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ORIGINAL ARTICLE

Effect of sexual dimorphism on muscle strength in cachexia

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Abstract
Background Reduced muscle strength is a cardinal feature in cachexia. We investigated whether weight loss is associated differently with muscle strength in men and women in a large cohort of hospitalized patients.
Methods One thousand five hundred hospitalized patients (whereof 718 men, mean age 57.6±16.0 years, mean body mass index (BMI) 24.6±4.8 kg/m²) were included in the study. Non-edematous involuntary weight loss was determined with Subjective Global Assessment; isometric maximal muscle strength was evaluated by hand grip strength. Mid-upper arm circumference and triceps skinfold were used to calculate arm muscle area. Interrelationship between sex and weight loss was evaluated by regression analysis performed with the general linear model (GLM) allowing adjustment for continuous and categorical variables and corrected for age, arm muscle area (AMA), BMI, and diagnosis category (benign/malignant disease) as potentially confounding covariates.
Results Both men and women exhibited a significant stepwise decrease of hand grip strength with increasing weight loss. Age, sex, moderate and severe weight loss, BMI, and AMA were significant predictors of hand grip strength. The GLM moreover revealed a significant sex × weight loss effect, since grip strength was similarly decreased in moderate weight loss in men and women when compared to control patients without weight loss (8.5% in men and 10.5% in women, not significant (n.s.)), but the further reduction of grip strength in severe weight loss was significantly different between men and women (10.6% vs. 4.1%, $P=0.033$).
Conclusions Our findings indicate sex-specific differences in muscle strength response to weight loss.

Keywords Weight loss · Muscle strength · Sexual dimorphism

1 Introduction

Involuntary weight loss or cachexia is frequently observed in chronic disease with a reported prevalence between 5% and 80% depending on clinical population [1, 2]. Loss of muscle mass is a cardinal feature in cachexia [3] which results in measurable impairment of muscle function. When nutritional intake is reduced or requirements are increased, a compensatory loss of whole body protein occurs. It is known that protein is preferably lost from muscle in cachexia as it represents the largest protein reserve [4, 5]. Muscle strength of upper as well as lower extremities is reduced in patients with clinically relevant weight loss [6–8]. In cancer patients, cachexia has even been shown to be an independent predictor of hand grip strength [9]. However, the etiology of muscle dysfunction in weight loss is not yet completely understood.

In disease, several factors may further interact on muscle strength. Bed rest [10, 11], muscle disuse [12], inflammation, infection, endotoxemia, corticosteroids and stress [13, 14], muscle relaxants, hypoxia, as well as oxidative stress all have

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adverse effects on muscle function [15]. Impaired muscle function has severe consequences affecting functional status, recovery, and outcome. It is therefore not surprising that reduced hand grip strength is an excellent predictor of outcome in the clinical setting. Next to age, sex is one of the major determinants of muscle strength both in healthy and sick individuals [16]. Due to greater muscle mass, men generally exhibit greater grip strength than women [17]. In this large cross-sectional study, we investigated whether involuntary weight loss is differently associated with muscle strength in men and women.

2 Methods

2.1 Patients

One thousand five hundred patients were included in the pooled analysis. Patients were originally consecutively recruited in prospective cross-sectional studies at the Dept. of Gastroenterology, Infectiology and Rheumatology or Dept. of Oncology at the University Hospital Charite [9, 18–20] with the same method protocol. Patients were assessed within 48 h of admission to hospital. Patients under the age of 18 years or with neuromuscular disease, hemiplegia, and osteoarthritis were a priori not considered for inclusion due to bias in hand grip strength measurements.

All patients gave written informed consent and the Ethics Committee of the Charite Universitätsmedizin Berlin approved each study. Demographic characteristics, age and sex, diagnosis, and comorbidities as well as length of hospital stay were recorded.

2.2 Anthropometric measurements

Body weight was measured in light clothes with a portable electronic scale (Seca 910, Hamburg, Germany) to the nearest 0.1 kg and height was measured with a portable stadiometer (Seca 220 telescopic measuring rod) to the nearest 0.1 cm. Weight and height were used to calculate body mass index (BMI; weight (kg)/height (m)²).

Mid-upper arm circumference (of the nondominant arm) was measured to the nearest 0.1 cm with a nonelastic tape measure and triceps skinfold was measured to the nearest 0.1 mm with a Holtain caliper (Crymych, UK) on the nondominant relaxed arm midway between the tip of the acromion and the olecranon process. Arm muscle area (AMA) was calculated applying the formula by Gurney [21].

2.3 Nutritional status

Involuntary, non-edematous weight loss was determined with the validated Subjective Global Assessment as described by Detsky et al. [22]. In brief, the method relies on the patient's history regarding weight loss in the last 6 months, nutritional intake, gastrointestinal symptoms, functional capacity, and physical signs of malnutrition (loss of subcutaneous fat or muscle mass, edema, and ascites). Patients were classified as without weight loss (A), with moderate weight loss in case of involuntary weight loss ≥5%/6 months (B) or severe weight loss in case of involuntary weight loss ≥10%/6 months (C).

2.4 Maximal isometric skeletal muscle strength

Hand grip strength as indicator of muscle strength of the upper extremities was measured in the nondominant hand with a Jamar dynamometer (Sammons Preston Rolyan, Chicago, USA). The patients performed the test while sitting comfortably with shoulder adducted and neutrally rotated forearm, elbow flexed to 90°, and forearm and wrist in neutral position. The patients were instructed to perform a maximal isometric contraction. The test was repeated within 30 s and the highest value of three tests was used for the analysis.

2.5 Inflammation

C-reactive protein as indicator of inflammation was determined by standard laboratory methods.

Table 1 Diagnoses in the study population

	Type	Percent
Malignant disease (*n*=597)	Colorectal cancer	19.6
	Head and neck cancer	13.2
	Hematologic disease	11.4
	Urogenital and mamma cancer	9.6
	Pancreatic cancer	9.4
	Gastric cancer	8.0
	Hepatic cancer	7.7
	Lung	6.2
	Biliary cancer	4.5
	other	10.4
Benign disease (*n*=903)	Inflammatory bowel disease	33.8
	Hepatic disease	20.3
	Benign colon disease	10.4
	Heart disease	8.1
	Gastro-oesophageal disease	4.6
	Biliary disease	3.4
	Pancreatic disease	2.3
	Lung	1.6
	Diabetes	1.5
	Other	14.0

Table 2 Demographic and clinical characteristics of the study population

	All (n=1,500)	Males (n=718)	Females (n=782)	P value
Age (years)	57.9±16.0	58.1±15.3	57.6±16.6	n.s.
Malignant disease (%)	39.8	42.2	37.6	n.s.
Moderate and severe weight loss: n (%)	424/290 (28.3/19.3)	208/158 (29/22)	216/132 (27/16.9)	0.016
BMI (kg/m²)	24.6±4.8	24.8±4.5	24.4±5.1	n.s.
Arm muscle area (cm²)	47.3±14.9	51.7±14.5	43.3±14.2	<0.0001
Hand grip strength (kg)	34.6±11.1	35.1±11.2	23.1±8.2	<0.0001
CRP (mg/dl) (subcohort: 53%)	3.0±4.6	3.3±4.8	2.7±4.4	n.s.

2.6 Statistics

Statistical analysis was carried out using the software package PASW 18, SPSS Inc., Chicago, USA.

All data are given as mean and standard deviation. Box plots displaying minimum, maximum and 25th, 50th as well as 75th percentiles were used in order to portray hand grip strength. Pearson's correlation was calculated to assess the relationship between variables. Multiple comparison between the patients with no, moderate and severe weight loss was performed with one-way between-groups analysis of variance.

In order to investigate the interrelationship between sex and disease-related malnutrition, a regression analysis was performed with the general linear model (GLM) allowing adjustment for continuous and categorical variables and corrected for age, AMA, BMI, and diagnosis category (benign/malignant) as covariates. Estimated marginal means, i.e., means adjusted for confounding covariates were calculated for hand grip strength for men and women, respectively. An acceptable level of statistical significance was established a priori at $p<0.05$.

3 Results

One thousand five hundred patients (whereof 718 men, 47.9%) were included. Mean age was 57.6±16.0 years, mean BMI was 24.6±4.8 kg/m². Five hundred ninety-seven patients (39.8%) had malignant disease. Four hundred twenty-one patients (28.1%) exhibited moderate weight loss (mean weight loss, −8.5±4.9%) and 290 patients (19.3%) suffered severe weight loss (mean weight loss, −14.7±6.2%).

Fifty percent of male patients with moderate weight loss had malignant diseases compared to 46.3% in women (n.s.) whereas 47% of male patients with severe weight loss exhibited malignant disease compared to 50% in women (n.s). Diagnoses, demographic, and clinical characteristics stratified according to sex and nutritional status are given in Tables 1 and 2.

Both men and women with moderate and severe weight loss exhibited significant lower values of hand grip strength compared to patients without weight loss (see Fig. 1 and Table 3). There was a significant reduction of hand grip strength with increasing age (males: $r=-0.403$, $p<0.00001$; females: $r=-0.363$, $p<0.00001$). Hand grip strength was moreover correlated with AMA (males: $r=0.365$, $p<0.00001$; females: $r=0.173$, $p<0.00001$), but only very weakly with BMI (males: $r=-0.085$, $p=0.025$; females: $r=-0.111$, $p=0.002$). C-reactive protein (CRP) was only available in a subcohort of patients (793 patients), but as expected, hand grip strength was inversely associated with CRP (males: $r=-0.2$, $p<0.00001$; females: $r=-0.224$, $p<0.00001$).

In order to investigate possible sex-related impact of malnutrition-related muscle weakness, a GLM regression

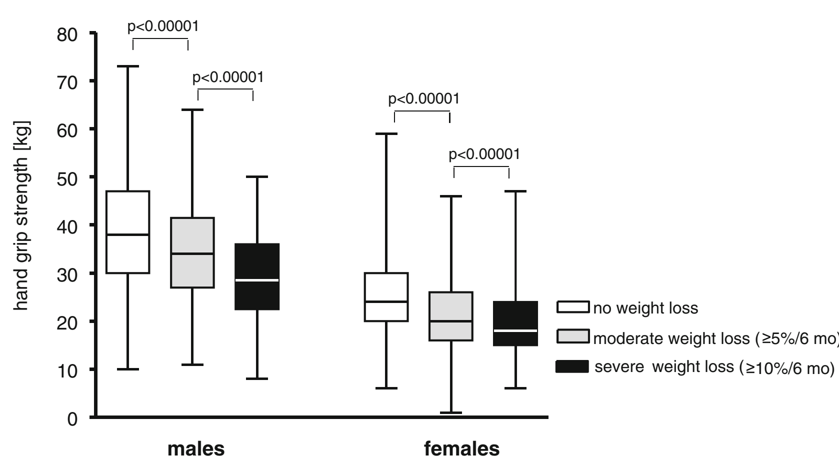

Fig. 1 Absolute unadjusted hand grip strength values in cachexia, stratified according to sex. Multiple comparisons between the groups was performed with one-way between groups analysis of variance

Table 3 Hand grip strength according to nutritional status: absolute means and means adjusted for confounding factors in males and females

Nutritional status	Grip strength (kg)	
	Unadjusted means	Means adjusted for age, BMI, arm muscle area and malignant vs. benign disease
Males		
No weight loss	38.3±11.3	36.5±0.5 (35.5–37.4)
Moderate weight loss	34.1 ±10.4	33.3±0.6 (32.2–34.6)
Severe weight loss	29.2±9.5	29.8±.07 (28.5–31.2)
Females		
No weight loss	25.2±7.9	25.4±0.4 (24.6–26.2)
Moderate weight loss	21.1±8.0	22.7±0.6 (21.5–23.9)
Severe weight loss	19.2±7.3	21.7±0.8 (20.4–23.3)

analysis adjusted for confounding variables such as age, sex, and BMI was performed. The GL model revealed that sex had a significant impact on the response of grip strength to weight loss (see Table 4). Grip strength was similarly decreased in moderate weight loss in men and women when compared to patients without weight loss (8.5% in males and 10.5% in females), but the further reduction of grip strength in severe weight loss was significantly different between men and women (10.6% vs. 4.1%, $p<0.001$; see Fig. 2). Thus men experienced a much greater reduction of muscle strength (18.2%) in severe weight loss compared to good nutritional status than women (14.2%), corresponding to approximately 3.1 kg greater loss of grip strength in men than women (see Table 4). When the GLM regression analysis was stratified according to younger and higher age (<70 and >70 years), this phenomenon was only seen in younger patients (n=1,142, 76%) with a significantly greater overall grip strength reduction of 21.7% in severely weight-losing men compared to 15.9% in weight-losing women, $p<0.0001$ (data not shown).

Table 4 Significant interrelationship between sex and cachexia with regard to hand grip strength

	Hand grip strength (kg)	
	B coefficient	*P* value
Age (years)	−0.250	<0.0001
Male vs. female sex	7.958	<0.0001
Moderate weight loss[a]	−2.795	<0.001
Severe weight loss[a]	−3.753	<0.001
BMI (kg/m²)	−0.228	<0.0001
AMA (cm²)	0.20	<0.0001
Sex-specific impact		
Nutritional status × male sex		
Moderate weight loss vs. no weight loss	−0.415	n.s.
Severe weight loss vs. moderate weight loss	−2.732	0.033
Severe weight loss vs. no weight loss	−3.145	0.006

[a] Versus good nutritional status

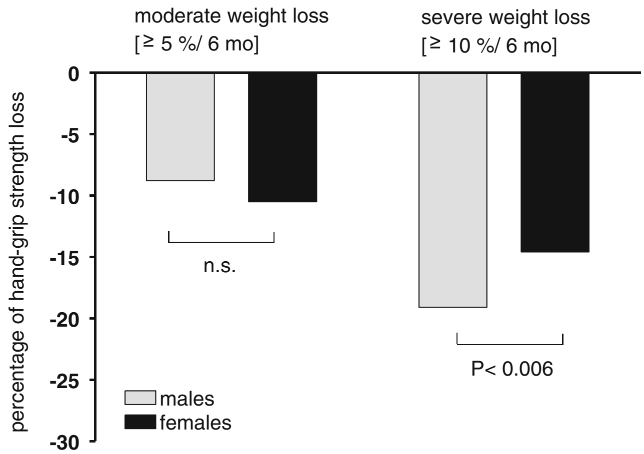

Fig. 2 Percentage hand grip strength reduction in moderate and severe cachexia, stratified according to sex

4 Discussion

In this large cross-sectional study, we observed a greater discrepancy in hand grip strength values between well-nourished and weight-losing men than between well-nourished and weight-losing women. In severe weight loss in particular, our male study participants exhibited a larger percentage reduction in hand grip strength values than women did. When analyzing the data stratified according to age, however, this applied only to patients younger than 70 years, whereas there were no differences in grip strength response to weight loss in higher age between men and women.

It has previously been shown that weight loss or underweight has different impact in men and women. Wolf reported sex-related differences regarding the response of the hormone ghrelin and the adipocytokine leptin to weight loss in cancer patients [23].

In cachexia or underweight, testosterone levels are frequently decreased in men [24]. Smith et al. observed low testosterone with higher-than-normal values of luteinizing hormone (LH) in severely malnourished but otherwise healthy men [25]. Similarly, Chlebowski observed lower levels of free and total testosterone in cancer patients with the greatest weight deficit relative to their ideal weight, although LH levels were normal or increased [26]. Lado Abeal et al., moreover, revealed sex differences regarding the impact of disease-related malnutrition on the hypothalamic−pituitarygonadal axis. Again, underweight men (defined by a BMI<18.5 kg/m²) had low testosterone levels with normal or above normal LH levels, whereas malnourished women had depressed gonadotropin levels [27].

It is therefore tempting to speculate that the greater loss of muscle strength in men which we observe in this study population is due to decreased free testosterone, which correlates with muscle strength in men [28]. We, moreover, did not find these sex-related differences in older patients which might be explained by the already reduced testosterone levels in higher age.

There is much evidence that age-associated loss of muscle strength is different in men and women. Shepard found greater loss of hand grip strength in elderly men than women in a cross-sectional study [29]. This has been attributed to the reduction of sexual hormones. In the elderly, sex hormone status is an important factor for muscle mass in men but not in women [30]. This partly explains why muscle strength is more preserved in women than men in higher age, although estrogen, which also exerts a protective effect on muscle, declines after menopause as well [31]. Kirchengast et al. observed that men appear to be more prone to sarcopenia, loss of muscle mass and strength, in higher age, whereas sarcopenia appears to be more prevalent in women under the age of 70 [32]. Another potential influencing factor which cannot be disregarded is inflammation, as increased levels of C-reactive protein correlated with lower muscle strength values in a subgroup of our study population. The association between CRP and grip strength in elderly in particular has been reported by others [33, 34].

Our findings are invariably limited due to their cross-sectional design and lack of hormone values, but clearly imply that men experience a greater loss of more grip strength in weight loss of more than 10%. Hand grip strength correlates well with functional status and quality of life [9]. Reduced grip strength is a predictor of impaired outcome, such as increased postoperative complications, increased length of hospitalization, higher rehospitalization rate, and decreased physical status [35]. In men in particular, low grip strength in health predicts increased long-term risk of functional limitations and disability as well as all-cause mortality [36, 37]. In contrast to women, high grip strength also appears to be protective against premature mortality in men [17, 38]. These findings suggest that higher strength signifies greater physiologic and functional reserve.

In conclusion, our results show sex-specific differences in muscle strength in severe weight loss. This implies that sex-specific aspects might also be relevant for anticatabolic treatment such as nutritional or physical therapy. Further studies should therefore investigate sex-related response to nutritional repletion or physical exercise in cachectic patients.

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