Diagnostic criteria for sarcopenia relate differently to insulin resistance

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Abstract Skeletal muscle is important in insulin-stimulated glucose uptake. Sarcopenia is, therefore, a possible risk factor for insulin resistance. Currently, different diagnostic criteria for sarcopenia include low muscle mass, muscle strength, and walking speed. We assessed these muscle characteristics in relation to insulin resistance in nondiabetics. This cross-sectional study included 301 nondiabetics, mean age 65.9 years. Area under curve (AUC) calculations of insulin and glucose from a 2-h oral glucose tolerance test (OGTT) and homeostasis model assessment of insulin resistance (HOMA-IR) were used as measures of insulin resistance.

Muscle characteristics were relative muscle mass (total or appendicular lean mass (ALM) as percentage of body mass), absolute muscle mass (ALM/height² and total lean mass), handgrip strength, and walking speed. All muscle characteristics were standardized and analyzed in linear regression models, stratified by gender. For both males and females, relative muscle mass was inversely associated with AUC insulin, AUC glucose, and HOMA-IR (ALM percentage all $p \leq 0.004$). Absolute muscle mass was positively associated with AUC insulin and HOMA-IR (ALM/height² all $p < 0.001$) but not with AUC glucose. Adjustments for fat mass attenuated aforementioned associations. There were no associations between handgrip strength and insulin resistance. Walking speed was inversely associated with AUC insulin in males ($p = 0.032$). The association between muscle characteristics and insulin resistance was strongest for relative muscle mass. Diagnostic criteria for sarcopenia relate differently to insulin resistance. The role of muscle tissue as an internal glucose-regulating organ is better reflected by relative muscle mass than by absolute muscle mass, muscle strength, or walking speed.

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Introduction

“Sarcopenia” was introduced as a term to describe low muscle mass at older age (Rosenberg 1997; Baumgartner

et al. 1998) but has also been used to describe low muscle strength (Lauretani et al. 2003) or a low walking speed or muscle strength combined with low muscle mass (Cruz-Jentoft et al. 2010; Fielding et al. 2011). Although clinical importance of low muscle mass is underscored by its associated increased risk of mortality (Bunout et al. 2011), physical disability (Baumgartner et al., 1998; Janssen et al. 2002), and cognitive decline (Burns et al. 2010), no consensus on the definition of sarcopenia has been reached yet (Cruz-Jentoft et al., 2010; Fielding et al., 2011). Various quantification methods of muscle characteristics and correction factors have been proposed (Baumgartner et al., 1998; Janssen et al., 2002; Janssen et al. 2004; Newman et al. 2003; Lauretani et al., 2003), which are mainly based on associations with disability in elders.

Little attention has been paid, so far, to the role of various diagnostic criteria for sarcopenia in the association with insulin resistance. Insulin resistance has mainly been associated with higher body mass index (BMI) (Wilson et al. 1986; Helmrich et al. 1991) and higher (visceral) fat percentage (Despres et al. 2001). Since skeletal muscle accounts for approximately 75 % of whole-body insulin-stimulated glucose uptake (Corcoran et al. 2007), it is important to understand which diagnostic criteria for sarcopenia relate to glucose handling expressed as insulin resistance. Only few studies have investigated this association, with conflicting results. It was shown that a lower lean mass as percentage of body mass associated with insulin resistance (Srikanthan and Karlamangla 2011). Other cross-sectional studies showed an association between higher total lean mass (Lee et al. 2011) or quadriceps mass with insulin resistance, not taking possible confounders into account (Barzilay et al. 2009). After adjustment for weight or BMI, higher quadriceps mass and higher muscle strength were associated with a lower level of insulin resistance (Barzilay et al., 2009; Sayer et al. 2005; Lazarus et al. 1997). These results indicate that important differences exist depending on which diagnostic criteria for sarcopenia are used, which is further complicated by the use of different adjustment models.

We hypothesized that a higher amount of muscle mass will generate a higher capacity for insulin-stimulated glucose uptake and will, therefore, be associated with a lower level of insulin resistance. We expect that this association is influenced by fat mass, which is positively associated with insulin resistance

(Peppas et al. 2010). Since there is little overlap in the prevalence of sarcopenia when different definitions are applied in the same study population (Bijlsma et al. 2012), we expect that not all diagnostic criteria for sarcopenia are suitable to reflect muscle tissue as an internal glucose-regulating organ. We expect that muscle mass will show a stronger association with insulin resistance than muscle strength and walking speed. To test these hypotheses, we examined the association between different diagnostic criteria for sarcopenia and valid measures of insulin resistance derived from an oral glucose tolerance test (OGTT) (Takeuchi et al. 2000) in nondiabetic middle-aged and older adults stratified by sex.

Methods

Study design

Analyses were performed on a total of 301 middle-aged and older adults including participants of the MYOAGE study and the Leiden Longevity Study (LLS). The MYOAGE study comprises 35 young (aged 18 to 30 years) and 75 relatively healthy and cognitively active older participants (aged 69 to 81 years), recruited in 2010 and 2011 in Leiden, The Netherlands, as part of a European cohort study. The group of elderly participants was recruited based on their activity levels (high or relatively low). Application of exclusion criteria was aimed to select healthy participants, minimizing the confounding effect of disease on muscle mass, i.e., dependent living situation, unable to walk a distance of 250 m, presence of comorbidity (neurologic disorders, metabolic diseases, rheumatic diseases, recent malignancy, heart failure, severe chronic obstructive pulmonary disease (COPD), and hemocoagulative syndromes), use of specified medication (immunosuppressive drugs, insulin, and anticoagulation), immobilization for 1 week during the last 3 months, and orthopedic surgery during the last 2 years or still causing pain or functional limitation. For the present analyses, only the subgroup of older adults was selected; four participants were excluded due to previous history of diabetes mellitus and one participant due to missing data on body composition, and the remaining 70 participants were included for analyses.

The LLS consists of long-living Caucasian siblings of 420 families together with their middle-aged offspring, and the partners of the offspring as controls

(Schoenmaker et al. 2006). The study included 674 participants of the middle-aged to older offspring and their partners, who were assessed in the period from 2006 to 2008 (Schoenmaker et al., 2006). There were no selection criteria on health or demographic characteristics (Westendorp et al. 2009). A subgroup of 380 middle-aged participants living in close proximity to the research center were invited to come to the research center in a fasting state; 274 of these participants agreed to participate. For the present analysis, 24 participants were excluded because of previous history of diabetes mellitus, 15 because of unreliable OGTT, one because of nonadherence to the fasting state, and three due to missing data on body composition (Roizing et al. 2010), and the remaining 231 were included for analyses. The Medical Ethics Committee of the Leiden University Medical Center approved both studies, and written informed consent was obtained from all participants.

Oral glucose tolerance test

After 12 h of fasting, glucose tolerance as a measure of insulin resistance was assessed according to 2-h OGTT, conducted with a standard loading dose of 75 g of glucose in 0.3 L of water. Venous blood samples were drawn at time points 0, 30, 60 and 120 min in both studies and additionally, at 15 and 90 min in the MYOAGE study cohort. All serum measurements were performed using fully automated equipment. For insulin levels, the Immulite 2,500 from DPC (Los Angeles, CA, USA) and for glucose, the Hitachi Modular P800 from Roche (Almere, The Netherlands) were used.

Assessment of body composition

In the MYOAGE study, body composition was measured by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500, Hologic Inc., Bedford, PA, USA). Measurements were performed with dual-energy X-ray beams at 60 and 140 KeV, operated by a trained technologist. Single rectilinear scanning mode was used on a 148×330-pixel matrix in a 196×80-cm window. Standard regions were drawn and adapted manually when necessary.

In the LLS, body composition was measured using direct segmental multifrequency bioelectrical impedance analysis (BIA) (InBody (720) body composition

analyzer, Biospace Co., Ltd., Seoul, South Korea). We have previously shown this technique to be a valid tool for the assessment of whole-body composition and segmental lean mass measurements in our sample of middle-aged people (Ling et al. 2011). Excellent agreements were observed between BIA and DXA in total lean mass (intraclass correlation coefficient (ICC) female=0.95, $p<0.001$, ICC male=0.96, $p<0.001$) and fat mass (ICC female 0.97 $p<0.001$, ICC male 0.93 $p<0.001$) (Ling et al., 2011).

Diagnostic criteria for sarcopenia

As described previously, muscle mass was grouped into relative and absolute measures (Estrada et al. 2007). Relative muscle mass corrects muscle mass for body mass and was defined as lean mass divided by body mass in percentage (Janssen et al., 2002) or appendicular lean mass (ALM, the sum of lean mass of both arms and legs) divided by body mass in percentage (Estrada et al., 2007). Absolute muscle mass was defined as ALM divided by height squared ($\text{ALM}/\text{height}^2$) (Baumgartner et al., 1998) or total lean mass in kilograms (Melton et al. 2000).

Handgrip strength was measured with a Jamar dynamometer (Sammons Preston, Inc., Bolingbrook, IL, USA). All participants were asked to stand upright and hold the dynamometer in the hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the hand. The participant was allowed to perform three trials with both the right and the left hands and the best score was used for analyses.

Walking speed was measured during a 4-m walking test from a standing start. Participants were instructed to walk at normal pace to the end of the corridor to prevent slowing down before the 4-m line (Guralnik et al. 2000). Duration of the 4-m walking test was recorded using a sensor unit containing accelerometers and gyroscopes (DynaPort Hybrid, McRoberts, The Netherlands) attached with a waist strap.

Participant characteristics

Height and body mass were collected for all participants. Comorbidity was defined as a sum score of diseases including myocardial infarction, stroke, hypertension, arthritis, COPD, and malignancy. Smoking was defined as current smoking or past smoking with

more than 10 pack years. The presence of sarcopenia was assessed according to cutoff values for ALM/height² (for males below 7.26 kg/m² and for females below 5.5 kg/m² (Baumgartner et al., 1998)) and with a walking speed below 0.8 m/s, or grip strength below cutoff (30 kg for males and 20 kg for females) (Cruz-Jentoft et al., 2010).

Statistical analyses

Continuous variables with Gaussian distribution are presented as mean (standard deviation) and those with non-Gaussian distribution as median (interquartile range (IQR)). Variables with non-Gaussian distribution were logarithmically transformed and used in all calculations. OGTT-derived areas under the curves (AUCs) were calculated using the trapezoid rule (Takeuchi et al., 2000); the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by dividing the product of fasting glucose level (in millimole per liter) and fasting insulin level (in millunit per liter) by 22.5 (Matthews et al. 1985).

All muscle characteristics were standardized in *Z* scores in order to compare effect estimates. The

associations between muscle characteristics and insulin resistance were assessed using linear regression models, stratified by sex. In the first model, analysis was adjusted for age, gender, and cohort. In the second model, further adjustments for fat mass were applied. For combined analyses of males and females, sex-specific tertiles of ALM percentage and ALM/height² were calculated. In this combined analyses, regression analyses were adjusted for age, cohort, and sex. Differences between muscle characteristics for the association with OGTT-derived measures of insulin resistance were tested for significance, without taking covariance into account, using *Z* values calculated with the formula $((b1 - b2) / \sqrt{(se^2 + se^2)})$ and *p* values derived from the standard normal distribution table. SPSS 17.0 for Windows was used for all analyses. *P* values <0.05 were considered statistically significant.

Results

Characteristics of the study participants are shown in Table 1. The mean age of participants of the MYOAGE

Table 1 Characteristics of study participants

	Male (<i>N</i> =146)	Female (<i>N</i> =155)
All values are expressed as mean (standard deviation), unless indicated otherwise		
<i>BMI</i> body mass index, <i>IQR</i> interquartile range, <i>ALM</i> appendicular lean mass, <i>OGTT</i> oral glucose tolerance test, <i>AUC</i> area under curve measured during 120-min oral glucose tolerance test		
^a Sum score of total number of diseases (myocardial infarction, stroke, hypertension, arthritis, chronic obstructive pulmonary disease, and malignancy)		
^b Smoking was defined as current smoking or more than 10 pack years		
^c Lean mass as percentage of total body mass		
^d ALM as percentage of total body mass		
^e ALM divided by squared height		
^f Data available in a subgroup of <i>N</i> =159		
Age (years)	67.4 (7.1)	64.4 (7.7)
Females, <i>n</i> (%)		
Height (m)	1.78 (0.06)	1.66 (0.06)
Total body mass (kg)	83.9 (11.2)	71.9 (11.2)
BMI (kg/m ²)	26.4 (3.3)	26.0 (4.1)
Total number of diseases, median (IQR) ^a	0 (0–1)	0 (0–1)
Smoking, <i>n</i> (%) ^b	95 (66.0)	67 (43.2)
Diagnostic criteria for sarcopenia		
Lean mass percentage (%) ^c	71.5 (6.6)	62.0 (7.2)
ALM percentage (%) ^d	31.8 (3.1)	26.9 (3.0)
ALM/height ² (kg/m ²) ^e	8.3 (0.7)	6.9 (0.7)
Total lean mass (kg)	59.6 (6.7)	44.1 (4.9)
Handgrip strength (kg)	43.8 (7.9)	28.8 (5.0)
Walking speed (m/s) ^f	1.1 (0.2)	1.2 (0.2)
OGTT-derived measures of insulin resistance		
Fasting glucose (mmol/L)	5.2 (0.6)	5.1 (0.5)
Fasting insulin, median (IQR) (mU/L)	6.0 (4–10)	6.0 (3–9)
AUC insulin (median, IQR)	93.7 (62.2–139.0)	89.1 (65.8–139.3)
AUC glucose	14.6 (3.6)	14.3 (3.7)
HOMA-IR, median (IQR)	1.48 (0.81–2.22)	1.20 (0.65–2.10)

study was 74.1 years and 63.3 years for the LLS. Equal numbers of males and females were included in both cohorts. According to cutoff values for sarcopenia, 16 (5.3 %) participants had low ALM/height², of which four (1.7 %) participants simultaneously had a low walking speed or grip strength.

Table 2 shows the results of the association between different standardized diagnostic criteria for sarcopenia and OGTT-derived measures of insulin resistance. Overall, associations were comparable in males and in females. Relative muscle mass, expressed as lean mass percentage and ALM percentage, was inversely associated with ln AUC insulin, AUC glucose, and ln HOMA-IR when adjusting for age and cohort (Table 2). When adjusting for fat mass, the statistically significant inverse associations attenuated. Absolute muscle mass, expressed as ALM/height² and total lean mass, was positively associated with AUC insulin and HOMA-IR, but not with AUC for glucose (Table 2). When adjusting for fat mass, the positive associations with ln AUC insulin disappeared. The positive association between absolute muscle mass and ln HOMA-IR also disappeared in females after adjustments for fat mass but remained statistically significant in males. There was no association between handgrip strength and the AUC for insulin, glucose, and HOMA-IR in both models. In females, walking speed was not associated with the AUC for insulin, glucose, and HOMA-IR. In males, walking speed was inversely associated with ln AUC insulin but not with AUC glucose or ln HOMA-IR.

Relative muscle mass expressed as lean mass percentage and ALM percentage was most strongly inversely associated with AUC insulin, AUC glucose, and HOMA-IR. When comparing the effect estimates of lean mass percentage and ALM percentage given in Table 2 (model 1), these were not statistically significantly different in their association with insulin resistance. In contrast, the effect estimates of lean mass percentage and ALM percentage were significantly different from the effect estimates of absolute muscle mass (ALM/height² and total lean mass) (all $p < 0.001$). Walking speed was inversely associated with AUC insulin in males but with a lower effect estimate as compared to relative muscle mass ($p < 0.001$).

Combined analyses for males and females are presented in Fig. 1. This figure visualizes the inverse association for relative muscle mass and the positive association for absolute muscle mass with OGTT-derived measures for insulin resistance.

Discussion

In middle-aged and older nondiabetic adults, diagnostic criteria for sarcopenia relate differently to insulin resistance. Relative muscle mass, expressed as lean mass percentage and ALM percentage, was inversely associated with OGTT-derived measures of insulin resistance. After adjustment for fat mass, this association attenuated. Absolute muscle mass, expressed as ALM/height² and total lean mass, was positively associated with AUC insulin and HOMA-IR and was not associated with AUC glucose. After adjustment for fat mass, the association attenuated but remained significant for HOMA-IR in males. Handgrip strength was not associated with OGTT-derived measures of insulin resistance. Walking speed was only associated with AUC insulin in males and with a lower effect estimate as compared to relative muscle mass. To the best of our knowledge, this is the first study comparing different muscle characteristics included in diagnostic criteria for sarcopenia in the context of insulin resistance. We conclude that diagnostic criteria for sarcopenia cannot be used interchangeably. Relative muscle mass is the best predictor of insulin resistance in middle-aged to older nondiabetic participants, which strengthens the case to define sarcopenia using relative muscle mass.

This study clearly shows that relative muscle mass is strongly related to OGTT-derived measures of insulin resistance. The results are in accordance with previous studies. An inverse association was observed between relative muscle mass and insulin resistance as measured with HOMA-IR (Srikanthan and Karlamangla 2011). Midthigh cross-sectional area as measured with computed tomography (CT), standardized for body mass was inversely associated with insulin resistance in older nondiabetic adults (Kalyani et al. 2011). Contrarily, absolute muscle mass, unadjusted for body mass, has been found to be associated with higher insulin resistance in cross-sectional analyses (Barzilay et al., 2009; Lee et al., 2011; Park et al. 2009).

In recent years, some researchers preferred to define sarcopenia based on low walking speed or low muscle strength combined with low muscle mass, instead of muscle mass only (Cruz-Jentoft et al., 2010; Fielding et al., 2011). In this study, we show that the role of muscle tissue as an internal glucose-regulating organ is better reflected by muscle mass

Table 2 Association between measures of insulin resistance and standardized diagnostic criteria for sarcopenia in study participants, stratified by gender ($n=301$)

OGTT-derived measures for insulin resistance						
Adjusted for age, cohort						
Male		Female		Further adjusted for fat mass		
Beta (95 % CI)	p value	Beta (95 % CI)	p value	Beta (95 % CI)	p value	p value
Ln Insulin AUC						
Z total lean mass (%) ^a	<0.001	-0.29 (-0.39, -0.19)	<0.001	-0.33 (-0.68, 0.02)	0.067	-0.16 (-0.41, 0.09)
Z ALM (%) ^b	<0.001	-0.30 (-0.41, -0.19)	<0.001	-0.18 (-0.38, 0.02)	0.071	-0.15 (-0.32, 0.33)
Z ALM/height ² (kg/m ²)	0.026	0.19 (0.07, 0.32)	0.003	-0.05 (-0.17, -0.08)	0.48	0.01 (-0.14, 0.15)
Z lean mass (kg)	0.07	0.15 (-0.03, 0.33)	0.095	-0.04 (-0.18, 0.10)	0.58	-0.03 (-0.20, 0.15)
Z handgrip strength (kg)	0.64	-0.06 (-0.24, 0.12)	0.52	0.02 (-0.11, 0.14)	0.76	-0.07 (-0.23, 0.10)
Z walking speed (m/s) ^c	0.032	0.02 (-0.10, 0.14)	0.75	-0.12 (-0.23, -0.01)	0.039	0.03 (-0.08, 0.14)
Glucose AUC						
Z total lean mass (%) ^a	0.069	-1.32 (-1.99, -0.65)	<0.001	-0.74 (-3.04, 1.57)	0.53	-0.89 (-2.51, 0.73)
Z ALM (%) ^b	0.004	-1.51 (-2.23, -0.80)	<0.001	-1.63 (-2.89, -0.36)	0.012	-1.12 (-2.28, 0.05)
Z ALM/height ² (kg/m ²)	0.79	0.78 (-0.03, 1.59)	0.059	-0.20 (-1.03, 0.63)	0.63	-0.08 (-1.03, 0.87)
Z lean mass (kg)	0.68	0.46 (-0.66, 1.58)	0.42	-0.07 (-0.97, 0.82)	0.87	-0.36 (-1.52, 0.80)
Z handgrip strength (kg)	0.40	-0.25 (-1.37, 0.87)	0.66	0.32 (-0.48, 1.12)	0.43	-0.29 (-1.37, 0.78)
Z walking speed (m/s) ^c	0.23	-0.34 (-1.13, 0.45)	0.40	-0.46 (-1.29, 0.37)	0.27	-0.29 (-1.07, 0.48)
Ln HOMA-IR						
Z total lean mass (%) ^a	<0.001	-0.42 (-0.56, -0.27)	<0.001	0.08 (-0.39, 0.54)	0.74	-0.02 (-0.37, 0.33)
Z ALM (%) ^b	<0.001	-0.37 (-0.53, -0.20)	<0.001	0.04 (-0.22, 0.30)	0.76	0.06 (-0.20, 0.31)
Z ALM/height ² (kg/m ²)	<0.001	0.43 (0.25, 0.60)	<0.001	0.18 (0.02, 0.34)	0.030	0.19 (-0.01, 0.39)
Z lean mass (kg)	<0.001	0.44 (0.19, 0.69)	0.001	0.19 (0.01, 0.36)	0.040	0.20 (-0.05, 0.44)
Z handgrip strength (kg)	0.10	-0.11 (0.37, 0.15)	0.40	0.14 (-0.02, 0.30)	0.09	-0.13 (-0.35, 0.11)
Z walking speed (m/s) ^c	0.43	-0.09 (-0.19, 0.18)	0.93	-0.04 (-0.21, 0.13)	0.63	0.01 (-0.15, 0.18)

OGTT oral glucose tolerance test, CI confidence interval, ALM appendicular lean mass, AUC area under curve measured during 120-min oral glucose tolerance test, HOMA-IR homeostasis model assessment for insulin resistance calculated as dividing the product of fasting glucose and insulin by 22.5.

^a Lean mass as a percentage of total body mass

^b ALM as percentage of total body mass

^c Data of walking speed available in a subgroup of $N=159$

^d All muscle characteristics included in diagnostic criteria for sarcopenia were standardized and are presented in Z scores. Beta indicates the change in OGTT-derived measure for insulin resistance with 1 SD increase of muscle characteristics

Values in bold are statistically significant

than by muscle strength or walking speed. This can be explained by involvement of other systems besides muscle mass in the generation of strength, such as neural control and joint function. Previous studies in older nondiabetic adults reporting on the association between muscle strength or walking speed and insulin resistance show conflicting results (Lazarus et al., 1997; Barzilay et al., 2009; Kuo et al. 2009; Sayer et al., 2005). In older adults, weight or BMI-adjusted handgrip strength was inversely associated with insulin resistance (Lazarus et al., 1997; Sayer et al., 2005). Barzilay et al. showed a trend towards a positive association between unadjusted quadriceps strength and HOMA-IR but an inverse association with quadriceps strength divided by quadriceps mass (Barzilay et al., 2009). In the National Health and Nutrition Examination Survey (NHANES), no association was found between peak leg strength and HOMA-IR

in men and women aged over 50 years, but there was an inverse association between insulin resistance and walking speed in men only (Kuo et al., 2009). Comparing these studies is difficult since a variety of adjustment models and statistical methods were used.

The positive association between absolute muscle mass with insulin resistance can be explained by the effect of fat mass, since this association attenuated after adjustment for fat mass in this study. Adjusting muscle mass for height only, as was first suggested by Baumgartner et al. (1998), seems to be insufficient to account for the influence of fat mass. A higher lean mass at older age is often accompanied by higher fat mass (Estrada et al., 2007; Newman et al., 2003). Fat mass is an inducer of insulin resistance by secretion of adipokines, inflammatory mediators, and growth factors, although some adipokines are associated with

Fig. 1 Sex-specific tertiles of the relative muscle mass ALM percentage (a, c, e) and absolute muscle mass ALM/height² (b, d, f) in relation to OGTT-derived measures of insulin resistance. OGTT-derived measures of insulin resistance: Ln AUC insulin (a, b), AUC glucose (c, d), and Ln HOMA-IR (e, f). *Appendicular lean mass (ALM) percentage* ALM as percentage of total body mass, *ALM/height²* ALM divided by squared height, *OGTT* oral glucose tolerance test, *AUC* area under curve measured during 120-min oral glucose tolerance test, *HOMA-IR* homeostasis model assessment for insulin resistance calculated by dividing the product of fasting glucose and insulin by 22.5. *P* for trend from linear regression analysis adjusted for cohort, gender, and age. Bars indicate adjusted means and standard error. *NS* not significant; ***=*P*<0.001

lower insulin resistance such as adiponectin. Tumor necrosis factor- α (TNF- α), adiponectin, and leptin are the main adipokines that appear to be involved in the cross-talk between fat mass and skeletal muscle mass (Peppas et al., 2010). The secretion of inflammatory cytokines could also lead to a reduction in muscle mass, as in longitudinal studies, TNF- α , interleukin-6, and C-reactive protein have been associated with loss of muscle mass (Aleman et al. 2011; Schaap et al. 2009). Future research is needed to further explore causal mechanisms. Another example of the interaction between muscle and fat is that increased deposition of lipids in the myotubes leads to muscle lipoprotein lipase overexpression, which in turn, is associated with insulin resistance (Corcoran et al., 2007). Furthermore, reduced mitochondrial function in aged muscle is associated with insulin resistance that may impair the stimulating action of insulin on mitochondrial protein synthesis and function. Through these closed loops, insulin resistance can increase the rate of loss of skeletal muscle mass and vice versa (Guillet and Boirie 2005; Lee et al., 2011; Park et al., 2009).

The strength of this study was the ability to compare different measures of muscle mass or muscle function in the association with insulin resistance. Furthermore, the use of OGTT is a more sensitive test for skeletal muscle insulin resistance than fasting estimates of insulin resistance such as HOMA-IR as was reported in previous studies (Antuna-Puente et al. 2011; Abdul-Ghani et al. 2007). Fasting indices for insulin resistance such as the HOMA-IR primarily reflect hepatic insulin resistance (Antuna-Puente et al., 2011; Abdul-Ghani et al., 2007). A clamp study would be the gold standard to differentiate between muscle insulin resistance and hepatic insulin resistance. The limitation of this study was that only cross-sectional data were available, which makes causal inference difficult. Study sample size was relatively small although this did not prevent meaningful results. Furthermore, we cannot generalize the results to older frail participants, as the study population consisted of relatively healthy middle-aged and older participants.

In conclusion, diagnostic criteria for sarcopenia relate differently to insulin resistance. Lower relative muscle mass is most strongly associated with insulin resistance. ALM/height², the parameter most often used in literature to define sarcopenia, does not correct for body fat and is, therefore, an inadequate reflection

of the association between muscle mass and insulin resistance. Handgrip strength and walking speed are not reflecting the role of muscle tissue as an internal glucose-regulating organ. The definition of sarcopenia should include relative muscle mass hereby intrinsically adjusting for fat mass to reflect its function as an internal organ. In future studies, assessment of relative muscle mass in larger study cohorts including the general population could be of additional value to decide on cutoff values for a low relative muscle mass as predictor of insulin resistance.

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