ORIGINAL ARTICLE

Change of skeletal muscle mass in patients with pheochromocytoma

Seung Hun Lee[1] · Mi Kyung Kwak[1] · Seong Hee Ahn[2] · Hyeonmok Kim[3] · Yoon Young Cho[4] · Sunghwan Suh[5] ·
Kee-Ho Song[6] · Jung-Min Koh[1] · Jae Hyeon Kim[7] · Beom-Jun Kim[1]

Abstract

The effects of catecholamine excess due to pheochromocytoma on body composition, including skeletal muscle mass, are unknown. Here, we investigated the effects of catecholamine metabolites on body composition in subjects with pheochromocytoma. After body compositions using bioelectrical impedance analysis, urinary metanephrine (UM), and urinary normetanephrine (UNM) were measured in 16 patients with pheochromocytoma and 224 patients with nonfunctioning adrenal incidentaloma (NFAI), we compared skeletal muscle mass and fat mass (FM) between the two groups. After adjustments for confounders, UM ($\beta = -0.171$, $P = 0.006$) and UNM ($\beta = -0.249$, $P < 0.001$) levels were correlated inversely with skeletal muscle mass index (SMI), but not FM or percentage FM (pFM), in all subjects. Patients with pheochromocytoma had lower ASM by 7.7% ($P = 0.022$) and SMI by 6.6% ($P = 0.001$) than patients with NFAI. Conversely, FM and pFM were not statistically different between the two groups. The odds ratio for low skeletal muscle mass in the presence of pheochromocytoma was 10.33 (95% confidence interval, 2.65–40.22). Our results indicate that patients with pheochromocytoma have a reduced skeletal muscle mass and suggest that catecholamine excess has adverse effects on skeletal muscle metabolism.

Keywords Pheochromocytoma · Catecholamine · Skeletal muscle · Sarcopenia

Introduction

There has been increase in aging population throughout the worldwide [1]. This has resulted in an increase in the incidence of sarcopenia, a loss of skeletal muscle mass and diminished muscle function (strength or performance) with

✉ Jae Hyeon Kim
    jaehyeon@skku.edu

✉ Beom-Jun Kim
    umkbj0825@amc.seoul.kr

[1] Division of Endocrinology and Metabolism, Department of Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea

[2] Division of Endocrinology and Metabolism, Department of Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea

[3] Department of Medicine, Seoul Medical Center, Seoul, South Korea

age [2, 3]. The prevalence of sarcopenia is 12.1% of men and 11.9% of women according to the Korea National Health and Nutrition Examination Survey [4]. Sarcopenia is associated with increased morbidity and mortality [5], suggesting that the maintenance of muscular function into old age is critical to healthy aging.

Catecholamines, such as epinephrine and norepinephrine, are secreted from the adrenal medulla and sympathetic nervous system and exert considerable influence on the body's energetic processes. They can influence metabolism

[4] Division of Endocrinology and Metabolism, Department of Medicine, Gyeongsang National University School of Medicine, Jinju, South Korea

[5] Division of Endocrinology and Metabolism, Department of Medicine, Dong-A University Medical Center, Dong-A, University College of Medicine, Busan, South Korea

[6] Division of Endocrinology and Metabolism, Department of Medicine, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, South Korea

[7] Division of Endocrinology and Metabolism, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, South Korea

directly via adrenoreceptors in metabolically active organs and tissues [6, 7]. As a metabolically active organ, skeletal muscle can be modulated by catecholamines. The role of β-adrenoreceptors, especially β_2-adrenoreceptor, has been investigated in skeletal muscle because β_2-adrenoreceptor is the predominant catecholamine receptor subtype in skeletal muscle [8, 9]. β_2-adrenoreceptor stimulation can increase the rate of protein synthesis and suppress protein degradation by activating cAMP-protein kinase A (PKA) via the $G\alpha_s$-cAMP signaling pathway [9, 10] and by activating phosphoinositol 3-kinase (PI3K)-AKT signaling via the $G\beta\gamma$ pathway [11, 12], resulting in skeletal muscle hypertrophy. However, animal and human studies have demonstrated complex results. Short-term activation of the β_2-adrenergic system by a β-agonist increases skeletal muscle mass [9, 12–14], whereas chronic activation of the β_2-adrenergic system shows no anabolic effect or induces skeletal myotoxicity [9, 15, 16]. Various mechanisms underlying the impact of chronic activation have been suggested, such as increased muscular atrophy and apoptosis, decreased muscle-specific capillary blood flow, and increased oxidative stress [9, 15–17]. In addition, α-adrenoreceptor activation may cause skeletal muscle wasting via vasoconstriction and dysregulation of exercising skeletal muscle blood flow [18] because α-adrenoreceptor is expressed at greater levels in highly vascularized skeletal muscles [19]. Thus, to date, the role of catecholamines in human skeletal muscle function remains unclear.

Pheochromocytoma (PHEO) is a catecholamine-producing tumor occurring in the adrenal medulla [20], and PHEO patients are a good model to investigate the role of catecholamines in the human body. Although many reports describe the relationship of PHEO with glucose intolerance [21–23], dyslipidemia [6], and obesity [7, 24], the specific effects of catecholamines on sarcopenia have not been examined. In the present study, we examined the associations of catecholamines with body composition and compared body composition in patients with PHEO with that in patients with nonfunctioning adrenal incidentaloma (NFAI). In addition, PHEO is reported to alter energy metabolism via a diverse mode of action. Therefore, we compared alterations in skeletal muscle mass with those in fat mass (FM) in both patient groups.

Materials and methods

Study participants and protocol

The study population was based on the Asan Medical Center (AMC) and Samsung Medical Center (SMC) cohort, a subset of a randomized multicenter trial (Co-work Of Adrenal Research study; clinicaltrial.gov no. NCT01382420) conducted at three medical centers in South Korea [25]. From July 2011 to June 2014, 985 consecutive patients with newly diagnosed adrenal incidentaloma (AI) were recruited from AMC ($N = 616$) and SMC ($N = 369$) (Fig. 1). The adrenal masses (size ≥ 1 cm) were detected by computed tomography performed for an unrelated disease. A total of 297 subjects with suspected overt or subclinical hypercortisolism (SH), primary aldosteronism, congenital adrenal hyperplasia, primary or metastatic adrenal carcinoma, or adrenal tuberculosis were excluded. As described previously [25], diagnostic criteria for SH were cortisol levels after a 1 mg overnight dexamethasone suppression test (1 mg DST) of > 138 nmol/l (5.0 μg/dl) or cortisol levels after 1 mg DST of > 61 nmol/l (2.2 μg/dl) with the presence of either low levels of ACTH [< 2.2 pmol/l (< 10 pg/ml)] or dehydroepiandrosterone-sulfate [DHEAS; < 2.17 μmol/l (< 80 μg/dl) in males or < 0.95 μmol/l (< 35 μg/dl) in females]. Among the remaining 688 subjects (632 with NFAI and 56 with histologically confirmed PHEO after adrenalectomy), 240 subjects (224 with NFAI from both AMC and SMC, and 16 with PHEO from AMC) were referred from the health promotion center because of AI, and underwent bioelectrical impedance analysis (BIA). Therefore, these 240 subjects with available BIA data were included in this study.

Patients were asked to complete a questionnaire to provide information such as smoking habits (current smoker), alcohol intake (≥ 3 units/day), regular outdoor exercise (≥ 30 min/day), history of medication use, previous medical or surgical procedures, and reproductive status including menstruation. The symptoms suggestive of PHEO were defined following a previous description [26], with these including headache, tachycardia/palpitation, sweating, and uncontrolled or paroxysmal hypertension. Patients with chronic controlled hypertension without typical symptoms were regarded as asymptomatic patients.

Patient height (cm) and weight (kg) were measured using a standardized protocol, with the patients wearing only light clothing and no shoes. Body mass index (BMI; kg/m^2) was calculated according to their height and weight. After the patients had rested for more than 15 min, blood pressure (BP; mmHg) and pulse rate (PR) were recorded twice and averaged, with BP being measured using a mercury manometer with an appropriate cuff size.

This study was approved by the Institutional Review Board of AMC and SMC. Written informed consent was provided by all enrolled participants.

BIA measurement

BIA was performed only once, at the health promotion center before registration. This analysis was performed in the morning after an overnight fast, but not after adrenalectomy. Parameters of body composition such as FM (kg),
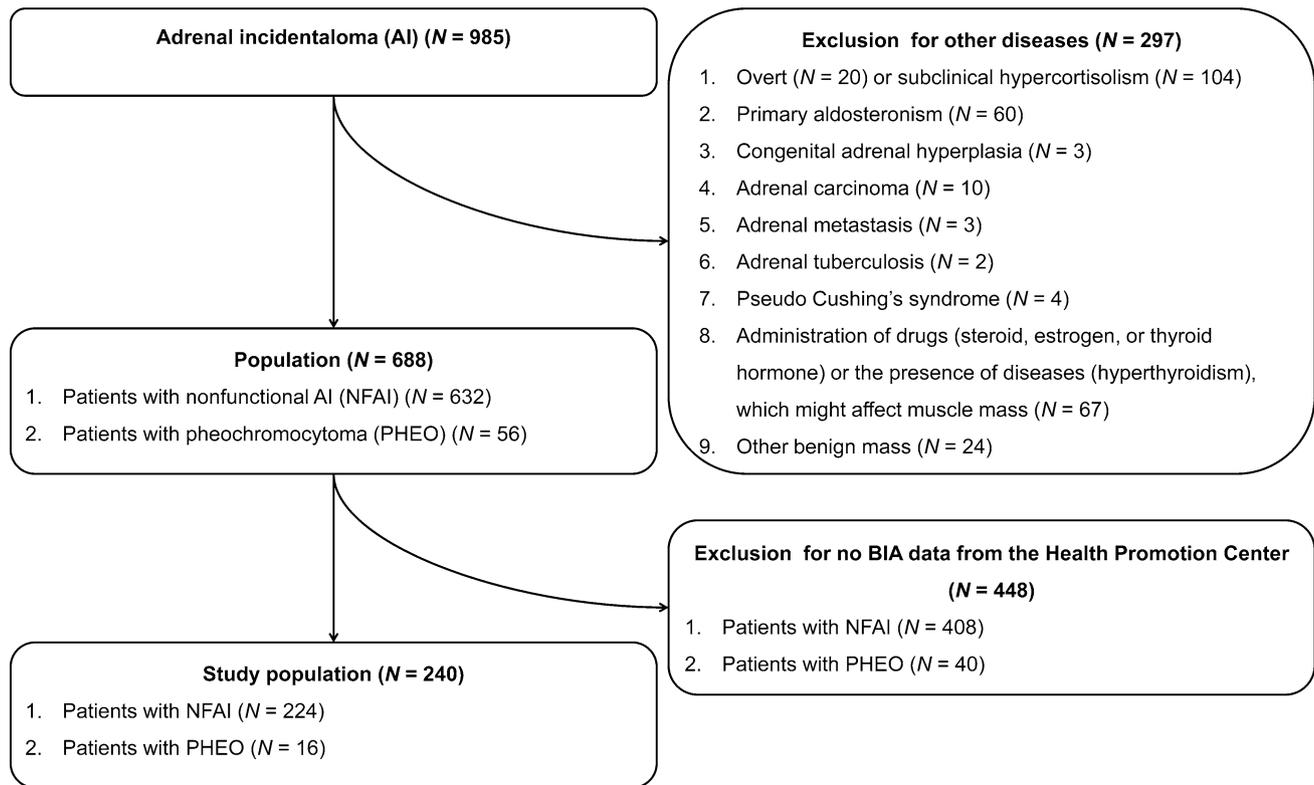
Fig. 1 A flowchart of patients in this study

percentage FM [pFM (%)], and skeletal muscle mass of the arms and legs were measured using a direct segmental multi-frequency BIA (In-Body720; Biospace Co., Ltd, Seoul, Korea) at both AMC and SMC. Appendicular skeletal muscle mass (ASM) was calculated as the sum of skeletal muscle mass in the arms and legs. Low skeletal muscle mass was defined by skeletal muscle mass index [SMI (kg/m^2); ASM (kg) divided by height squared (m^2)] on BIA, using cutoff points of <6.75 kg/m^2 for men and <5.07 kg/m^2 for women, according to the consensus report of the Asian Working Group for Sarcopenia [2].

Hormonal and biochemical measurements

Twenty-four hour urinary fractionated metanephrines, such as urinary metanephrine (UM) and normetanephrine (UNM), were measured using an Agilent 1100 high-performance liquid chromatography (HPLC) system (Agilent Technologies, Santa Clara, CA, USA) at AMC and an Agilent 1200 HPLC system with an electrochemical detector (Agilent Technologies) at SMC. Although two different kits were used to measure urine fractionated metanephrines [a HPLC kit (Chromsystems, Munich, Germany) and a commercially available HPLC kit (Bio-Rad Laboratories, Hercules, CA, USA)], the Passing-Bablok correlation test revealed

no statistical deviation of the two kits for UM and UNM levels in 21 identical urine samples [26]. Both the intra- and inter-assay imprecision of urine fractionated metanephrines at SMC and AMC were <10% of the coefficient of variation.

At the AMC, fasting plasma glucose (FPG) was measured by a hexokinase method using a Glucose HK Gen.3 kit (Roche Diagnostics, Basel, Switzerland) on a Cobas Integra-800 analyzer (Roche Diagnostics), while at the SMC it was performed using a GLU kit (Roche Diagnostics) on a Roche Modular Analytics system (Roche Diagnostics). Glycated hemoglobin (HbA1c) was measured at the AMC by turbidometric inhibition immunoassay (TINIA) using a HbA1c Gen.2 kit (Roche Diagnostics) on a Cobas Integra-800 analyzer (Roche Diagnostics), and at the SMC by HPLC assay using G8 Elution buffers HSi No. 1, No. 2, No. 3 kit (TOSOH, Yokkaichi, Japan) on an HLC-723G8 (TOSOH).

Statistical analysis

Data are presented as mean ± standard deviation (SD), median (interquartile range), or numbers (percentages), unless otherwise specified. The baseline characteristics were compared by Student's t test or Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables.

For assessing whether associations between UM or UNM levels (expressed as a continuous variable) and body composition were modified by sex (coded as 0 and 1 for women and men, respectively, and expressed as a categorical variable), interaction analysis was performed. Multiple linear regression analyses were performed after adjustment for potential confounders to investigate the association of UM or UNM levels with ASM, SMI, FM, and pFM. Age, sex, BMI, and regular outdoor exercise were included as potential confounders. The distributions of UM and UNM levels, and their associations with SMI, were investigated using Pearson correlation and scatter plots. UM and UNM levels were log-transformed because of skewed distribution. The multi-variable-adjusted least-square mean levels [95% confidence intervals (CIs)] of ASM, SMI, FM, and pFM according to absence or presence of PHEO were estimated and compared through analysis of covariance after adjusting confounders. Odds ratios (ORs) and 95% CIs per log-unit increase in UM

and UNM levels or according to the presence of PHEO for low skeletal muscle mass were generated through multiple logistic regression analyses after adjustment for confounders. SPSS statistical software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the 240 study subjects are listed in Table 1. BMI was significantly lower ($P = 0.011$) in the PHEO group than in the NFAI group. Tumor diameter ($P = 0.001$), UM levels ($P < 0.001$), and UNM levels ($P < 0.001$) were significantly greater in the PHEO group than in the NFAI group. Thirteen of the sixteen patients (81.2%) with PHEO were asymptomatic. Patients with PHEO had higher systolic BP, diastolic BP, and PR than patients with NFAI, despite the

Table 1 Baseline characteristics of subjects ($N = 240$)

Group	NFAI ($N = 224$)	PHEO ($N = 16$)	P
Age (years)	54.4 ± 7.6	52.1 ± 10.6	0.396
Male, N (%)	157 (70.1%)	10 (62.5%)	0.722
Height (cm), mean ± SD	166.4 ± 8.0	168.1 ± 6.9	0.421
Weight (kg), median [IQR]	71.2 [63.0–78.9]	66.4 [60.0–71.0]	0.117
BMI (kg/m²), median [IQR]	**25.3 [23.3–27.4]**	**23.7 [22.3–24.4]**	**0.011**
Regular exercise, N (%)	77 (34.4%)	6 (37.5%)	> 0.999
Current smoker, N (%)	59 (26.3%)	3 (18.8%)	0.653
Alcohol use (≥ 3 units/day), N (%)	14 (6.2%)	2 (12.5%)	0.653
Symptoms suggestive of PHEO[a], N (%)	**0 (0.0%)**	**3 (18.8%)**	**< 0.001**
Systolic blood pressure (mmHg), median [IQR]	**115.0 [105.0–123.0]**	**125.0 [115.8–132.5]**	**< 0.024**
Diastolic blood pressure (mmHg), mean ± SD	**68.9 ± 10.5**	**78.3 ± 8.6**	**< 0.001**
Pulse rate (/min), median [IQR]	**67.5 [64.0–70.0]**	**75.0 [70.0–81.2]**	**< 0.001**
Anti-hypertensive medication, N (%)	**25 (11.2%)**	**7 (43.8%)**	**0.001**
Class of anti-hypertensive medication			> 0.999
Beta-adrenergic blockers, N (%)	3 (12.0%)	0 (0.0%)	
Alpha-adrenergic blockers, N (%)	0 (0.0%)	0 (0.0%)	
Others, N (%)	22 (88.0%)	7 (100.0%)	
Site			0.466
Bilateral, N (%)	22 (9.8%)	0 (0.0%)	
Left, N (%)	127 (56.7%)	9 (56.3%)	
Diameter (cm), median [IQR]	**1.5 [1.1–1.9]**	**3.0 [1.6–5.0]**	**0.001**
FPG (mg/dl), median [IQR]	101.0 [93.0–113.0]	102.0 [91.0–132.0]	0.947
HbA1c (%), median [IQR]	5.6 [5.4–6.1]	5.9 [5.5–6.3]	0.364
Anti-diabetic medication, N (%)	31 (13.8%)	2 (12.5%)	> 0.999
UM (μg/day), median [IQR]	**98.5 [69.3–127.8]**	**194.9 [125.4–433.9]**	**< 0.001**
UNM (μg/day), median [IQR]	**220.8 [167.3–290.7]**	**707.5 [466.9–1312.3]**	**< 0.001**

BMI body mass index, *IQR* interquartile range, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *NFAI* nonfunctioning adrenal incidentaloma, *PHEO* pheochromocytoma, *SD* standard deviation, *UM* urine metanephrine, *UNM* urine normetanephrine

Significant results ($P < 0.05$) are in bold

[a]Symptoms suggestive of PHEO include headache, tachycardia/palpitation, sweating, and uncontrolled or paroxysmal hypertension

more frequent use of anti-hypertensive medication. The other variables, including classification of anti-hypertensive medication (including beta-adrenergic blockers), FPG, HbA1c, and the use of anti-diabetic medication, were comparable between the two groups.

The baseline characteristics were compared according to the referrals from the health promotion centers (Supplementary Table S1). No significant difference was observed in the proportion of patients with PHEO [56 of 688 all referred patients (8.1%) vs. 16 of 240 patients referred from the health promotion center (6.7%); $P = 0.463$]. Patients referred from the health promotion center showed a non-significant tendency for higher participation in regular outdoor exercise (6 of 16; 37.5%) than those referred from others (12 of 40; 30.0%; $P = 0.072$). Both UM ($P = 0.098$) and UNM ($P = 0.081$) demonstrated a non-significant tendency towards lower levels in patients who were referred from the health promotion center with PHEO. In patients with NFAI, the proportion undertaking regular outdoor exercise was higher in those referred from the health promotion center (77 of 224, 34.4%) than in those referred from others (117 of 408, 28.7%; $P = 0.024$). Notably, the patients with NFAI on referral from the health promotion center included a higher proportion of males ($P = 0.005$), and had a lower age ($P = 0.035$), a higher average height ($P = 0.001$), a higher average weight ($P = 0.001$), and smaller adenomas ($P < 0.001$), than patients referred from others.

As a preliminary analysis, the distribution of UM and UNM levels and their associations with SMI were investigated with scatter plots. In men ($N = 163$), both UM ($\gamma = -0.210$, $P = 0.007$) and UNM levels ($\gamma = -0.144$, $P = 0.049$) showed inverse correlations with SMI (Supplementary Fig. S1). In women ($N = 76$), UM levels ($\gamma = -0.213$, $P = 0.048$) showed an inverse correlation with SMI, and UNM levels ($\gamma = -0.177$, $P = 0.067$) had a tendency of inverse correlation with SMI (Supplementary Fig. S1). We then examined whether any relationship of urinary fractionated metanephrines with body composition was modified by sex. We observed no interaction between UM or UNM levels and sex for any value of body composition (P for tests of interaction $= 0.430$–0.921). Therefore, instead of separating men and women, we performed further analyses together after adjustment for sex. In the multiple linear regression analyses for assessing the independent association of UM and UNM with body composition (Table 2), both UM levels ($\beta = -0.171$, $P = 0.006$) and UNM levels ($\beta = -0.249$, $P < 0.001$) showed inverse associations with SMI in all subjects, after adjusting potential confounders, including age, sex, BMI and regular outdoor exercise. Furthermore, after adjustment for confounders including the use of beta-adrenergic blocking agents, inverse correlations between SMI and UM ($\beta = -0.169$, $P = 0.007$) and SMI and UNM ($\beta = -0.248$, $P < 0.001$) were persistent (data not shown). However, both UM and UNM levels had no correlation with ASM, FM, and pFM.

Figure 2 shows the comparison of body composition between subjects with PHEO ($N = 16$) and NFAI ($N = 224$). After adjustment for confounders, patients with PHEO had 7.7% lower ASM ($P = 0.022$) and 6.6% lower SMI ($P = 0.001$) than those with NFAI (Fig. 2). Furthermore, after adjustment for confounders including the use of beta-adrenergic blocking agents, the patients with PHEO had 7.8% lower ASM ($P = 0.020$) and 6.6% lower SMI ($P = 0.001$) than those with NFAI (data not shown). However, there was no statistically significant difference in FM and pFM between patients with PHEO and those without NFAIs. We also compared body composition between patients with PHEO ($N = 16$) and healthy subjects without adrenal lesions ($N = 47$), with these healthy subjects being matched 1:3 with the patients with PHEO in terms of sex, age (± 1.0 years), and BMI (± 0.5 kg/m^2; Supplementary Table S2). As shown in Supplementary Fig. S2, the patients with PHEO showed a non-significant trend for 8.9% lower ASM ($P = 0.095$) and 10.6% lower SMI ($P = 0.011$) than healthy subjects without adrenal lesions. There were no statistically significant differences in FM and pFM between

Table 2 Multiple linear regression analyses for the association of UM and UNM levels with ASM, SMI, FM, and pFM ($N = 240$)

| Variable	UM				UNM			
	β^a	SE	Beta^b	P	β	SE	Beta	P
ASM (kg)	−0.433	0.273	−0.063	0.114	−0.488	0.283	−0.066	0.087
SMI (kg/m^2)	**−0.171**	**0.062**	**−0.102**	**0.006**	**−0.249**	**0.063**	**−0.138**	**<0.001**
FM (kg)	−0.465	0.338	−0.051	0.171	−0.040	0.353	−0.004	0.911
pFM (%)	−0.588	0.420	−0.058	0.163	−0.111	0.439	−0.010	0.801

UM and UNM were log-transformed because of their skewed distributions. The multivariable adjustment factors in these analyses were age, sex, body mass index, and regular outdoor exercise

ASM appendicular skeletal muscle mass, *SMI* skeletal muscle mass index, *FM* fat mass, *pFM* percentage FM, *UM* urine metanephrine, *UNM* urine normetanephrine

Significant results ($P < 0.05$) are in bold

[a]Unstandardized coefficient. [b]Standardized coefficient. The Enter method was applied to this model

Fig. 2 **a** Appendicular skeletal muscle mass (ASM), **b** skeletal muscle mass index (SMI), **c** fat mass (FM), and **d** percentage fat mass (pFM) according to the nonfunctioning adrenal incidentaloma (NFAI) ($N = 224$) and pheochromocytoma (PHEO) ($N = 16$) groups. Data are expressed as mean $\pm$ SEM, which were calculated after adjusting for age, sex, body mass index, and regular outdoor exercise
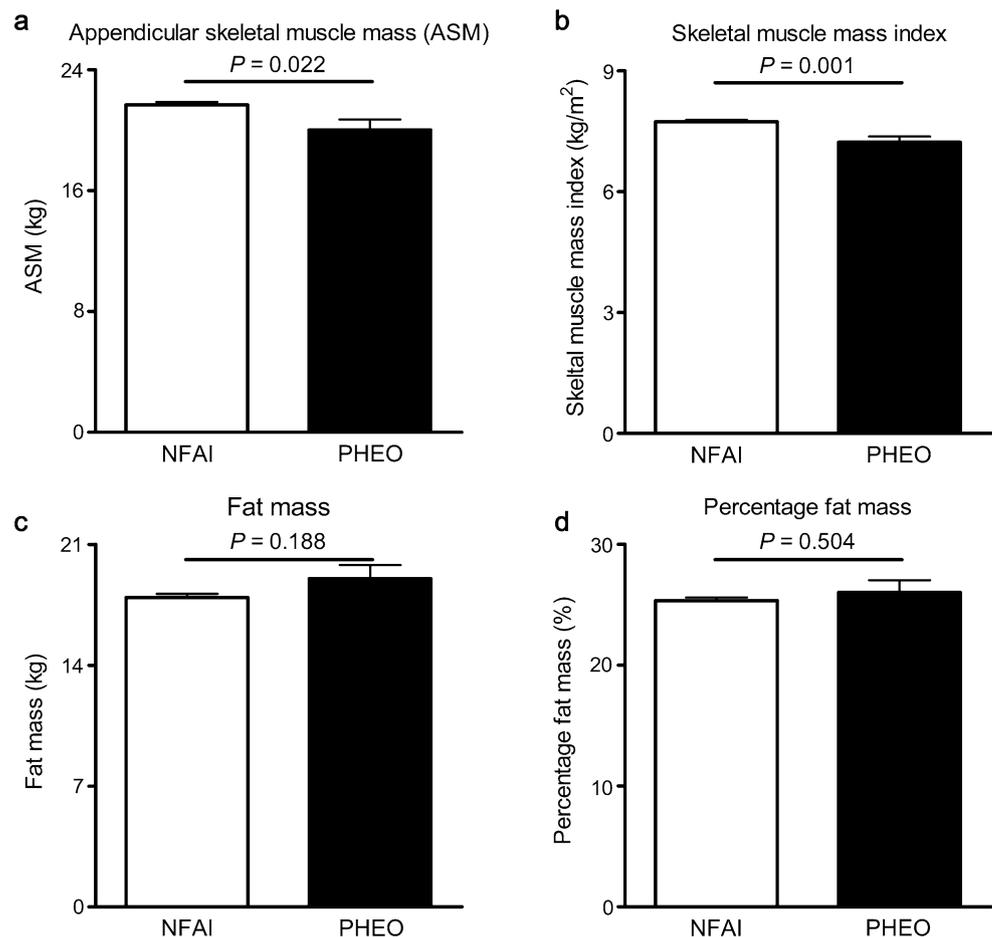
patients with PHEO and healthy subjects without adrenal lesions.

In the multiple logistic regression analyses (Table 3), ORs (95% CI) per log-unit increase in UM and UNM levels for low skeletal muscle mass were 8.95 (2.19–38.46) and 4.04 (1.79–9.14), respectively. The OR of the PHEO group for low skeletal muscle mass was 12.37-fold higher (95% CI, 2.54–60.16) than that of the NFAI group (Table 3).

Discussion

Our results indicate that patients with PHEO have lower skeletal muscle mass and higher risk of low skeletal muscle mass than patients with NFAI. Consistently, UM and UNM levels were inversely correlated with SMI. To the best of our knowledge, this is the first finding to show that catecholamine excess in PHEO might contribute to a higher probability for low skeletal muscle mass.

Human ageing is associated with both sarcopenia [2] and a marked increase in basal activity of the sympathetic nervous system [27]. However, the role of catecholamine excess in the decline of skeletal muscle mass in humans

Table 3 Multiple logistic regression analyses for determining the ORs for low skeletal muscle mass according to (1) the levels of UM and UNM and (2) the presence of PHEO

Variable	OR	95% CI	P
Log-unit increment in UM or UNM levels			
UM level	**8.95**	**2.19–38.46**	**0.002**
UNM level	**4.04**	**1.79–9.14**	**0.001**
PHEO	**10.33**	**2.65–40.22**	**0.001**

Low skeletal muscle mass was defined by SMI ($=$ASM/height^2) using cutoff points of <6.75 kg/m^2 for men and <5.07 kg/m^2 for women, as suggested by the consensus report of the Asian Working Group for Sarcopenia [2]

Multivariable adjustment factors in these analyses were age, sex, body mass index, and regular outdoor exercise

Significant results ($P < 0.05$) are in bold

ASM appendicular skeletal muscle mass, *CI* confidence interval, *SMI* skeletal muscle mass index, *OR* odds ratio, *PHEO* pheochromocytoma, *UM* urine metanephrine, *UNM* urine normetanephrine

remains unclear. To investigate the roles of catecholamines in human skeletal muscle metabolism, we used PHEO as a human model of excessive catecholamine production.

Weight loss by the catecholamine-induced hypermetabolic state [7] might be a confounding factor for interpreting the effects of catecholamines on skeletal muscle mass. Therefore, we examined alterations in skeletal muscle mass and FM in our analyses. Although FM and pFM were similar between patients with PHEO and NFAI, ASM and SMI were significantly lower in patients with PHEO. Similarly, both UM and UNM levels were inversely correlated with SMI, but not with FM and pFM. Finally, a recent study showed that patients with NFAI may have a higher risk of atherosclerosis than age-, sex-, or BMI-matched subjects without adrenal lesions, and suggested that the body composition of patients with NFAI may differ from that of healthy subjects without adrenal lesions [28]. Therefore, we investigated whether the inverse association between PHEO and SMI remained in a comparison between patients with PHEO and healthy subjects without adrenal lesions, and found that SMI was significantly lower in patients with PHEO than in age-, sex-, and BMI-matched subjects without adrenal lesions. Together, these results suggest a detrimental effect of catecholamine excess on skeletal muscle metabolism in humans.

The results of this study and those of a previous study that stated the importance of β-adrenergic signaling in skeletal muscles [9] highlight the significance of understanding these mechanisms for the identification of new therapeutic targets for aging-associated sarcopenia. For instance, the expression of interleukin-6 (IL-6), which regulates skeletal muscle mass [29, 30], is stimulated by epinephrine in rat skeletal muscle cells in vivo and in vitro [31]. Similar to the paradoxical effects of β-adrenergic agonists on skeletal muscle mass, a slight increase in circulating IL-6 levels due to exercise, which eventually returns to baseline, exerts a positive impact on skeletal muscles, whereas a continuous increase due to cachexia exerts deleterious effects on skeletal muscles [29]. These results suggest the existence of common pathways between catecholamine-induced and aging- or cachexia-induced sarcopenia.

The major strengths of this study are the enrollment of consecutive patients with newly diagnosed AI to minimize selection bias and the measurement of urinary fractionated metanephrines, which is superior to the measurement of urine catecholamine for determining catecholamine excess [20]. Despite these strengths, several potential limitations should be considered when interpreting our results. First, this study was based on cohorts of patients with AI. Because PHEO is a rare neuroendocrine tumor, the proportion of patients with PHEO was low (56 of 985 AI patients; 5.7%), which is consistent with results of a previous report on AI according to the European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors (median: 7.0%; range: 1.5–14%) [32], and with

the results of a recent study on AI in Korea (84 of 1149 AI patients, 7.3%) [33]. In addition, the BIA data were available for some, but not all the patients. In patients with PHEO, changes in receptor affinity and density, as well as the metabolic capacity of the primary metabolic organs, result in a heterogeneous metabolic response to catecholamine stimulation [34]. Therefore, the presence of a selection bias is possible. However, the proportions of patients with PHEO and fractionated metanephrine levels were similar between patients with and without BIA data and we, therefore, think that the results were not substantially affected by any selection bias. Furthermore, patients with PHEO also had lower SMI than age-, sex-, and BMI-matched healthy subjects without adrenal lesions. Although further extensive studies including large numbers of patients with PHEO and other ethnic groups are warranted, our results suggest that catecholamine excess might contribute to a high probability for low skeletal muscle mass. Second, this study was of a cross-sectional design, so we could not investigate whether skeletal muscle mass increased after adrenalectomy in patients with PHEO. Thus, further studies on changes in skeletal muscle mass after adrenalectomy are needed. Third, we did not measure grip power as an indicator of muscle strength or gait speed as an indicator of physical performance. In the diagnosis of sarcopenia, the confirmation of a reduction in skeletal muscle mass in addition to low muscle strength and/or physical performance is important [2]. However, owing to the absence of a measure of muscle strength and physical performance, we could only present data indicating lower skeletal muscle mass in patients with PHEO. Thus, further studies need to include measures of muscle strength and physical performance to ascertain the risk of sarcopenia in patients with PHEO. Finally, the precision of BIA in measuring muscle mass is controversial [35]. However, the Asian Working Group for Sarcopenia considers BIA to be acceptable for muscle measurements [2].

In summary, patients with PHEO have a high risk of sarcopenia, and catecholamines can adversely affect skeletal muscle metabolism. Additional studies are necessary to unravel the complex mechanisms linking the marked increase in basal sympathetic activity and sarcopenia with aging in humans.

Compliance with ethical standards

Conflict of interest The authors report no potential conflicts of interest.

Research involving human participants All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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