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Low fat-free mass as a marker of mortality in community-dwelling healthy elderly subjects†

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Abstract

Background: low fat-free mass has been related to high mortality in patients. This study evaluated the relationship between body composition of healthy elderly subjects and mortality.
Methods: in 1999, 203 older subjects underwent measurements of body composition by bioelectrical impedance analysis, Charlson co-morbidity index and estimation of energy expenditure through physical activity by a validated questionnaire. These measurements were repeated in 2002, 2005 and 2008 in all consenting subjects. Mortality data between 1999 and 2010 were retrieved from the local death registers. The relationship between mortality and the last indexes of fat and fat-free masses was analysed by multiple Cox regression models.
Results: women's and men's data at last follow-up were: age 81.1 ± 5.9 and 80.9 ± 5.8 years, body mass index 25.3 ± 4.6 and 26.1 ± 3.4 kg/m^2, fat-free mass index 16.4 ± 1.8 and 19.3 ± 1.9 kg/m^2 and fat mass index 9.0 ± 3.2 and 6.8 ± 2.0 kg/m^2. Fifty-eight subjects died between 1999 and 2010. The fat-free mass index (hazard ratio 0.77; 95% confidence interval 0.63–0.95) but not the fat mass index, predicted mortality in addition to sex and Charlson index. The multiple Cox regression model explained 31% of the variance of mortality.
Conclusion: a low fat-free mass index is an independent risk factor of mortality in elderly subjects, healthy at the time of body composition measurement.

Keywords: *body composition, fat-free mass, fat-free mass index, mortality, older people*

Introduction

Ageing has been associated with weight and body composition changes. Longitudinal studies have demonstrated a decrease in fat-free mass in healthy elderly subjects but controversial results regarding fat mass [1–3]. These changes in body composition may be detrimental to health. For instance, a low fat-free mass has been associated with reduced muscle strength, exercise tolerance, quality of life, immune dysfunctions and increased hospital stays [4–6]. In contrast, an increased fat mass, as found in obesity, has been related to a higher risk of cardio-vascular diseases, certain cancers, osteoarthritis and respiratory problems.

In clinical routine, body composition is often evaluated in terms of body mass index (BMI = weight (kg)/height (m)^2). Several studies have demonstrated the impact of BMI on mortality in older subjects. They described a J-shaped or U-shaped relationship [4, 7–11] with the lowest mortality occurring with a BMI around 23–28 kg/m^2. However, BMI gives only a crude estimation of body composition. Therefore, recent cohort studies evaluated the association of fat and fat-free masses, generally adjusted for body height, with mortality. Some found a relationship between low fat-free mass and increased mortality risk in elderly subjects [12–16], while others could not consistently confirm these findings [17, 18]. Similarly, some studies described a positive relationship between obesity, especially in the abdominal area, and increased risk of mortality [13, 15] but this was refuted by others [17–19]. These controversies may be partly explained by the confounding impact of physical activity and co-morbidities, which are often not described in the aforementioned studies.

This study's aims were to evaluate the relationship between body composition and mortality, specifically in healthy white community-dwelling subjects ≥65 years, while taking into account physical activity and co-morbidity. We hypothesised that a low fat-free mass and a high fat mass were associated with a higher risk of mortality, once adjusted for co-morbidities and physical activity.

Methods

Subjects and study design

This longitudinal study includes 203 healthy white subjects aged ≥65 years, who were recruited through advertisements in newspapers and leisure clubs in 1999. We excluded subjects with decompensated heart, lung, kidney or liver failure, symptomatic neurological disorders, known active cancer or chronic infectious diseases, significant mental impairment, involuntary weight loss or gain over 3% in the last 3 months, and hospitalisation in the last 6 months [1]. The volunteers were sent an invitation letter for the Geneva University Hospital, a health questionnaire and a physical activity questionnaire, and were asked not to perform any strenuous physical activity and to drink at least 1 l of liquid the day before coming to the hospital. On the study day, the volunteers reviewed the questionnaires with the investigators and underwent a measurement of body composition by bioelectrical impedance analysis (BIA) between 7:30 and 9:00 am.

The questionnaires and BIA measurements were repeated in 2002, 2005 and 2008 in all included subjects who could be reached by phone and consented to participate. None of the subjects clinically showed signs of oedema or ascites. Mortality data between January 1999 and December 2010 were retrieved from official sources detailed thereafter. The relationship between mortality and the last available body composition of each subject was evaluated, while taking into account health status and physical activity.

All subjects signed an informed consent. The Geneva University Hospital Ethical Committee approved the

protocol. This study was supported by the Public Foundation Nutrition 2000Plus.

Anthropometry and body composition

Body height was measured to the nearest 0.5 cm with a height gauge and body weight to the nearest 0.1 kg on a balance beam scale (Seca, Germany), with the subject in underclothing and without shoes, on the day of body composition measurement.

Body composition was measured by BIA. After cleaning the skin with 70% alcohol, adhesive electrodes (3M Red Dot, *M Health Care, Borken, Germany) were placed on the right hand and foot, the subject lying on his back as generally described. A Xitron 4000B device (Xitron Technologies, San Diego, CA, USA) applied an alternating electrical current of 50 kHz and 0.8 mA to these electrodes. Resistance and reactance were measured and fat-free mass was calculated by the following equation [20], validated against dual-energy X-ray absorptiometry (DXA) in elderly subjects [21]:

Fat-free mass (kg) = − 4.104 + (0.518 × height^2/R) + (0.231 × weight) + (0.13 × reactance) + (4.229 × sex), where sex = 1 for men and 0 for women.

Fat-free and fat-free masses were normalised for height by calculating indexes of fat and fat-free masses (fat mass index (FMI) = fat mass (kg)/height (m)^2; fat-free mass index (FFMI) = fat-free mass (kg)/height (m)^2).

In order to determine whether there is a cut-off of body composition associated with an increased risk of mortality, we performed four dichotomous categorisations of FFMI, according to our previously published age- and gender-specific percentiles of FFMI [22] (< or ≥ percentile 10, < or ≥25, < or ≥50, < or ≥75) and four dichotomous categorisations of FMI (< or ≥ percentile 10, < or ≥25, < or ≥50, < or ≥75).

Health questionnaire

The health questionnaires allowed for the calculation of the Charlson co-morbidity index, which reports 19 medical conditions weighted 1–6 by severity and whose total score ranges from 0 (no co-morbidity) to 37 [23]. It is strongly associated with mortality and disability [24].

Physical activity questionnaires

The physical activity questionnaire was a frequency questionnaire encompassing leisure and non-leisure physical activities of the previous week, validated against heart rate monitoring in subjects aged 35–69 years [25]. The frequency and duration of each physical activity were multiplied by the body weight and the metabolic equivalent [26] of the analysed activity to obtain weekly energy expenditure. Analysed activities were all activities besides sleeping. The energy expenditures of the different activities were added up and divided by 7 to obtain daily energy expenditure by physical activity.

Mortality

Mortality was searched for in all subjects who could not be reached by phone at any one of the follow-up visits.

For the subjects living in the Geneva area, mortality data from January 1999 to December 2010 were retrieved from the official death website and the registry office from the Geneva area. For the subjects living in the Lausanne area (n = 8), the investigators checked with the administration of the cities they were living in at the last follow-up, whether they were still alive by December 2010. As mortality data could not be retrieved for the subjects living in France (n = 10), they were excluded from the analysis.

Statistics

The normality of the distribution of continuous data was verified. Data between alive and deceased subjects were compared with unpaired t-tests.

Univariate Cox regressions (Model 1) assessed the relationship between mortality and sex, the last available age, BMI, FMI and FFMI, physical activity and Charlson index. The Cox regressions between mortality and physical activity and between mortality and Charlson index did not respect log-linearity. This led to a categorisation of physical activity as < or ≥ the median value of energy expenditure through physical activity, i.e. 1,533 kcal/day for men and 1,317 kcal/day for women. Charlson index was categorised as 0 if the subject was healthy or 1 if his score was >0. Univariate Cox regressions also assessed the association between mortality and the percentile categories of FFMI and FMI that take into account age and gender by definition. Kaplan–Meier curves illustrated survival according to percentile categories of body composition.

Multiple Cox regression models determined the association of mortality with age- and sex-adjusted body composition, physical activity and Charlson index (Model 2). A third model of multiple Cox regression (Model 3) evaluated the relationship between mortality and the following predictors: age, sex, FMI and FFMI, categories of physical activity and of Charlson index. The empirical method of Harrell states a necessity of at least 10 observations per predictor in multivariable prognostic models [27]. In our study, we observed a total of 58 deaths, and used six predictors of mortality, which followed the rule of Harrel. For each Cox model, the hazard proportional assumptions were checked by the proportional-hazards assumption test. We calculated hazard ratios (HRs) with their 95% confidence intervals and the adjusted R-squared (R^2), corresponding to the variance of mortality explained by each variable or model.

Significance was set at $P < 0.05$. Statistical analyses were performed with Stata software version 12 (TX, USA).

Results

Characteristics of the subjects at last follow-up are shown in Table 1. Their mean age was greater than 80 years.

Table 1. Characteristics at last follow-up of subjects alive versus deceased (mean ± SD)

	Women			Men		
	Total ($n = 102$)	Alive ($n = 82$)	Deceased ($n = 20$)	Total ($n = 101$)	Alive ($n = 63$)	Deceased ($n = 38$)
Age (years)	81.1 ± 5.9	80.8 ± 0.7	82.6 ± 0.9	80.9 ± 5.8	79.9 ± 0.7	82.5 ± 1.0*
Height (cm)	158.2 ± 5.6	158.5 ± 0.6	157.3 ± 1.2	168.9 ± 7.7	169.5 ± 0.9	167.9 ± 1.5
Weight (kg)	63.5 ± 12.9	64.3 ± 1.4	60.2 ± 3.0	74.4 ± 10.8	76.6 ± 1.3	70.8 ± 1.7*
BMI (kg/m^2)	25.3 ± 4.6	25.6 ± 0.5	24.3 ± 1.1	26.1 ± 3.4	26.7 ± 0.4	25.1 ± 0.5*
FFMI (kg/m^2)	16.4 ± 1.8	16.5 ± 0.2	15.6 ± 0.4*	19.3 ± 1.9	19.7 ± 0.2	18.6 ± 0.3*
FMI (kg/m^2)	9.0 ± 3.2	9.0 ± 0.3	8.7 ± 0.8	6.8 ± 2.0	7.0 ± 0.2	6.5 ± 0.3
Physical activity (kcal/day)	1,392 ± 563	1,470 ± 577	1,067 ± 365*	1,534 ± 545	1,641 ± 537	1,357 ± 516*
Charlson index	1.8 ± 2.5	1.5 ± 0.3	2.9 ± 0.6*	3.0 ± 2.8	2.5 ± 0.3	3.8 ± 0.5*

BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index.
*$P < 0.05$ (unpaired t-test) between deceased and alive subjects.

Compared to population-specific norms of subjects aged 75–84 years, their mean FFMI was between 50th and 75th percentile and their mean FMI between 25th and 50th percentile for women and 50–75th percentile for men [26].

Of the 203 included subjects, 58 died during the 11 years of follow-up, with a higher death rate in men than in women (37.6% versus 19.6%, $P = 0.005$). Mean time until death was 1,980 ± 1,051 days in women and 1,176 ± 855 days in men ($P = 0.003$) and, until end of follow-up of the people who were alive, 1,690 ± 1,204 days in women and 1,460 ± 1,089 days in men (P = ns). Men and women who had died had a lower FFMI, physical activity and a higher Charlson score than the subjects who were still alive.

Univariate Cox regressions for the prediction of mortality (Table 2, Model 1) were significant for BMI, FFMI, FMI and physical activity. Regarding dichotomous percentile categories of body composition, FFMI was below percentile 10, 25, 50 and 75, in 17, 42, 85 and 131 subjects, respectively. Only FFMI < percentile 10 (HR 2.05, CI 1.03–4.05, $P = 0.040$) predicted mortality. The other percentile categories of FFMI and FMI were not associated with mortality. Kaplan–Meier curves (Figure 1) illustrate that a FFMI < percentile 10 was associated with a lower survival than a FFMI ≥ percentile 10.

Cox regressions adjusted for age and gender (Table 2, Model 2) were significant for the FFMI and the Charlson category. The multiple Cox regression model including age, sex, FFMI, FMI, physical activity and Charlson index (Table 2, Model 3) was significant for sex, FFMI and Charlson index and explained 31% (adjusted R^2) of the variance of mortality. Replacing FFMI and FMI by BMI decreased the adjusted R^2 to 27%, which highlights the importance of body composition compared to BMI.

Discussion

This study found that, in community-dwelling subjects ≥65 years, FFMI is associated with mortality when taking into account co-morbidities, age and gender. Body composition was measured in relatively healthy subjects as shown by the low Charlson index at the time of measurement. The Kaplan–Meier curves suggest that the cut-off associated with increased risk of mortality is an FFMI < percentile 10, based on previously published normative values. This corresponds to a FFMI <16.9 and <13.7 kg/m^2 for men and women with a mean age of 80 years, respectively [22]. No association between weight, BMI, FMI and mortality could be found in this population.

Three studies reported a negative relationship between total body fat-free mass and mortality in community-dwelling subjects, as in our study. An impressive Danish study included over 50,000 men and women aged 50–64 years who underwent BIA measurements and were followed for a median time of 5.8 years [13]. Exclusion criterion was active cancer. The authors used a BIA equation validated against a four-compartment model based on total body potassium counting and dilutometry in Danish subjects aged 35–65 years. They showed that a low FFMI (<19.7 and 16.6 kg/m^2 in men and women, respectively) predicted mortality. Their cut-offs of FFMI associated with mortality were higher than those in our study but their subjects were younger and from another geographical background. Another study included over 10,000 US men aged 20–75 years at baseline and participating in the NHANES I and II Surveys [28]. Their body composition was measured by skinfold thickness and was expressed as indexes. Mean follow-up time was 14.6 years for NHANES I and 12.9 years for NHANES II. The authors demonstrated a negative relationship between FFMI and mortality but did not analyse specifically subjects ≥65 years, did not mention the ethnicity of their subjects, nor included women and used skinfold thickness which is known for its interobserver variability. Finally, fat-free mass/height was associated with mortality in 1,413 Chilean people aged 74.3 ± 5.6 years at time of body composition measurement by DXA and followed for a median of 1,594 days [14]. The authors had excluded subjects with cancer, cardiac or renal failure. Our study demonstrates the same association but also takes into account co-morbidities.

In two studies, physical activity was evaluated by questionnaires. In the first one, 2,819 Danish subjects aged 35–65 years and without previous coronary heart disease, stroke or cancer, underwent a measurement of body

Table 2. Multiple Cox regression model investigating the relationship of mortality and body composition

	Univariate Cox regression (Model 1)				Multiple Cox regression (Model 2)				Multiple Cox regression (Model 3)			
	HR	95% CI	*P*	Adjusted R^2	HR	95% CI	*P*	Adjusted R^2	HR	95% CI	*P*	Adjusted R^2
Age (years)	1.07	1.03–1.11	0.001	0.109	–	–	–	–	1.03	0.99–1.08	0.170	0.312
Sex (man)	2.72	1.57–4.68	0.001	0.130	–	–	–	–	6.61	2.35–18.6	≤0.001	
BMI (kg/m^2)	0.96	0.90–1.03	0.252	0.001	0.95	0.88–1.02	0.207	0.093	–	–	–	
FFMI (kg/m^2)	1.00	0.90–1.12	0.927	0.001	0.81	0.69–0.97	0.018	0.263	0.77	0.63–0.95	0.015	
FMI (kg/m^2)	0.92	0.84–1.01	0.091	0.021	0.99	0.89–1.11	0.900	0.206	1.10	0.95–1.29	0.193	
Physical activity												
<Median value (kcal/day)	1.00	–	–	–	1.00	–	–	–	1.00	–	–	
≥Median value (kcal/day)	0.58	0.33–1.00	0.052	0.031	0.68	0.38–1.20	0.186	0.223	0.74	0.41–1.35	0.325	
Charlson index												
Healthy	1.00	–	–	–	1.00	–	–	–	1.00	–	–	
Diseased	2.74	1.60–4.70	≤0.001	0.133	1.97	1.10–3.50	0.021	0.257	1.96	1.10–3.49	0.022	

BMI, body mass index; FFMI, fat-free mass index; FMI, fat mass index.
Model 1: univariate Cox regression.
Model 2: same as Model 1 but with each parameter adjusted for age and gender.
Model 3: model including age, sex, FFMI, FMI, physical activity and Charlson index.

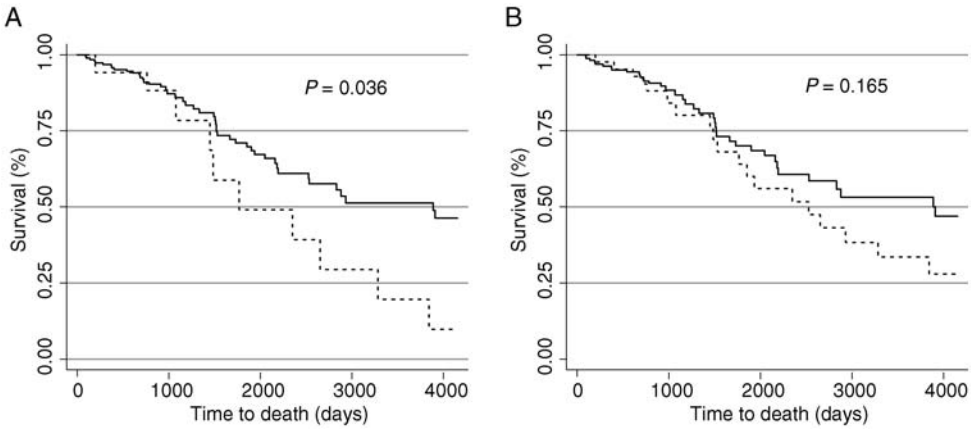

Figure 1. Kaplan–Meier curves illustrate the survival according to percentiles of FFMI. Figures A and B represent Kaplan–Meier survival curves of subjects with a FFMI < percentile 10 (dotted line; $n = 7$) versus those with a FFMI ≥ percentile 10 (plain line; $n = 138$) (A) and the subjects with a FFMI < percentile 25 (dotted line; $n = 23$) versus those with a FFMI ≥ percentile 25 (plain line; $n = 122$) (B). *P* indicates the degree of significance between the binary data, by log-rank test.

composition by BIA and a questionnaire on leisure-time activity [18]. Mortality was assessed on an average of 13.6 years later. The authors stratified the subjects according to physical activity and found a negative relationship between FFMI and mortality in active men but no relationship in women. The second study included almost 10,000 US men and women, stratified by gender and age categories (18–64 years, 65–75 years and >75 years). FFMI determined by BIA and adjusted for physical activity, was associated with mortality only in men aged 65–75 years [17]. None of these studies can be consistently compared with ours as the variables entered in the regression models differed but all agree on some link between FFMI and survival.

The association of fat mass and mortality in elderly subjects is unclear. The aforementioned studies described an increased risk of mortality with high FMI [13, 28] as well as with weight and fat loss [29]. Allison *et al.* [30] found a decreased risk of mortality with fat mass loss. These apparently contradictory results regarding the relationship between fat mass loss and mortality may be explained by the wide age range of the subjects, the methods of body composition measurement used, the consideration of confounding factors as co-morbidities and physical activity, and possibly by a non-linear relationship of body composition changes and mortality. In our study, FMI did not contribute to mortality. Our elderly subjects may have been healthier at time of body composition measurement than in the other studies, leading to an absence of impact of FMI on mortality. Interestingly, some papers described an increased risk of mortality in elderly subjects with a BMI below 18.5 kg/m^2 and ≥35 kg/m [2, 4, 7, 8, 10]. The BMI range of our subjects was 17–36 kg/m^2, which indicates that only a small percentage of subjects had a BMI associated with

increased mortality and also explains the absence of relationship between BMI and mortality in our study.

The limitation of our study is the report of only 58 deaths during follow-up, which precludes analysis stratified by gender. Our subjects had a BMI of 17–36 kg/m^2, implying that our results need confirmation in subjects with higher and lower BMI. We did not look at the impact of body composition changes on mortality and it would be interesting to evaluate whether they are better predictors of mortality than absolute values. Indeed, a loss of fat mass and fat-free mass has been associated with mortality [29].

Conclusion

Our study showed that FFMI is an independent risk factor of mortality in subjects ≥65 years, healthy at the time of body composition measurement. Future studies should evaluate whether body composition changes better predict mortality than single values of FFMI and FMI, and whether this association is stronger in diseased than in healthy subjects.

Key points

- Longitudinal study.
- Healthy patients at the time of body composition measurement.
- Fat-free mass predicts mortality.

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Conflict of interest

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Clinical benefits of oral nutritional supplementation for elderly hip fracture patients: a single blind randomised controlled trial

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Abstract

Background: malnutrition is an important risk factor for poor outcome in patients recovering after hip fracture surgery. This study aimed to investigate the clinical, nutritional and rehabilitation effects of an oral nutritional supplementation (ONS) in an inpatient rehabilitation setting.
Methods: this was an observer-blinded randomised controlled trial of elderly post-surgical proximal femoral fracture patients. A ready-to-use oral liquid nutritional supplementation (18–24 g protein and 500 kcal per day) in addition to