されていな

表1　転倒リスク指標(Fall risk index)

1)過去1年に転んだことがありますか(はい，いいえ)
　はい の場合転倒回数(　　回/年)
2)つまずくことがありますか(はい)
3)手摺につかまらず，階段の昇り降りをできますか(いいえ)
4)歩く速度が遅くなってきましたか(はい)
5)横断歩道を青のうちにわたりきれますか(いいえ)
6)1キロメートルくらい続けて歩けますか(いいえ)
7)片足で5秒くらい立っていられますか(いいえ)
8)杖をつかっていますか(はい)
9)タオルを固く絞れますか(いいえ)
10)めまい，ふらつきがありますか(はい)
11)背中が丸くなってきましたか(はい)
12)膝が痛みますか(はい)
13)目が見にくいですか(はい)
14)耳が聞こえにくいですか(はい)
15)物忘れが気になりますか(はい)
16)転ばないかと不安になりますか(はい)
17)毎日お薬を5種類以上飲んでいますか(はい)
18)家の中で歩くとき暗く感じますか(はい)
19)廊下，居間，玄関によけて通る物がおいてありますか(はい)
20)家の中に段差がありますか(はい)
21)階段を使わなくてはなりませんか(はい)
22)生活上家の近くの急な坂道を歩きますか(はい)

いため，このままでは具体的にカテゴライズすることができないのが問題である．

サルコペニアと転倒

われわれは，杏林大学病院高齢診療科ともの忘れセンターに通院中の患者を対象として，EWGSOPのアルゴリズムに基づいて高齢サルコペニア患者の実態を調査した．なお，握力は介護予防のチェックに用いられている男性30 kg，女性20 kg，筋肉量はDXAの代わりにバイオインピーダンス法を使用した(基準はDXAと同じく身長で補正した四肢筋量がYAM-2SD以下を使用)．その結果，2/3の男性患者と半数の女性患者がサルコペニアであることがわかった．これは下方らが発表している性・年代別サルコペニアの頻度[4]よりもはるかに高く，高齢診療科ともの忘れ外来通院者の多くがサルコペニアの状態にあることを示すものである．

また，サルコペニアの基準を満たした者と，満たさなかった者でどのような測定値に違いがあるかを検討したところ，サルコペニア患者群の方が下腿最大周囲長や上腕周囲長，補正四肢筋量など筋肉量に関連する指標が低値を示したほか，握力，開眼片脚立ち時間(いずれも男性のみ)も有意に低値を示した．しかしながら，EWGSOPのアルゴリズムの中に含まれている歩行速度やtimed up & goテスト，年齢，過去1年間の転倒歴には統計的な違いは認められなかった．すなわち，EWGSOPのアルゴリズムでサルコペニアを診断する場合，歩行速度は有意な決定要因にはならないことになる．

次に，サルコペニアによって生じる重大なイベントである"転倒"と筋肉量(補正四肢筋量)，筋力(握力)，身体機能(歩行速度)との関係につ

いて検討したところ，“過去1年間に転倒した患者”と“しなかった患者”との間で，握力と歩行速度，バランス能力に違いが認められたが，補正四肢筋量や下腿最大周囲長，上腕周囲長に差は認められなかった．このことから，転倒は筋力や身体機能とは関係するものの，必ずしも筋肉量とは関係しないと考えられる．

ここで紹介したわれわれの研究結果は横断的解析結果であり，現在転倒の発生について前向きにフォローしている．参考として，2012年のLandiらの報告[5]では80歳以上の260名の高齢者を対象にEWGSOPのアルゴリズムに従ってサルコペニアを分類した結果，66名(25.4%)がサルコペニアと診断され，そのような高齢者は2年間の追跡期間中に18名(27.3%)が転倒し，非サルコペニア対象者(転倒率9.8%)よりも3.2倍(多因子で調整後)リスクが高いことが報告された．この結果から，EWGSOPの基準にのっとったサルコペニアの診断は転倒のリスク予測として有効であると結論している．

転倒リスクの評価

サルコペニアは転倒発生の重要な要因であるがすべての要因ではない．なぜなら先述したように転倒の発生には多要因がかかわるからである．鳥羽らは，転倒リスクが高い高齢者をより簡便な方法で検出するため転倒リスク指標(fall risk index; FRI)を考案した．FRIは自己記入式の調査票であり，歩行やバランス，筋力に関する8項目(サルコペニアのチェック項目を内包)，感覚器，認知などに関する8項目，環境要因に関する5項目の計21項目と，過去1年間での転倒歴を問う全22項目から成っている(表1)．二者択一形式であり，転倒しやすい側の回答数が多い人ほど，転倒リスクが高い[6]．大河内らは地域在住高齢者に対してFRIを行い，その後半年間転倒の有無を追跡調査した結果，「過去の転倒歴」，「歩行速度が遅くなった」，「杖の使用」，「背中が丸くなった」，「5種類以上の服薬」という5項目が，アンケート調査後の転倒発生と関連することを報告している[7]．また，転倒スコアはもの忘れ外来に通院する“転倒しやすい患者”において，片足立ち持続時間，Up and Goテスト，Functional reachに匹敵する有用な検査である可能性をわれわれは確認している[8]．以上より，FRIは簡易で信頼性の高いマススクリーニングツールということができる．

さいごに

サルコペニアは本来筋肉量の減少と定義されていたが，2010年のEWGSOPのコンセンサスレポートでは筋肉量減少以外に筋力低下，身体機能低下の3つの要因で診断する流れが提唱された．海外の報告ではサルコペニックな高齢者は転倒リスクが3倍高いことが報告されたが，転倒の多要因性を考えた場合，果たして筋肉量，筋力，身体機能のいずれに重きを置くべきか，わが国での検証が必要と考える．

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学術集会案内

第 16 回超音波骨折治療研究会

会期：2013（平成 25）年 1 月 19 日（土）13：00 ～ 18：00（予定）
会場：東京ステーションコンファレンス
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東京ステーションコンファレンス　TEL：03-6888-8080
会長：佐藤 啓二（愛知医科大学医学部整形外科学）
教育研修講演（日本整形外科学会教育研修講演申請予定）
演題：「間葉系幹細胞の至適な培養環境をめざして」
講師：戸口田 淳也先生（京都大学再生医科学研究所再生医学応用研究部門組織再生応用分野教授）
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