與健康有關的骨骼肌減少症的意義

The significance of sarcopenia in relation to health

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Sarcopenia is a lack of skeletal muscle. Knowledge of this condition is incomplete because an accurate method for the measurement of total muscle mass is lacking. In the absence of such a method, regional measurements are used commonly. When these are based on anthropometry, the values are inaccurate, but they are important because of their relationships to risk factors for some diseases and because large amounts of data are available. It is suggested that low values for the body mass index IBMI) indicate low values for fat-free mass (FFM) of which muscle is known to be a major constituent. Furthermore, low values for the BMI and the circumferences or areas of arm muscle are associated with increased mortality rates.

Introduction

By definition, sarcopenia is a deficiency in the amount of skeletal muscle. The brief account that follows evaluates the methods available to measure skeletal mass and presents the basis for concluding that sarcopoenia has adverse effects on health. Partly because the present methods for the measurement of skeletal muscle than can be applied to large samples are limited in accuracy, conclusions relating to the relationships between sarcopenia and health must be inconclusive although they are highly suggestive.

The measurement of total msucle mass

The daily excretion of creatinine in urine can be used to calculate total muscle mass. A constant diet must be maintained for several days prior to the application of this method and the urine collection must be complete[1]. All body creatinine is in muscle and is excreted in urine at a constant rate[2]. It is assumed that the creatine content of muscle is constant and that it is converted to creatinine at a constant rate but these assumptions are unproven. Furthermore, there is uncertainty about the conversion factor to be used when muscle mass is calculated from creatine excretion; the suggested values range from 17–20 kg muscle/g creatinine. Alternatively, muscle mass can be calculated from the dilution of labeled creatinine in muscle biopsies but the underlying assumptions are not well established[3] and the applicability of this method is limited. The urinary excretion of 3-methyl histidine (3-MH) has been used to calculate muscle mass, but only 60% of urinary 3-MH comes from muscle[4]. The accuracy of estimates from creatinine and 3-MH excretion is limited by marked day-to-day variability even when the protein intake is constant[1].

The body mass index (BMI, kg/m^2) provides only an indirect index of muscle mass but this index is important because serial data are available for large samples. Some interpret this index as an index of obesity but BMI values are also influenced by muscle mass which is a major component of body weight, especially in lean individuals. In samples unselected for obesity or leanness, there are correlations of about 0.6 between BMI and either fat-free mass (FFM) or arm muscle area[5].

Associations between sarcopenia and health could be established from studies of FFM because muscle is a major constituent of FFM. The several methods for the estimation of FFM include densitometry and hydrometry. There are, however, errors in the estimated values for FFM and the proportion of FFM that is muscle varies with age and gender. Furthermore, the methods for the measurement of FFM are not applicable to large samples.

Total body potassium has been interpreted as an index of muscle mass, but muscle contains only about 60% of the body potassium. Others have used measures of total body potassium and total body nitrogen to calculate muscle mass with the assumption that the potassium/nitrogen ratio differs between muscle and the non-muscle fraction of FFM and that this ratio is fixed in each of these fractions[6–7]. These assumptions are incorrect and this method markedly underestimates muscle mass[8–10].

Regional measurements of muscle

The regional measurement of muscle is potentially important because local values may be predictive of total body muscle. Although limited in accuracy, anthropometric estimates of limb muscle mass are important in relation to sarcopenia because they provide values for large samples. In the anthropometric approach, the circumference of a limb and a skinfold thickness at the same level are used to calculate 'muscle circumference' or 'muscle area'. Making several assumptions that are inaccurate, a value is obtained for the circumference or the cross-sectional area of 'muscle plus bone.' Even if adjusted for the bone that is included, these circumferences and areas exceed those from computed tomography or photon absorptiometry by amounts that increase with adiposity[11–12] but pairs of values are highly correlated. These

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Table 1. Major studies that relate low BMI values to mortality rates after excluding current smokers.

Author	Tayback et al.[18]	Yao et al.[21]	Wienpahl et al.[24]	Cornoni-Huntley et al.[25]	Lindsted et al.[26]
Sample	4710 men aged 55–74 yrs	3043 men aged 40–59 yrs	2453 men aged 30–79 yrs. and 2731 women aged 40–79 yrs	438 men, 1034 women aged 65–74 yrs	8828 men aged from less than 40 yrs (22.8%) to 80 yrs or older (5.6%)
Exclusion of early follow-up deaths	1 yr	5 and 10 yrs	5 yrs	7 yrs	no
Exclusion of those with disease at entry	yes	yes	yes	yes	no
Exclusion of ex-smokers	no	no	yes	yes	no
Follow-up	9 yrs	17–20 yrs	15 yrs	7–13 yrs	26 yrs
Mortality rate	Increased if BMI <22.0 kg/m^2	Increased if BMI <23.3 kg/m^2	Increased if BMI <24.1 kg/m^2 (men) or <23.5 kg/m^2 (women)	Increased if BMI <21.4 kg/m^2 and sum of triceps and skinfold thicknesses <16.0 mm (men) or BMI <25.0 kg/m^2 (women)	Decreased if BMI ≤22.3 or <20.0 kg/m^2

anthropometric values are closely related to FFM, total muscle mass of one or all limbs, and maximum oxygen consumption[9,13–15].

Cross-sectional areas of limb musculature can be obtained from computed tomography and water-suppressed magnetic resonance imaging. After bone is excluded from these measurements, the remaining FFM is almost entirely muscle. These methods are not applicable to large samples. Additionally, high frequency energy absorption (HFEA) at 15–40 MHz is being developed for the measurement of cross-sectional muscle areas in the limbs[16]. The principle of HFEA is similar to that of total body electrical conductivity (TOBEC) which provides values for FFM that are not influenced by bone or adipose tissue[17]. Dual-energy X-ray absorptiometry (DEXA) can measure FFM, excluding bone, in whole limbs[9] and is likely to be used more widely in the future.

Sarcopenia and mortality rates

Most of the literature reviewed in this section is based on BMI values, which are interpreted as approximate indices of muscle mass at low BMI values; the other literature reviewed relates to anthropometric estimates of limb muscle circumferences and areas. There is a lack of reports that relate mortality rates to FFM, creatinine excretion, or muscle mass values from DEXA.

Studies based on BMI

Effective studies of the relationships between baseline BMI and subsequent mortality rates require: (i) the enrollment of large samples, (ii) the exclusion of smokers, and (iii) the exclusion of those who have diseases at entry or die soon after entry. Smoking is an important confounding variable because it is associated with low BMI values and with increased mortality rates[18]. There is no consistency across studies in the periods for which early deaths were excluded but usually these periods extend for one to 10 years.

There is evidence that low BMI values in adulthood are associated with increased mortality rates, independent of tobacco smoking and pre-existing disease. It is reasonable to interpret these low BMI values as indicative of sarcopenia but the closeness of the relationship between low BMI values and muscle mass is uncertain.

Sorlie et al.[19] analysed data from 5209 subjects in the Framingham Study. There were moderately higher six-year mortality rates in the groups with BMI <20 kg/m^2, compared with groups with higher BMI, that were not due to diseases recognized at entry or to current smoking. A later analysis of Framingham Study data by Harris et al.[20] included 1723 who never smoked and were aged 65 years at entry. This analysis showed a higher mortality rate for those with low BMI at entry (BMI <23.0 kg/m^2 for men; BMI <24.1 kg/m^2 for women) during the interval from 4–23 years after entry compared to those with higher BMI at entry (BMI = 23.0 – 25.3 kg/m^2 for men; BMI = 24.1 – 26.1 kg/m^2 for women). The increased mortality rates in association with low BMI at entry were due to increased incidences of cardiovascular diseases in each sex and cancer in women.

Tayback et al.[18] found higher mortality rates at BMI values <22 kg/m^2 than at BMI values from 22–30 kg/m^2 in a nine-year follow-up of 4710 subjects aged 55–74 years at entry (Table 1). These differences were noted after the exclusion of deaths during the first year after entry and after adjustments for current smoking, high blood pressure and poverty. These salient features of this and other major studies are shown in Table 1.

A sample of 3043 US railroad men aged 40–59 years at entry was followed for 17–20 years[21]. The greater mortality rate at BMI <23.3 kg/m^2, compared to that for the group with BMI 23.3–25.5 kg/m^2, was independent of current smoking. In this study, those with cardiovascular disease at entry were excluded and analyses were made that excluded those who died during the first five years and the first 10 years after entry.

Vanderbroucke et al.[22] reported 25-year mortality rates for 3091 Dutch subjects aged 40–65 years. In those who were not

current smokers at entry, the mortality rate was increased for men with BMI <23.5 kg/m^2 but there was not a corresponding increase for women. Those who died soon after entry into the study were not excluded from the analyses.

Lew and Garfinkel[23] analysed data from the large American Cancer Society Study. After excluding those who reported a history of cancer, heart disease, stroke or recent weight loss, there was an increased 12-year mortality rate for those who were not current smokers and had BMI values <17.6 kg/m^2 for men and <16.4 kg/m^2 for women. This study is limited in value because the data were self-reported and the procedures for excluding those with pre-existing diseases were not optimal.

Wienpahl and associates[24] reported 15-year mortality rates for 5184 Afro-Americans enrolled in the Kaiser Permanente Health Plan who were aged more than 30 years (men) or 40 years (women) at entry. Data for those with a history or evidence of cardiovascular illness or diabetes at entry and data for those who died within five years of entry were excluded. For those who had never smoked, the mortality rates were increased if BMI was <24.1 kg/m^2 for men or <23.5 kg/m^2 for women at entry compared to the rates for those with higher BMI values. The authors concluded that neither smoking behaviour nor illnesses that preceded entry, or became evident soon after entry, explained the increased mortality rates in the low BMI groups.

Data from the US National Health and Nutrition Survey I - Epidemiologic Follow-up Study[25] provide 7–13 year mortality rates for whites (438 men, 1034 women) aged 65–74 years who were 'never smokers.' After excluding deaths during the first seven years of follow-up, the mortality rate was increased for men when BMI <21.4 kg/m^2 and the sum of triceps and skinfold thickness was <16.0 mm and for women when BMI <25 kg/m^2.

These reports indicate that low BMI values, which are probably indicative of sarcopenia, are associated with increased mortality rates in non-smokers and in those free of clinical disease at entry. Nevertheless, an opposite conclusion has been reported from a study by Lindsted et al.[26]. These workers analysed self-reported data from 8828 Seventh-Day Adventist men. There were no exclusions from the study on the basis of medical histories or examinations at entry nor did they exclude subjects who died soon after entry. For all deciles of age, for all-cause mortality, and for deaths due to ischemic heart disease, cancer or cerebrovascular disease, the 26-year mortality rates were least for the group with BMI <20 kg/m^2.

The results from these studies indicate that sarcopenia, indexed by a low BMI, is associated with an increased mortality rate in middle-aged and elderly individuals when effects of smoking and pre-existing disease are removed. This tentative conclusion is supported by the results of studies based on arm muscle circumferences and areas from anthropometry that will now be considered.

Studies based on arm muscle values

Some studies have related the circumference or the area of arm muscle to mortality rates. The most important of these studies is that of Menotti et al.[27] which showed that low arm muscle circumference values, calculated from anthropometric data, were associated with increased mortality rates in a 25-year follow-up of 4267 men aged 40–59 years at entry. This effect of arm muscle circumference remained significant after controlling for current smoking and 10 other potential predictors at entry including blood pressure, serum cholesterol and level of physical activity. Similar conclusions have been reached from other smaller studies. It is considered that any effect of arm muscle on mortality rates would be due to its association with total muscle mass.

Possible mechanisms

It is postulated that low values for BMI and the circumference or area of arm muscle reflect low values for FFM. Low FFM is associated with increased mortality rates for patients in surgical intensive care, perhaps due to reduced host defenses leading to an increased incidence of infections, or due to a micronutrient deficiency[28]. In patients dying of starvation, malignancy or chronic infection, there is a loss of fat followed by a loss of FFM. Death occurs when FFM is decreased by about 40%[11], or when arm muscle area (excluding bone) becomes less than about 12 cm^2. Involuntary weightloss in the elderly is associated with a loss of FFM, particularly in men, and is highly predictive of mortality[20,29]. When BMI values are low, hypertension is less prevalent and, in men but not women[30–31], unfavorable lipid profiles are more common.

Fractures resulting from falls are an important cause of death in the elderly. The likelihood of falls is increased by the reductions in muscle strength that occur with aging[32–34]. These falls are more likely to result in fractures if there is a lack of bone mineral. Both bone mineral mass and bone mineral density are affected by muscle strength and FFM[35–37]. This may be one mechanism by which sarcopenia increases mortality rates.

Conclusion

Central adiposity, particularly an increase in visceral adipose tissue is associated with greater risks of some cardiovascular and some metabolic diseases and they may be responsible for increased mortality rates. Somewhat contrariwise, it can be speculated that sarcopenia, especially in the extremities, where 75% of skeletal muscle is located[38], may increase mortality rates by associations with increased incidences of infections due to immuno-incompetence, of cardiovascular diseases through undersirable lipid profiles and of fractures through a lack of bone mineral. Further comparisons are needed of these risk factors among groups differing in BMI and in the cross-sectional circumferences and areas of limb musculature.

Additionally, more direct serial studies are needed of the associations between sarcopenia and mortality rates but methods for the measurement of total muscle mass, that could be recommended for such studies are lacking. Such studies require accurate measures of muscle mass which could be obtained for total limbs by DEXA or perhaps for cross-sections of limbs by HFEA. The findings from such studies may indicate that sarcopenia, independent of smoking and pre-existing diseases, is a determinant of mortality rates in late middle age and old age. Such a finding would be of major importance because, in the absence of existing disease, sarcopenia can be reversed by physical activity regimens even at very old ages[39].

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