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Early View

Original article

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Please cite this article as: Sato H, Nakamura H, Nishida Y, *et al*. Energy expenditure and physical activity in COPD by the DLW method and an accelerometer. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00407-2020).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Energy expenditure and physical activity in COPD by the DLW method and an accelerometer

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Take home message: Although total energy expenditure and physical activity level in COPD patients were underestimated by an accelerometer, they can be predicted using indices of the accelerometer and clinical parameters such as the 6-min walking distance and grip strength.

Abstract

Although weight loss suggests poor prognosis of COPD, only a few studies have examined total energy expenditure (TEE) or physical activity level (PAL) using the doubly labeled water (DLW) method. We evaluated TEE and PAL using the DLW method together with a triaxial accelerometer to elucidate the relationships between TEE, PAL and clinical parameters leading to a practical means of monitoring COPD physical status.

This study evaluated 50- to 79-year-old male patients with mild to very severe COPD (n=28) or at risk for COPD (n=8). TEE, activity energy expenditure for 2 weeks, and basal metabolic rate were measured by DLW, an accelerometer, and indirect calorimetry, respectively. All patients underwent pulmonary function, chest-computed tomography, 6-min walk, body composition and grip strength (GS) tests. Relationships between indices of energy expenditure and clinical parameters were analyzed. Bland-Altman analysis was used to examine the agreement of TEE and PAL between the DLW method and the accelerometer.

TEE and PAL using DLW in the total population were 2273±445 kcal/day and 1.80±0.20, respectively. TEE by DLW was correlated well with that from the accelerometer and GS ($P<0.0001$), and PAL by DLW correlated well with that from the accelerometer ($P<0.0001$), GS and 6-min walking distance ($P<0.001$) among various clinical parameters. The accelerometer, however, underestimated TEE (215±241 kcal/day) and PAL (0.18±0.16), with proportional biases in both indices.

TEE and PAL can be estimated by the accelerometer in patients with COPD if systematic errors and relevant clinical factors such as muscle strength and exercise capacity are accounted for.

Keywords:

chronic obstructive pulmonary disease, doubly labeled water method, total energy expenditure, physical activity level, basic metabolic rate

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitations, with $\%FEV_1$ used as an index of the disease severity [1]. However, the introduction of the BODE index demonstrated that weight loss, dyspnea, and reduced exercise capacity should be simultaneously considered when trying to predict the COPD prognosis in addition to the obstructive disorder [2]. Furthermore, it has been reported that a low physical activity level (PAL) determined by a multisensory armband is the best predictor of poor COPD prognosis among all of the various clinical parameters, which include $\%FEV_1$, 6-min walking distance (6MWD), body mass index (BMI), the modified Medical Research Council (mMRC) dyspnea scale, and the BODE index [3]. Recent investigations have highlighted the importance of providing adequate nutrition and exercise in order to maintain ideal body weight, muscle volume and strength, and physical activity, which can lead to improvement in the quality of life (QOL) and prognosis in COPD [4-7]. However, only a few studies have investigated total energy expenditure (TEE) in COPD using the standard doubly labeled water (DLW) method [8, 9]. Although other previous studies that did use the DLW method have suggested that patients with severe and very severe COPD tended to have an increased basal metabolic rate (BMR) and decreased activity energy expenditure (AEE) [10, 11], the characteristics of energy expenditure remain unclear in patients with mild to moderate COPD who need to be prevented from developing physical inactivity and malnutrition. Although estimations of PAL by a pedometer or an accelerometer have shown a decrease in the PAL in accordance with the severity of airflow limitation [12, 13], it was reported that AEE determined by an accelerometer tended to underestimate values as compared to the DLW method [14], and that TEE calculated using the AEE and the predicted BMR was also possibly underestimated in COPD patients.

Therefore, the present study attempted to accurately measure TEE and PAL in patients with mild to moderate COPD using the DLW method and indirect calorimetry in conjunction with an accelerometer, in order to elucidate the relationships between the TEE and PAL and clinical COPD parameters, which included pulmonary functions, muscle volume and strength, and exercise capacity. We also tried to clarify the differences in the TEE and PAL assessments in COPD between the DLW method and the accelerometer, in order to evaluate the practical usefulness of the accelerometer.

Methods

Study population

This study enrolled patients with COPD (n=28) and those at risk for COPD (n=9). All patients were consecutive outpatients seen at the Saitama Medical University Hospital between June 2017 and February 2018, and who met the following criteria; male, age 50-79 years, presence of COPD [the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1, 2, 3, 4] or at risk for COPD (GOLD 0). COPD was diagnosed in accordance with the GOLD guideline 2020 [1]. All GOLD 0 patients had chronic respiratory symptoms including cough, sputum, or dyspnea on exertion and a ≥10 pack year smoking history in the absence of airflow limitation ($FEV_1/FVC \geq 0.7$) after inhalation of bronchodilators. Exclusion criteria are described in the online supplement. After one GOLD 0 patient discontinued the study due to acute bronchitis, a total of 36 patients were included in the analysis. This study was approved by the Institutional Review Board of Saitama Medical University Hospital (No.16-003-1), Keio University (Protocol No. 2015-03) and National Institutes of Biomedical Innovation, Health and Nutrition (Protocol No. 29). Written informed consent was obtained from each patient.

Pulmonary function tests and 6-min walk test (6MWT)

Pulmonary function tests were performed using a FUDAC-7 instrument (Fukuda Denshi Co., Ltd., Tokyo, Japan). Spirometry parameters, lung volume subdivisions, and the diffusing capacity of carbon monoxide (DL_{CO}) were measured in all patients. As indices of respiratory muscle strength, PEmax and PImax were measured using a spirometer, Autospiro AS-507 (Minato Medical Science, Co., Ltd., Osaka, Japan). The predicted pulmonary function values were calculated according to the Japanese Respiratory Society guidelines [15]. The 6MWT was performed by experienced technicians in accordance with the ATS guidelines except for duplication [16]. The following data were collected in all patients: baseline SpO_2 and heart rate (HR), lowest SpO_2 and highest HR during the test. Dyspnea and leg fatigue were also assessed by a modified Borg scale from 0 to 10, and the 6MWD was performed at the end of the test.

Questionnaires and chest-computed tomography (CT) analysis

At the beginning of the study, severity of dyspnea was estimated by the modified Medical Research Council (mMRC) dyspnea scale, while the disease-related QOL was evaluated by the COPD assessment test (CAT) score. A chest CT scanner (Somatom Emotion 16, Siemens Healthcare, Erlangen, Germany) and a Synapse Vincent volume analyzer (Fujifilm Medical Co., Ltd., Tokyo, Japan) were used for this study [17]. The conditions of the chest-CT analysis are presented in the online supplement.

Study schedule

This study was conducted in the hospital during two scheduled visits that occurred over 13-15 days. For both visits, patients arrived in a fasted state after overnight fasting. At visit 1, height, body weight, and other baseline information were obtained. BMR was measured by indirect calorimetry while the body composition was measured by bioelectrical impedance analysis (BIA). After taking DLW at visit 1, the physical activity was then measured using a triaxial accelerometer for 13-15 days. The 6MWT was performed within a month, while chest CT scans and pulmonary function tests were performed within 3 months before and after the study period. All of the examinations were performed under stable conditions.

Weight, body composition and grip strength (GS)

The methods for obtaining the weight, body composition and grip strength are shown in the online supplement.

Measurement of TEE by the DLW method

TEE was measured by the DLW method (modified two-point approach) as previously reported [18]. At visit 1, an oral dose of 0.1 g ^2H_2O and 2.0 g $H_2{}^{18}O$ (Taiyo Nippon Sanso, Tokyo, Japan) per kg of estimated total body water was given to each patient. The specific details are described in the online supplement.

Measurement and prediction of BMR

BMR was measured by indirect calorimetry (BMR_I) at visit 1 (Quark RMR, COSMED, Rome, Italy) [19], while BMR_G was predicted using the Ganpule equation [20, 21]. The detail is described in the online supplement.

Evaluation of PAL by the DLW method and an accelerometer

PAL_{DLW} was defined as follows:

PAL_{DLW} = TEE_{DLW} (TEE by DLW method)/BMR_I (BMR by indirect calorimetry)

In addition, physical activity was evaluated using a triaxial accelerometer (Active Style Pro, HJA-750C, Omron Healthcare, Kyoto, Japan), which was developed to classify locomotive and non-locomotive activities through the use of a ratio of unfiltered and filtered synthetic acceleration combined with a gravity-removal physical activity classification algorithm that was utilized for determining an accurate estimation of the AEE of non-locomotive activities [22]. Metabolic equivalents (METs) were estimated by applying different equations for different types of activities. This analysis used the 60-s epoch data. Periods with more than 60 min of consecutive non-wear time were classified as non-wear time, while a valid day was defined as 600 min or more per day of wear time. Patients wore the accelerometer on their waist for 13-15 days, except during bathing and sleep. AEE is reasonably measured by the device, which also provides data regarding steps/day, sedentary (<1.5 METs) time, and light (1.5≤ to <3.0 METs), moderate (3.0≤ to <6.0 METs), and vigorous (6.0 METs≤) walking and daily activity times. In this study, PAL_{ACC} (PAL estimated by an accelerometer) was calculated as follows:

$TEE_{ACC} = (BMR_G + AEE) \times 10/9$, $PAL_{ACC} = TEE_{ACC}/BMR_G$

[10/9 was added to the equation for the correction of diet induced thermogenesis (DIT)].

Statistical analysis

Data are presented as means±standard deviation (SD). Values were compared between the DLW and the accelerometer using Student's paired *t*-test. Multiple comparisons were performed using the Tukey-Kramer test. Univariate associations were analyzed using Pearson's correlation coefficient. Multiple regression analysis was performed to predict TEE_{DLW} and PAL_{DLW}. The Bland-Altman plot was used to evaluate the agreement of TEE and PAL between DLW and accelerometer methods, and of BMR between indirect calorimetry and the Ganpule equation. P values less than 0.05 were considered significant. All data were analyzed using JMP version 14 software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the patients

As shown in Table 1, the total population primarily consisted of patients with mild to moderate COPD (20/36), with a mean $\%FEV_1$ of 69.4.

TABLE 1 Patient characteristics

	All	GOLD 0	COPD (GOLD 1-4)	GOLD 0 vs. COPD
N	36	8	28 (1:6, 2:14, 3:6, 4:2)	
Age (years)	70.3±5.8	70.3±7.1	70.3±5.5	NS

mMRC	0.9±1.0	0.4±0.5	1.1±1.0	NS
CAT score	10.1±6.1	9.6±4.0	10.2±6.7	NS
BMI (kg/m^2)	21.9±3.2	21.2±3.7	22.1±3.2	NS
%FM	23.3±5.0	24.6±3.4	22.9±5.3	NS
FFMI (kg/m^2)	16.7±2.3	15.9±2.7	16.9±2.2	NS
SMI (kg/m^2)	9.1±1.0	8.8±1.2	9.2±0.9	NS
GS (kg)	33.9±7.0	29.6±6.1	35.1±6.8	P<0.05
%PEmax	72.6±18.7	71.8±22.1	72.8±18.0	NS
%PImax	87.6±29.3	89.8±15.7	87.0±32.3	NS
%VC	95.3±16.2	98.9±12.0	94.2±17.2	NS
%FEV_1	69.4±24.4	94.6±10.7	62.1±22.3	P<0.001
FEV_1/FVC (%)	55.4±17.4	78.5±7.8	48.8±13.2	P<0.0001
%RV	117.1±35.4	99.4±17.2	122.2±37.7	NS
% DL_{CO}/V_A	74.0±27.4	83.1±19.4	71.5±29.0	NS
%LAA	13.9±13.6	9.4±8.6	15.1±14.6	NS
6MWD (m)	435±95	442±23	433±107	NS
ΔSpO_2(%)	7.3±4.6	4.4±2.4	8.1±4.7	P<0.05
ΔHR (/min)	38.2±15.2	31.5±7.2	40.1±16.4	NS
dyspnea	2.2±2.2	1.1±1.4	2.5±2.4	NS
leg fatigue	0.7±1.3	0.8±1.2	0.7±1.3	NS

Data are presented as mean±SD. GOLD: the Global Initiative for Chronic Obstructive Lung Disease, COPD: chronic obstructive pulmonary disease, mMRC: modified Medical Research Council dyspnea scale, CAT: COPD assessment test, BMI: body mass index, FM, fat mass, FFMI: fat free mass index, SMI: skeletal muscle mass index, GS: grip strength, PEmax: maximum expiratory pressure, PImax: maximum inspiratory pressure, VC: vital capacity, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual volume, DL_{CO}: diffusing capacity of the lung for carbon monoxide, V_A: alveolar volume LAA: low attenuation area, MWD: minute walking distance, SpO_2: percutaneous oxygen saturation, HR: heart rate, NS: not significant.

Energy expenditure and physical activity in accordance with the severity of airflow limitation

BMI was lower in GOLD 3,4 versus GOLD 2 (Table 2). There were no differences in TEE_{DLW}, PAL_{DLW}, and BMR_I among patients at risk for COPD or with mild-to-very severe COPD. For the accelerometer, there was no difference in any of the parameters except for a decrease in the moderate walking time in GOLD 3,4 versus GOLD 1.

There were significant differences in the TEE between GOLD 1 and 2 that observed for the DLW and the accelerometer (Figure 1A). For PAL, there were significant differences observed for all comparisons between the DLW and the accelerometer (Figure 1B).

TABLE 2 Energy expenditure and physical activity

	All (G0-3, n=36)	GOLD 0 (n=8)	GOLD 1 (n=6)	GOLD 2 (n=14)	GOLD 3,4 (n=8)	COPD (G1-4, n=28)	Multiple comparison
Age (years)	70.3±5.8	70.3±7.1	68.8±8.9	71.4±4.4	69.6±4.5	70.3±5.5	NS
BMI (kg/m^2)	21.9±3.2	21.2±3.7	21.8±1.3	23.5±3.0	19.7±3.2$^{\#}$	22.1±3.2	$^{\#}$P<0.05
BMR_I (kcal/day)	1262±180	1229±234	1297±173	1316±158	1172±148	1271±165	NS
BMR_G (kcal/day)	1272±145	1254±201	1278±124	1309±133	1223±125	1278±129	NS
BMR_I/BMR_G	0.99±0.07	0.98±0.08	1.01±0.06	1.01±0.07	0.96±0.07	0.99±0.07	NS
TEE_{DLW} (kcal/day)	2273±445	2240±629	2496±435	2378±322	1956±296	2283±393	NS
TEE_{ACC} (kcal/day)	2058±315	1982±353	2168±292	2146±308	1897±269	2080±307	NS
TEE_{DLW}-TEE_{ACC} (kcal/day)	215±241	258±324	327±299	232±188	59±120	203±218	NS
PAL_{DLW}	1.80±0.20	1.80±0.22	1.92±0.16	1.81±0.19	1.67±0.21	1.80±0.20	NS
PAL_{ACC}	1.61±0.14	1.58±0.12	1.70±0.13	1.64±0.13	1.55±0.14	1.63±0.14	NS
PAL_{DLW}-PAL_{ACC}	0.18±0.16	0.22±0.16	0.22±0.16	0.18±0.18	0.12±0.09	0.17±0.16	NS
AEE_{ACC} (kcal/day)	580±178	529±156	674±180	623±181	484±162	594±184	NS
Steps/day	5978±3209	5808±3171	7778±3590	5874±2116	5079±4482	6055±3273	NS
Sedentary (min)	506±137	456±112	456±112	472±155	580±125	499±144	NS
Light walking (min)	38.8±27.6	30.0±18.5	40.3±22.5	35.7±20.8	51.9±44.6	41.3±29.5	NS
Mod. walking (min)	28.4±23.5	30.6±21.4	44.5±29.1	30.3±22.0	10.6±14.1*	27.7±24.3	*P<0.05
Vig. walking (min)	0.08±0.28	0.13±0.35	0.17±0.41	0.07±0.27	0	0.07±0.26	NS
Light daily activity (min)	261±83	243±84	301±83	267±80	237±87	266±83	NS
Mod. daily activity (min)	19.9±17.9	16.9±14.6	25.5±14.2	25.6±22.4	8.8±7.9	20.8±18.8	NS

Data are presented as mean±SD. GOLD: the Global Initiative for Chronic Obstructive Lung Disease, COPD: chronic obstructive pulmonary disease. BMI: body mass index, BMR: basal metabolic rate, BMR_I was measured by indirect calorimetry, BMR_G was predicted using the Ganpule equation. TEE: total energy expenditure, TEE_{DLW}: TEE by DLW, TEE_{ACC}: TEE by accelerometer. PAL: physical activity level, PAL_{DLW}: PAL by DLW, PAL_{ACC}: PAL by accelerometer. AEE_{ACC}: activity energy expenditure by accelerometer. Values for BMR, TEE, and AEE are expressed as kcal/day. walking: walking time (min). daily: daily activity time (min). Mod.:moderate. Vig.: vigorous. $^{\#}$P<0.05 vs. GOLD 2, *P<0.05 vs. GOLD 1. NS: not significant.

TABLE 3 Relationships between energy expenditure/physical activity and clinical parameters

	TEE_{DLW}		PAL_{DLW}	
	r	P	r	P
Age (years)	-0.361	< 0.05	0.132	NS
mMRC	0.217	NS	0.276	NS
CAT	0.282	NS	0.213	NS
BMI (kg/m^2)	0.623	< 0.0001	0.158	NS
%FM	0.005	NS	0.092	NS
FFMI (kg/m^2)	0.655	< 0.0001	0.226	NS
SMI (kg/m^2)	0.593	< 0.001	0.156	NS
GS (kg)	0.689	< 0.0001	0.538	< 0.001
%PEmax	0.255	NS	0.188	NS
%PImax	0.020	NS	0.280	NS
%VC	0.359	< 0.05	0.301	NS
%FEV_1	0.313	NS	0.394	<0.05
FEV_1/FVC (%)	0.143	NS	0.286	NS
% RV	0.165	NS	0.134	NS
% DL_{CO}/V_A	0.387	<0.05	0.258	NS
%LAA	-0.334	<0.05	-0.275	NS
6MWD (m)	0.355	<0.05	0.575	<0.001
△SpO_2 (%)	0.056	NS	0.142	NS
△HR(/min)	0.330	<0.05	0.520	<0.01
dyspnea	0.048	NS	0.009	NS
leg fatigue	-0.322	<0.05	-0.269	NS

TEE_{DLW}: total energy expenditure measured by DLW. TEE_{ACC} by accelerometer. PAL_{DLW}: physical activity level using TEE_{DLW}. mMRC: modified Medical Research Council dyspnea scale, CAT: COPD assessment test, BMI: body mass index, FM: fat mass, FFMI: fat free mass index, SMI: skeletal muscle mass index, GS: grip strength, PEmax: maximum expiratory pressure, PImax: maximum inspiratory pressure, VC: vital capacity, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, RV: residual volume, DL_{CO}: diffusing capacity of the lung for carbon monoxide, V_A: alveolar volume, LAA: low attenuation area, MWD: minute walking distance, SpO_2: percutaneous oxygen saturation, HR: heart rate. NS: not significant.

Validation of TEE_{ACC} and PAL_{ACC} in comparison with TEE_{DLW} and PAL_{DLW}, and of BMR_G to BMR_I by Bland-Altman plots

As shown in Figure 2, fixed bias was observed in both the TEE (A) [95% confidence interval (CI): 133.5–296.6 kcal/day, P<0.0001] and PAL (B) (95% CI: 0.129–0.235, P<0.0001) between the two methods. Proportional bias was also observed in both TEE (r=0.561, P=0.0004) and PAL (r=0.482, P=0.0029). No fixed bias was seen in BMR (95% CI: -25.8–4.1 kcal/day, NS) (C), whereas slight proportional bias was observed (r=0.399, P=0.016).

When TEE_{ACC} and PAL_{ACC} were calculated with BMR_I instead of BMR_G, the fixed and proportional biases to those values from DLW were still observed in TEE (mean: 227 kcal/day, P<0.0001, r=0.461, P=0.0046) and PAL (mean: 0.176, P<0.0001, r=0.451, P=0.0058), respectively, by Bland-Altman analyses.

Using AEE_{DLW} (defined as $0.9 \times TEE_{DLW} - BMR_I$), the difference between TEE_{DLW} and TEE_{ACC} correlated well with AEE_{DLW} (r=0.732, P<0.0001) and modestly with BMR_I (r=0.488, P=0.0025). The difference between PAL_{DLW} and PAL_{ACC} correlated well with AEE_{DLW} (r=0.680, P<0.0001), but not with BMR_I. A significant difference was apparent between AEE_{DLW} (784±275 kcal/day) and AEE_{ACC} (580±178 kcal/day, P<0.0001).

Univariate regression analysis between energy expenditure, physical activity, and clinical parameters

Various factors including age, BMI, fat-free mass index (FFMI), skeletal muscle mass index (SMI), GS, %VC, $\%DL_{CO}/V_A$, low attenuation area (LAA)%, 6MWD, ΔHR and leg fatigue during the 6MWT were associated with TEE_{DLW} (Table 3). In contrast, the factors related to PAL_{DLW} were limited to 6MWD, ΔHR during 6MWT, GS, and $\%FEV_1$. Figure 3 shows the association of the cardinal clinical parameters with TEE_{DLW} (Figure 3A) and PAL_{DLW} (Figure 3B).

Relationships between energy expenditure, physical activity, and the parameters of the accelerometer

As shown in Table 4, light and moderate daily activity times were correlated with both indices. Furthermore, there was a good correlation between TEE_{DLW} and TEE_{ACC}. These associations are shown in Figures 4A (TEE_{DLW}) and 4B (PAL_{DLW}).

TABLE 4 Relationships between energy expenditure/physical activity and parameters of the accelerometer

	TEE_{DLW}		PAL_{DLW}	
	r	P	r	P
Steps/day	0.185	NS	0.377	<0.05
Sedentary time (min)	0.022	NS	0.088	NS

Light walking time (min)	0.055	NS	0.191	NS
Moderate walking time (min)	0.205	NS	0.362	<0.05
Vigorous walking time (min)	0.380	<0.05	0.246	NS
Light daily activity time (min)	0.385	<0.05	0.465	<0.01
Moderate daily activity time (min)	0.551	<0.001	0.471	<0.01
TEE_{ACC} (kcal/day)	0.854	<0.0001	0.554	<0.001
PAL_{ACC}	0.531	<0.001	0.642	<0.0001
AEE_{ACC} (kcal/day)	0.722	<0.0001	0.635	<0.0001

TEE_{DLW}: total energy expenditure measured by DLW. PAL_{DLW}: physical activity level using TEE_{DLW}. TEE_{ACC}: TEE by accelerometer. AEE_{ACC}: activity energy expenditure by accelerometer. PAL_{ACC}: PAL using AEE_{ACC}. NS: not significant.

Prediction of TEE_{DLW} and PAL_{DLW} according to the accelerometer and clinical parameters

Since TEE_{DLW} correlated strongly with TEE_{ACC}, the following equation may predict TEE_{DLW} using the accelerometer: $TEE_{DLW} = -210.2 + 1.207 \times TEE_{ACC}$ (r=0.854, corrected coefficient of determination=0.721). When this equation was used to predict TEE_{DLW} based on TEE_{ACC} values in all 36 patients, the ratio of patients for whom predicted values were within ±10% of measured TEE_{DLW} was 58%. In contrast, PAL_{DLW} correlated modestly with PAL_{ACC} (r=0.642, corrected coefficient of determination=0.395). Multiple regression analyses including clinical parameters are shown in the online supplement.

Discussion

The present study demonstrated that BMR, TEE and PAL as evaluated by indirect calorimetry and DLW methods were preserved as nearly normal among patients at risk for or with mild-to-moderate COPD. These three indices tended to decrease in patients with severe-to-very severe COPD. Yamada et al. recently reported that elderly men in the Japanese community without any associated participation in sporting activities showed a mean BMI of 23.6, BMR_I of 1242 kcal/day, TEE_{DLW} of 2308 kcal/day, and PAL_{DLW} of 1.85 [23], similar to that found for COPD patients at GOLD 1 and 2 in this study. No significant difference in BMR was seen between measured values and prediction by the Ganpule equation even in COPD patients, although slight proportional bias was observed by Bland-Altman plots in the present study. The DLW method is the gold standard for measuring TEE [24]. However, since this method is difficult to apply during routine clinical practice, comparison of data from the DLW method and indirect calorimetry with that for the accelerometer and predicted BMR is important. The present study demonstrated that TEE and PAL by the DLW method correlated well with those from the accelerometer, but were underestimated by the accelerometer (fixed bias), as previously reported [14, 23]. In addition, in conjunction with the increases in TEE and PAL, the differences in TEE and PAL between the two methods also increased (proportional bias), respectively.

As stated in the Results, differences in TEE and PAL paralleled the AEE as evaluated by the DLW method. Since TEE and PAL are composed of BMR, AEE, and DIT, these three factors should be tested as causes for biases between DLW and accelerometer-based methods. Bland-Altman analyses using measured BMR values did not significantly improve the biases, and a previous study did not show significant changes in DIT in patients with COPD [25]. Underestimation of AEE by the accelerometer may thus be mainly responsible for the fixed and proportional biases between the two methods. One possibility is that energy expenditure by respiratory muscles that was not detected by the accelerometer could have been further increased during certain activities in COPD patients as compared to healthy subjects. The difference between AEE_{DLW} (784 kcal/day) and AEE_{ACC} (580 kcal/day) nearly corresponded to that between TEE_{DLW} (2273kcal/day) and TEE_{ACC} (2058 kcal/day) in the total population. Figure 1A also suggests that approximately 200–300 kcal/day should be added to the estimated energy expenditure by the accelerometer in COPD patients at GOLD 1 or 2.

As compared to the DLW method, accelerometers can provide additional information, such as steps/day and sedentary, walking, and daily activity times. Of interest is the observation that the associations of light and moderate daily activity times with TEE_{DLW} and PAL_{DLW} were greater than those observed for steps/day, sedentary time, and light and moderate walking times. As the present results showed the best index was moderate daily activity time (3.0–6.0 METs), further analysis of daily activities is needed to clarify how best to maintain physical activity in COPD.

In 2005, Pitta et al. reported that physical activity monitored by an accelerometer was significantly decreased in COPD patients versus healthy elderly subjects [26], in contrast to our findings. These differences may be partly attributable to the distinct study populations. Mean $\%FEV_1$ was 43% in COPD patients and 111% in healthy subjects in the study by Pitta et al., while values in our study were 62% and 95%, respectively. In addition, all GOLD 0 patients were symptomatic, with most requiring bronchodilator treatment. Moreover, use of long-acting inhaled bronchodilator may have contributed to the differences in outcomes between the study by Pitta et al. and the present investigation, as only salmeterol was available before 2005 while various kinds of long-acting muscarinic antagonists and β_2-agonists are now commonly available and in widespread use. In 2015, Waschki et al. reported that PAL evaluated by an accelerometer decreased proportional to the extent of airflow limitation in GOLD 0 to 4 [27]. This trend was consistent with our observations that PAL tended to decrease in GOLD 3 or 4 as compared to that observed in GOLD 1 or 2. One of the most important findings in the study by Waschki et al. was that PAL was significantly decreased at 3 years after baseline measures in all groups classified by GOLD stage. Inhibiting the progression of physical inactivity is thus important for every COPD patient, regardless of the degree of obstruction.

Analysis based on the DLW method demonstrated that TEE correlated modestly with %VC, $\%DL_{CO}/V_A$, and LAA% ($P<0.05$), but even better with GS and FFMI ($P<0.0001$). In addition, more significant correlations with PAL_{DLW} were seen for GS ($P<0.001$), 6MWD ($P<0.001$), and ΔHR during 6MWT ($P<0.01$) as compared to $\%FEV_1$ ($P<0.05$). These observations imply that energy expenditure and physical activity in COPD patients were primarily determined by muscle strength in general and exercise capacity, while the contributions of pulmonary function were relatively small, based on TEE measured using the standard DLW method. These findings were consistent with the notion that PAL_{DLW} correlated with changes in HR, but not with ΔSpO_2 or dyspnea during the 6MWT. This demonstrates that dyspnea on exertion may be unrelated to reduced physical activity in our study population. As expected, TEE_{DLW}, which is a very important index for determining energy intake in COPD, was more significantly related to BMI, FFMI, SMI, and GS than to the other factors.

Several limitations to this study need to be considered when interpreting the present findings. Due to the difficulties inherent in using the DLW method, the study population was relatively small. Furthermore, women were not included to avoid sex differences in TEE and PAL. In addition, the study population included only two patients with very severe COPD and excluded patients with diabetes mellitus who required medication.

In conclusion TEE and PAL were preserved in patients with mild-to-moderate COPD, as well as those at risk of COPD. TEE and PAL values as estimated by the accelerometer were lower than those from the DLW method, but correlated with each other and showed differences related to activity energy expenditure. TEE and PAL can also be estimated by the accelerometer with clinical parameters including exercise capacity and muscle strength. These observations may promote better monitoring of the physical status in patients with mild-to-moderate COPD and could help prevent the development of future weight loss and poor prognosis.

Acknowledgments: We thank Azusa Sasaki and Hitoshi Miyazawa for their skillful technical assistance.

Conflict of interest: All authors declare no conflicts of interest.

Support statement: This work was supported by the Japan Agency for Medical Research and Development [grant numbers JP17ek0210045 and JP20ek0210112].

Figure legends

FIGURE 1 Differences in TEE and PAL between the DLW method and the accelerometer (ACC). G=GOLD. Significant differences in TEE (A) (ALL, G1, G2) and PAL (B) (ALL, G0, G1, G2, G3,4) were observed between the two methods (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001).

FIGURE 2 Bland-Altman plots for TEE (A) and PAL (B) used to compare the values determined by the DLW and accelerometer methods, and for BMR (C) to compare the values obtained by indirect calorimetry and the Ganpule equation. Mean values are depicted by solid lines, while dotted lines show ranges within the 95% confidence interval (CI). The 95% CI for the difference in TEE was 133.5─296.6 kcal/day (P<0.0001) and that in PAL was 0.129─0.235 (P<0.0001) between the two methods. No difference in BMR (95% CI: -25.8─4.1 kcal/day, NS) was seen between measurements and the predicted values.

FIGURE 3 Correlations between TEE_{DLW} (A) or PAL_{DLW} (B) and clinical parameters. There was a good correlation between the GS, FFMI, and BMI and the TEE_{DLW} (A). 6MWD, GS, and the ΔHR during 6MWT were well correlated with the PAL_{DLW} (B).

FIGURE 4 Correlations between TEE_{DLW} (A) or PAL_{DLW} (B) and the accelerometer (ACC) parameters. TEE_{DLW} was strongly correlated with TEE_{ACC} (r=0.854, P<0.0001) (A), while the association between PAL_{DLW} and PAL_{ACC} was relatively modest (r=0.642, P<0.0001) (B). Light (1.5-3.0 METs) and moderate (3.0-6.0 METs) daily activity times were correlated with both indices (A, B).

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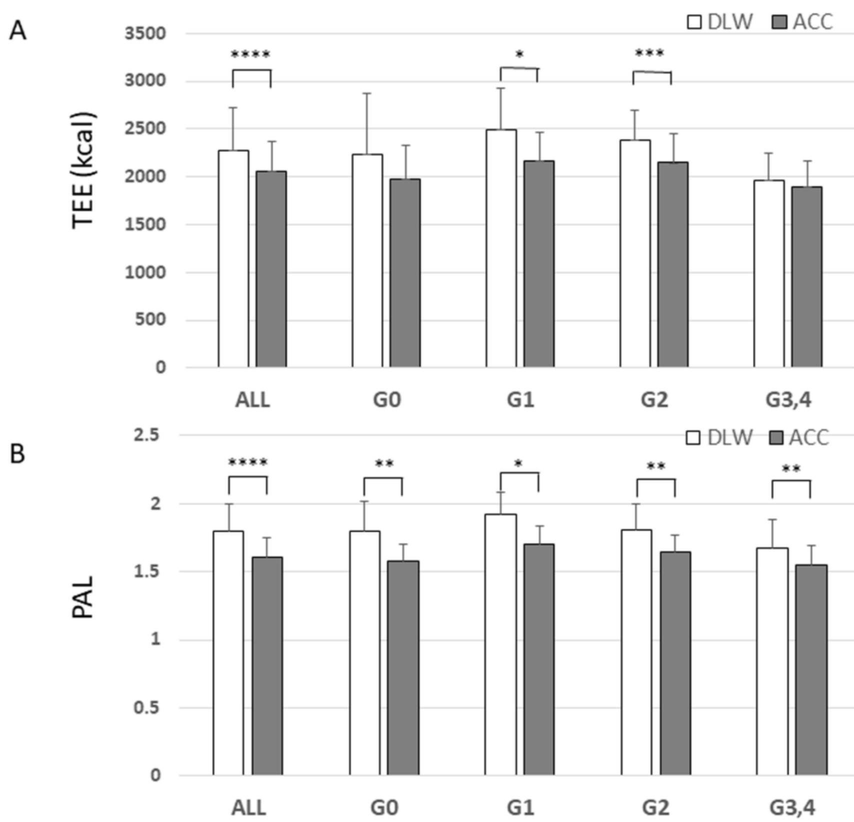
Fig. 1



A
B
DLW
ACC
TEE (kcal)
PAL
3500
3000
2500
2000
1500
1000
500
0
2.5
2
1.5
1
0.5
****
***
**
*
ALL
G0
G1
G2
G3,4

Fig. 2

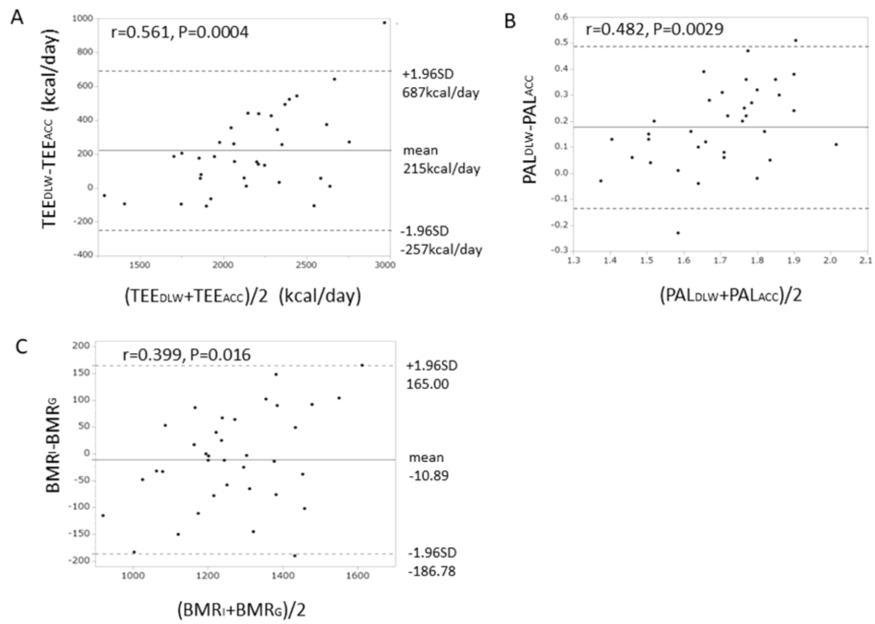
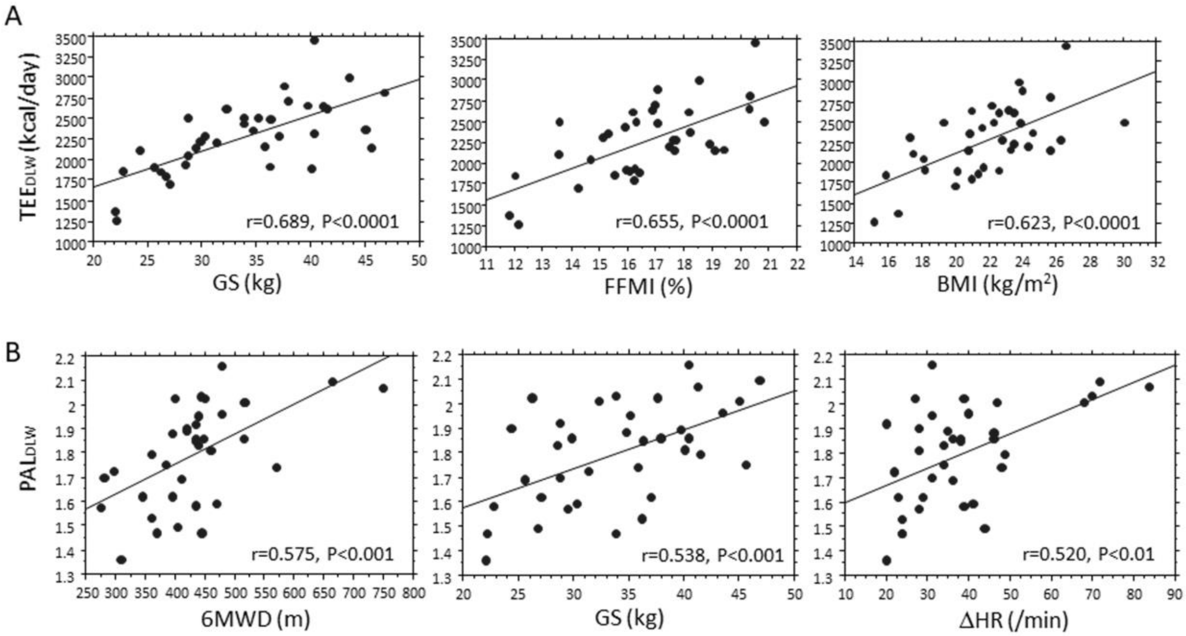
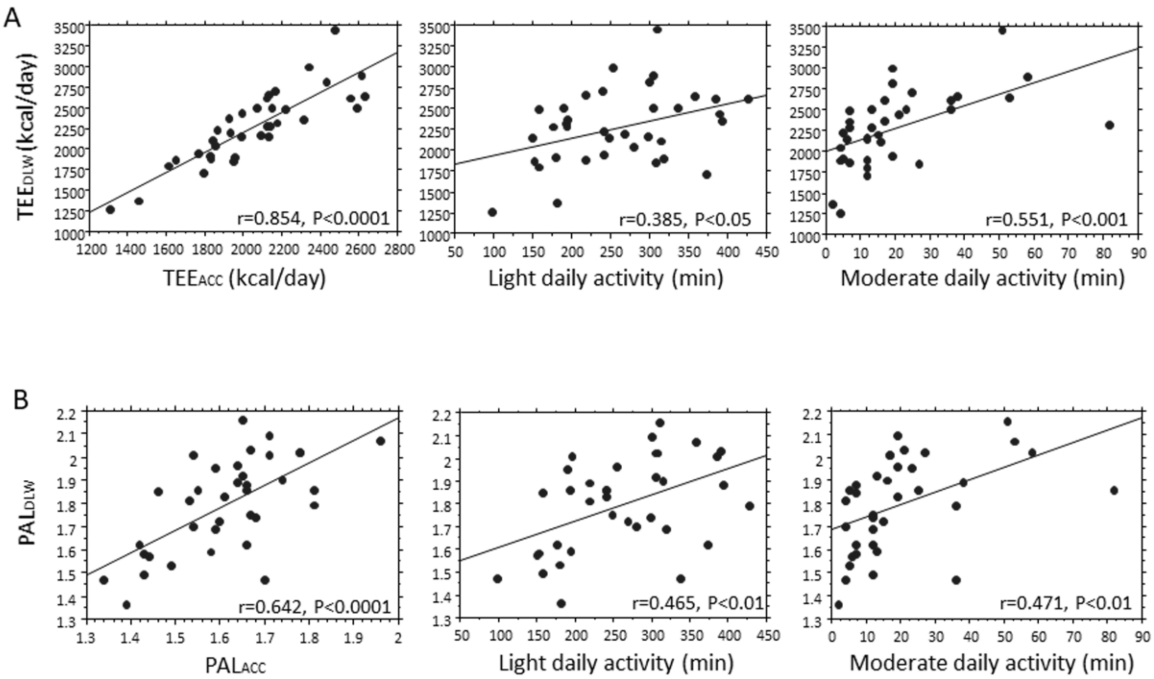

A
r=0.561, P=0.0004
TEEDLW-TEEACC (kcal/day)
(TEEDLW+TEEACC)/2 (kcal/day)
+1.96SD
687kcal/day
mean
215kcal/day
-1.96SD
-257kcal/day
B
r=0.482, P=0.0029
PALDLW-PALACC
(PALDLW+PALACC)/2
+1.96SD
0.488
mean
0.182
-1.96SD
-0.124
C
r=0.399, P=0.016
BMRI-BMRG
(BMRI+BMRG)/2
+1.96SD
165.00
mean
-10.89
-1.96SD
-186.78

Fig. 3



A
TEEDLW (kcal/day)
r=0.689, P<0.0001
GS (kg)
r=0.655, P<0.0001
FFMI (%)
r=0.623, P<0.0001
BMI (kg/m2)
B
PALDLW
r=0.575, P<0.001
6MWD (m)
r=0.538, P<0.001
GS (kg)
r=0.520, P<0.01
ΔHR (/min)

Fig. 4



A
TEEDLW (kcal/day)
r=0.854, P<0.0001
TEEACC (kcal/day)
r=0.385, P<0.05
Light daily activity (min)
r=0.551, P<0.001
Moderate daily activity (min)
B
PALDLW
r=0.642, P<0.0001
PALACC
r=0.465, P<0.01
Light daily activity (min)
r=0.471, P<0.01
Moderate daily activity (min)

Online supplement

Methods

Exclusion criteria

None of the patients were participating in any rehabilitation programs during the study period or experienced any exacerbation within 1 month prior to the study. Exclusion criteria were as follows: patients with infectious diseases, diabetes mellitus being treated with medication, dysphagia, or other serious diseases; patients treated with drugs affecting energy expenditure (thyroid hormone, beta-blocker, GLP-1 receptor agonist) or water balance (SGLT2 blocker); patients with weight loss more than 5% of body weight during the previous 3 months. All patients were treated with long-acting bronchodilators with the exception of two GOLD 0 patients.

Chest CT-analysis

Chest CT scans (Somatom Emotion 16, Siemens Healthcare, Erlangen, Germany) were performed with the use of 16 × 1.2 mm collimation, rotation time of 600 ms/rot, pitch factor 1.05, 130 kV peak, and automatic exposure control (Quality Reference mAs 100). Routine calibration of the CT scanner was conducted using air and water phantoms. For quantitative analysis of pulmonary emphysema, whole-lung CT images with 1.5 mm-thickness were obtained using a reconstruction kernel B41s medium+, with the percentage of the low attenuation area (LAA%) determined using a cutoff value of -950 Hounsfield units with a Synapse Vincent volume analyzer (Fujifilm Medical Co., Ltd., Tokyo, Japan).

Weight, body composition and grip strength

Body weight (BW) was measured without shoes and with light clothing using an electronic scale (BF-220, Tanita, Tokyo, Japan). BMI was calculated as BW (kg)/height (m)^2. Fat-free mass (FFM) and skeletal muscle mass (SMM) were measured by a bioelectrical impedance analyzer (SFB7, ImpediMed, Queensland, Australia). Fat-free mass index (FFMI) and skeletal muscle mass index (SMI) were calculated as FFM (kg)/height (m)^2 and SMM (kg)/height (m)^2. Grip strength (GS) of both hands was measured twice using a dynamometer (GRIP-D, Takei Scientific Instruments, Co., Ltd., Niigata, Japan) and the mean of the best efforts in each hand was used for analysis.

DLW method

An oral dose of 0.1 g ^2H_2O and 2.0 g $H_2{}^{18}O$ per kg of estimated total body water was given on visit 1. Baseline urine (BLU) and blood (BLB) samples were collected before a dose of DLW. Post-dose urine samples were collected at 2, 3 and 4 h (PD2U, PD3U and PD4U, respectively), while the post-dose blood samples were collected only at 4 h (PD4B). On the morning of visit 2, end-of-day samples were collected twice for urine (ED1U and ED2U) with an interval of 1 h, and once for blood (ED1B). Isotope analysis of the urine and blood samples was performed in duplicate using an isotope-ratio mass spectrometer (Hydra 20-20 Stable Isotope Mass Spectrometer, Sercon, Crewe, UK). The ^2H:^1H ratio was analyzed by hydrogen gas equilibration using a platinum catalyst. The ^{18}O:^{16}O ratio was analyzed after carbon dioxide equilibration. Isotope analyses were carried out at ESTech Kyoto (Kyoto, Japan). The average standard deviations for the analyses were 1.4±1.7 ‰ for ^2H and 0.13±0.15 ‰ for ^{18}O. Among the collected samples, the representative value of TEE was calculated by the average TEEs obtained from the urine samples (BLU, PD4U and ED2U) and blood samples (BLB, PD4B and ED1B).

Measurement and prediction of BMR

The patients were instructed to ingest only water for 12 h before the measurement. All tests were conducted between 8:30 and 10:00. The patients rested on a bed for 30 min before the measurement. A steady state was achieved for more than 5 min by the Quark BMR after 10-15 min of breathing while the patient lay awake in a supine position. BMR was calculated as the volume of oxygen consumed and the volume of carbon dioxide expired using the modified Weir equation [19]. We also used predicted BMR values that were obtained using the Ganpule equation as described below [20].

BMR_G = ((0.1238 + (0.0481 × BW kg) + (0.0234 × height cm)−(0.0138 × age)-sex*1)) × 1000/4.186

*1; male = 0.5473 × 1, female = 0.5473 × 2

The equation, which was developed by the National Institute of Health and Nutrition in Japan, has been reported to be able to better predict BMR in Japanese populations as compared to other equations such as the Harris-Benedict equation [21].

Results

Multiple regression analyses

In order to predict TEE_{DLW}, the best two parameters, GS and FFMI (Table 3) were added to TEE_{ACC} as predictor variables. Considering the number of patients (n=36), the number of variables was set to be at most 3 in this analysis. Calculated sample size for the multiple regression analysis was 36, when the conditions were as follows: α=0.05, 1-β=0.80, number of variables=3, and effect size f^2=0.35.

Table S1 Multiple regression analyses for predicting TEE_{DLW}

Model	Regression coefficient	Standardized coefficient	t	P-value	Corrected coefficient of determination
1 (constant)	138.082	138.082	0.37	0.714	0.525
GS(kg)	29.170	0.457	3.01	0.005	
FFMI(kg/m^2)	68.743	0.361	2.38	0.023	
2 (constant)	-242.019	-242.019	-0.94	0.354	0.734
TEE_{ACC}(kcal/day)	1.017	0.720	5.99	<0.0001	
GS(kg)	12.435	0.195	1.62	0.114	
3 (constant)	-494.291	-494.291	-1.66	0.106	0.746
TEE_{ACC}(kcal/day)	0.940	0.665	5.44	<0.0001	
GS(kg)	7.241	0.114	0.89	0.382	
FFMI(kg/m^2)	35.204	0.185	1.60	0.120	
4 (constant)	-534.562	-534.562	-1.83	0.077	0.747
TEE_{ACC}(kcal/day)	1.016	0.719	6.78	<0.0001	
FFMI(kg/m^2)	42.990	0.226	2.13	0.041	

TEE: total energy expenditure, DLW: doubly labeled water, ACC: accelerometer, FFMI: fat free mass index, GS: grip strength.

To predict PAL_{DLW}, the best two parameters, 6MWD and GS (Table 3) were added to PAL_{ACC} as predictor variables. The number of variables was also set to be at most 3.

Table S2 Multiple regression analyses for predicting PAL_{DLW}

Model	Regression coefficient	Standardized coefficient	t	P-value	Corrected coefficient of determination
1 (constant)	1.043	1.043	6.89	<0.0001	0.404
6MWD(m)	0.000911	0.424	2.95	0.006	
GS(kg)	0.0105	0.361	2.51	0.017	
2 (constant)	0.332	0.332	1.09	0.283	0.467
PAL_{ACC}	0.712	0.472	3.31	0.002	
6MWD(m)	0.000725	0.337	2.36	0.024	
3 (constant)	0.250	0.250	0.83	0.413	0.468
PAL_{ACC}	0.760	0.504	3.70	0.001	
GS(kg)	0.00944	0.324	2.38	0.023	
4 (constant)	0.323	0.323	1.10	0.278	0.505
PAL_{ACC}	0.601	0.399	2.79	0.009	
6MWD(m)	0.000573	0.266	1.87	0.071	
GS(kg)	0.00750	0.257	1.89	0.068	

PAL: physical activity level, DLW: doubly labeled water, ACC: accelerometer, MWD: minute walking distance, GS: grip strength