

GASTROENTEROLOGY

Change in body composition in patients with achalasia before and after peroral endoscopic myotomy

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Key words

abdominal fat, achalasia, bioelectrical impedance, peroral endoscopic myotomy; skeletal muscle.

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Abstract

Background and Aim: Patients with achalasia experience weight loss because of dysphagia caused by impaired relaxation of the lower esophageal sphincter. This study aimed to use dual bioelectrical impedance analysis (BIA) to determine the change in bodyweight and body composition in patients with achalasia before and after peroral endoscopic myotomy (POEM).

Methods: Patients with achalasia who underwent POEM from 2013 to 2018 ($n = 72$) were retrospectively analyzed for change in bodyweight before and after 3 months. Additionally, change in body composition was prospectively investigated in the final 10 of 72 patients using non-radiation dual BIA.

Results: Twenty patients (27.8%) were underweight (body mass index < 18.5) before undergoing POEM. No clinical parameters were identified to be associated with the underweight condition before POEM and be predictive of an increase in bodyweight after POEM. Low visceral fat volume observed on dual BIA correlated closely with the result obtained using computed tomography (Pearson correlation coefficient: $r = 0.850$, $P < 0.01$). Patients with achalasia had a statistically significant increase in visceral ($P < 0.01$) and subcutaneous fat volumes ($P < 0.01$) after POEM. Skeletal muscle mass index slightly increased ($P = 0.02$), although the value after POEM was still low. No blood biomarkers were indicators for low bodyweight or low visceral fat volume.

Conclusions: Dual BIA is an effective non-invasive tool to evaluate the change in body composition of underweight patients with achalasia. Skeletal muscle volume was not enough after POEM, although a rapid increase in the intra-abdominal fat volume was observed. Additional studies are warranted to understand the pathological implications.

Introduction

Achalasia is a well-known esophageal motility disorder with an estimated incidence of 1 per 100 000 person-years.^{1,2} The Auerbach plexus in the esophagus is damaged by an unknown cause, leading to impaired relaxation of the lower esophageal sphincter (LES) and abnormal peristalsis of the esophagus. The abnormal motility leads to dysphagia and vomiting, often with concomitant chest pain, causing weight loss.^{3,4} Currently, achalasia is defined and diagnosed using high-resolution manometry (HRM) based on the Chicago classification criteria (Fig. 1a).⁵

Interventions are the mainstay of achalasia treatment. Balloon dilation is considered the most accessible and the most preferred intervention.⁶ Surgical myotomy techniques such as the Heller myotomy were developed in 1913 and are curative for achalasia-related symptoms, although some patients are unwilling to undergo invasive therapy involving the creation of a skin incision.^{7,8} Peroral endoscopic myotomy (POEM) was developed in 2010, which is less invasive and as efficacious as surgical myotomy (Fig. 1b–d).^{9,10} The efficacy of these interventional procedures is sufficient, and the treatment success rate is reported to be more than 90%.¹¹ Hence, patients with achalasia

are able to consume larger portions of food soon after treatment, resulting in weight gain. However, change in bodyweight and body mass index (BMI) before and after treatment has been rarely investigated, and there is no clinical relevance of body composition in patients with achalasia. For the management of patients with achalasia, it is important to assess the body composition such as skeletal muscle and intra-abdominal fat volume because these factors could be related with quality of life, life-style-related disorders, and mortality.^{12,13}

Recently, dual bioelectrical impedance analysis (BIA) has been developed to determine not only skeletal muscle mass but also intra-abdominal fat volume by separately measuring the truncal impedance and surface impedance at the abdomen, which are indicative of the visceral adipose tissue and subcutaneous adipose tissue content, respectively.¹⁴ Before the use of dual BIA, adipose tissue distribution was quantitatively evaluated by computed tomography (CT), which has limitations such as requiring the use of a large instrument, high cost, and X-ray exposure.¹⁵ With dual BIA, the procedure can be easily replicated with a more compact instrument that does not expose the patient to X-rays.

The aim of this study was to clarify the characteristics of patients experiencing weight loss because of achalasia-related symptoms

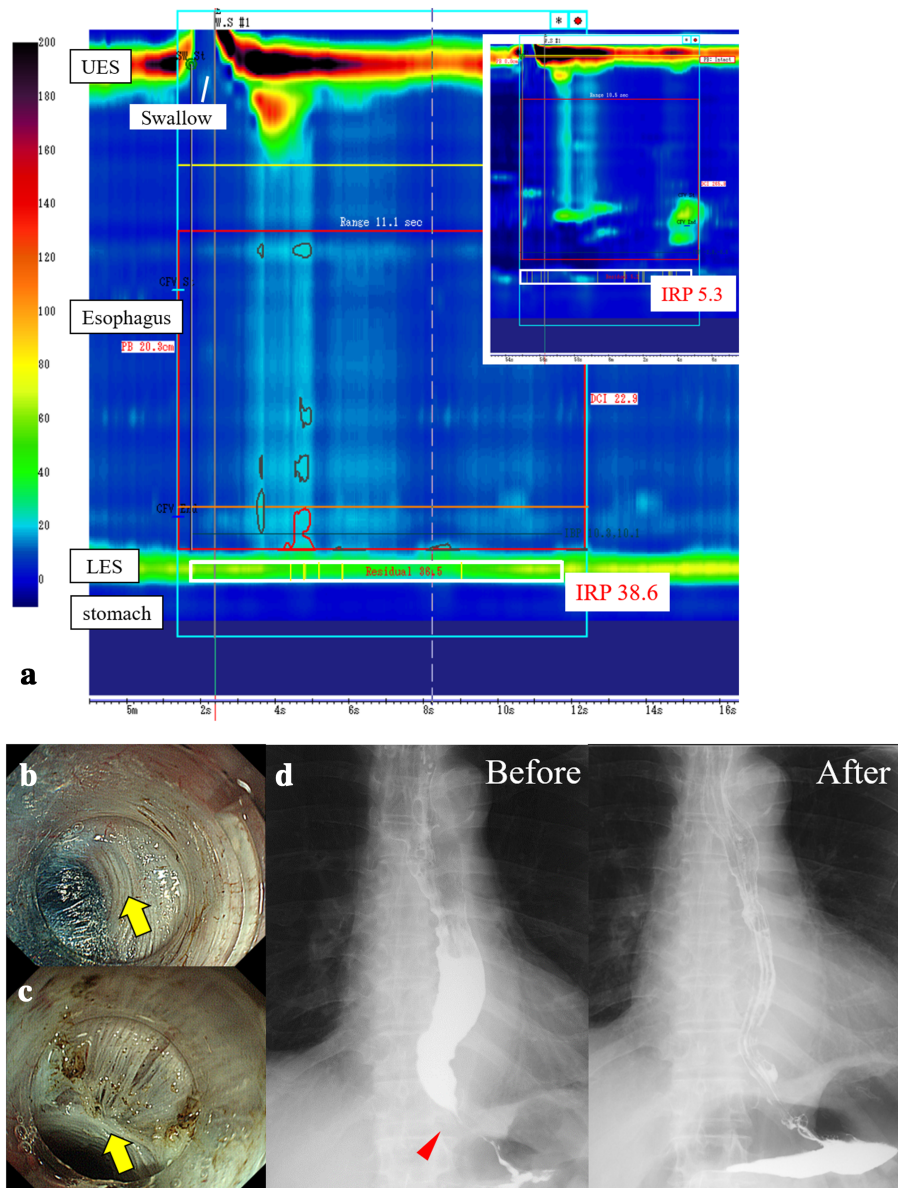


Figure 1 A patient with achalasia treated with peroral endoscopic myotomy (POEM). (a) The examination using high-resolution manometry showing achalasia with no normal peristalsis and elevated integrated relaxation pressure (IRP) (38.6 mmHg; the IRP measurement is taken after deglutitive upper sphincter relaxation). After POEM, the IRP level is totally reduced to 5.3 mmHg (insert). UES, upper esophageal sphincter; LES, lower esophageal sphincter. (b) POEM procedure. After accessing the submucosal space using a gastrointestinal endoscope, the submucosal layer is progressively dissected longitudinally along the muscular layer and a submucosal tunnel extending beyond the esophagogastric junction is created. (c) Myotomy of the circular esophageal and gastric muscle bundles (yellow arrow) is performed under direct vision. (d) An esophagogram recorded before and after POEM shows markedly improved esophageal emptying and decrease in esophageal diameter (red triangle indicating the tight lower esophageal sphincter).

and the mechanism behind the weight gain after POEM. Furthermore, as a pilot study, we aimed to determine the change in bodyweight and body composition in patients with achalasia before and after POEM using dual BIA. Clinical and hematological characteristics associated with low weight or low visceral fat volume were also investigated.

Methods

Statement of ethics. The present study was conducted prospectively and had a partially retrospective design. The study was approved by the Niigata University Review Board (2018-0276) and was also listed in the UMIN clinical Trials Registry (UMIN:

000035323). The study was conducted in accordance with the Declaration of Helsinki. Before the study, written informed consent was obtained from all patients in the prospective design, whereas an opt-out method was used for participants in the retrospective design.

Patients. In this study, patients with achalasia who underwent POEM between October 2013 and February 2019 were retrospectively analyzed for change in bodyweight before and 3 months after the procedure. From May 2018, the patients were also prospectively investigated for their muscle mass, skeletal muscle mass index (SMI), body water content, visceral fat area (VFA), and subcutaneous fat area (SFA) (Fig. 2). For BMI classification, a cut-off point of 18.5 was used for underweight as per the World Health Organization's guideline.¹⁶

Symptomatic severity and improvement in patients with achalasia were assessed using the Eckardt score. The Eckardt score is a widely used achalasia-related symptom score for dysphagia, regurgitation, chest pain, and weight loss and is used to assess the severity of achalasia symptoms and treatment efficacy. A higher Eckardt score reflects more severe achalasia symptoms (maximum: 12), while a lower score indicates milder symptoms (minimum: 0).^{17,18}

All patients with achalasia were diagnosed using established techniques, including upper gastrointestinal endoscopy, esophagography, and HRM using a Starlet device (Starmedical, Tokyo, Japan). Therefore, patients with secondary esophageal motility disorders, such as esophageal carcinoma, gastro-esophageal reflux diseases, and eosinophilic esophagitis, were completely excluded from this study. With respect to the parameters of HRM, integrated relaxation pressure (IRP) is the most important and widely accepted parameter for evaluating the degree of LES relaxation (Fig. 1a). This is measured after relaxation of the upper sphincter following deglutition from the time of anticipation of esophagogastric junction relaxation until peristaltic wave arrival. An IRP > 15 mmHg is defined as "impaired LES relaxation" and considered mandatory for the diagnosis of achalasia. Patients with other esophageal motility disorders, such as diffuse esophageal spasm or Jackhammer esophagus, were not recruited in this study.

Analysis of body composition using the novel instruments InBody770 and DUALSCAN. InBody770 (TAKUMI Co., Aichi, Japan) was used to estimate muscle mass,

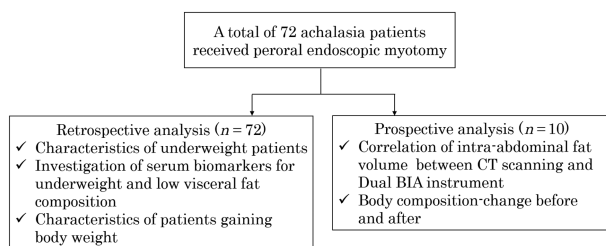


Figure 2 Study design: All 72 patients with achalasia who underwent POEM were eligible for our retrospective analysis. The last 10 patients were prospectively analyzed.

SMI, and body water content.^{19,20} InBody770 uses multiple currents at varying frequencies (1 kHz to 1 MHz), which can analyze the intracellular and extracellular water content separately, providing the most precise body water content analysis. Direct segmental measurements can analyze any body type accurately because each segment of the body is assessed separately at multiple frequencies. Furthermore, the 8-point tactile contact electrode system, which includes separate current and voltage electrodes, initiates measurement from a constant position on the wrist and ankle (Fig. 3a).

A DUALSCAN (Fukuda Co., Tokyo, Japan), an abdominal dual BIA machine, was used to measure VFA and SFA around the abdomen. First, the abdominal measurement unit (Fig. 3b, yellow arrow) calculates the total abdominal cross-section area. Next, an electric current is applied to four pairs of electrodes fixed on both hands and both feet, and the voltages are measured in an axial direction over the abdomen (Fig. 3b, insert). The impedance of the axial abdomen was used for calculating the lean body mass because most of the electrical current flows through the fat-free tissues.^{14,21,22} Electric current between two abdominal electrodes is used to calculate the SFA because the electric current flows through the SFA. Finally, the VFA is calculated from the two impedance datasets obtained during the measurement of the total abdominal cross-sectional area and SFA.

VFA and SFA measurements obtained using DUALSCAN were compared with those obtained using the abdominal axial-sectional image recorded with CT, which is considered the gold standard for body composition measurement (Fig. 3c).^{22,23}

Statistical analysis. For patient characteristics, continuous variables were expressed as mean \pm SD, and non-continuous data as ratios. The Mann–Whitney *U*-test was performed to compare non-parametric data. The Wilcoxon signed-rank test was used for the analysis of before-intervention and after-intervention data, with statistical significance assumed at $P < 0.05$. Statistical analysis was performed using GraphPad Prism version 8.02 (GraphPad Software Inc., San Diego, CA).

Results

In all, 72 patients with achalasia who underwent POEM were included for our retrospective analysis. The mean age at the time of POEM was 53.0 ± 17.6 years (range: 18–87 years), and the mean symptom duration was 6.5 ± 11.1 years (range: 0.2–54 years). The details of the patients' characteristics are shown in Table 1. Beginning May 2018, 10 patients who underwent POEM were prospectively analyzed (Fig. 2).

Correlation between low visceral fat area and subcutaneous fat area on dual bioelectrical impedance analysis and computed tomography. The correlation of measured intra-abdominal fat values between CT and dual BIA is summarized in Figure 4. Pearson correlation coefficient was used to determine the correlation between VFA and SFA values obtained using the two methods ($0.850 [P < 0.01]$ and $0.734 [P = 0.01]$, respectively). The results show a close correlation and thus indicate that dual BIA can be used as a substitute for CT in patients with achalasia, including those who are

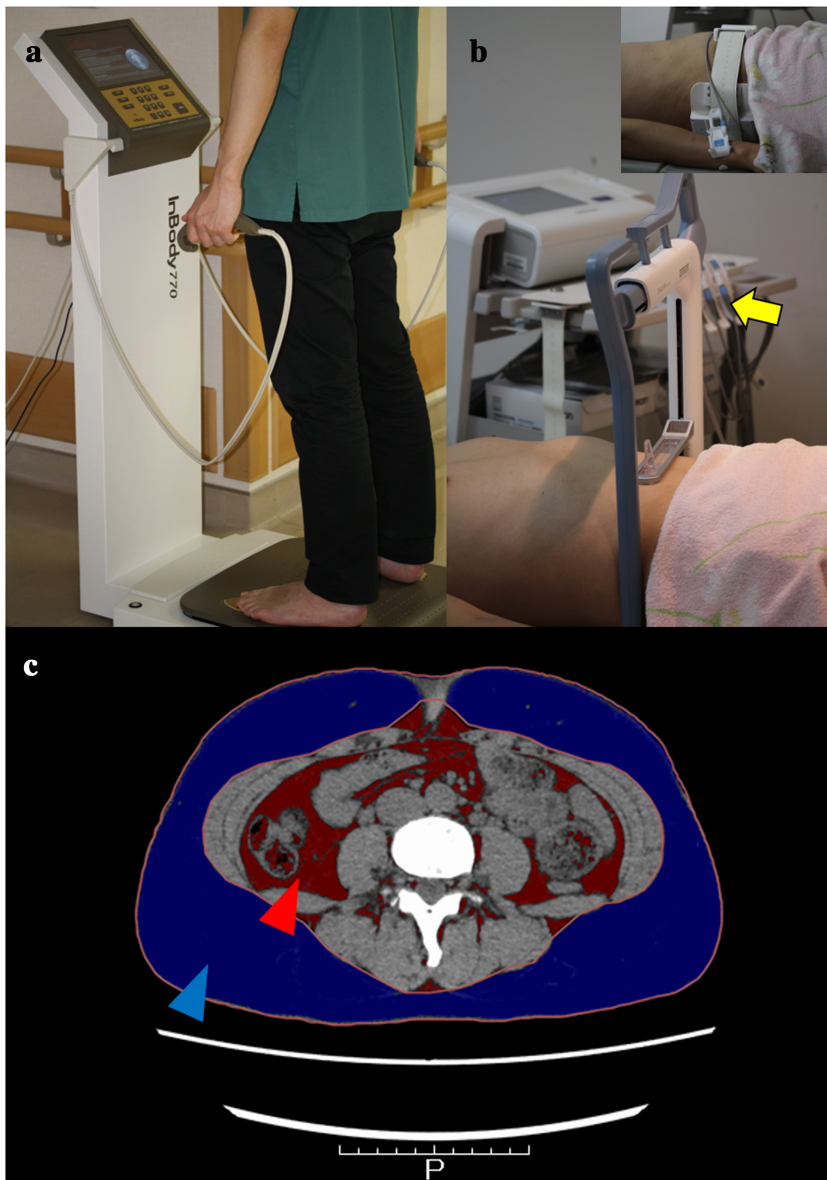


Figure 3 (a) Body composition and body water assessment using the InBody770 (TAKUMI Co., Aichi, Japan) and (b) visceral fat area and subcutaneous fat area evaluation using HDS-2000 DUALSCAN (FUKUDA Co., Tokyo, Japan). The yellow arrow indicates the abdomen measurement unit. (c) Computed tomography scan for the evaluation of visceral fat area (red solid area: red arrow) and subcutaneous fat area (blue solid area: blue arrow).

Table 1 Patients' characteristics

Patients' characteristics (n = 72)	
Age, years	53 ± 17.6 [†]
Sex (women : men)	33:39
Body mass index, kg/m ²	20.2 ± 3.4 [†]
Symptom duration, years	6.5 ± 11.1 [†]
Eckardt score (before)	6 ± 2.5 [†]
Eckardt score (after)	1 ± 0.9 [†]
IRP (LES pressure) (before)	29.3 ± 13.7 [†]
IRP (LES pressure) (after)	9.3 ± 4.7 [†]

[†]Mean ± SD.

IRP, integrated relaxation pressure; LES, lower esophageal sphincter.

underweight. CT scanning was not performed after POEM because there was a good correlation between BIA before POEM and excessive X-ray exposure should be avoided.

Clinical parameters and bodyweight before and after peroral endoscopic myotomy. Of 72 patients, 20 had a BMI < 18.5 and thus underweight,¹⁶ while 52 patients had a BMI ≥ 18.5 pre-POEM. The characteristics of these patients are summarized in Table 2. No significant differences were observed between two groups (BMI < 18.5 vs ≥ 18.5 pre-POEM) with respect to age (*P* = 0.70), sex (*P* = 0.66), duration of symptoms (*P* = 0.18), Eckardt score (*P* = 0.29), and IRP (*P* = 0.47). Furthermore, both groups had similar weight gain

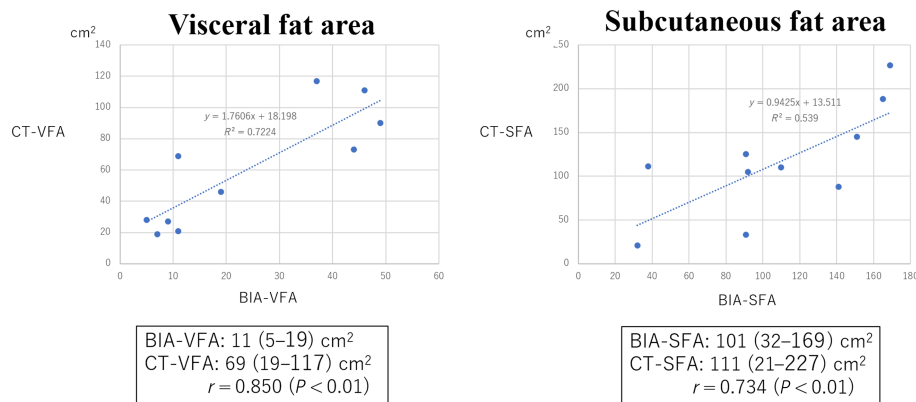


Figure 4 Correlation of the measured values of visceral fat area (VFA) and subcutaneous fat area (SFA) obtained by computed tomography (CT) scanning and dual bioelectrical impedance analysis (BIA).

(2.9 and 2.0 kg in the BMI < 18.5 and BMI ≥ 18.5 groups, respectively) with no significant differences between the two groups ($P = 0.28$).

The analysis of weight gain was performed in 60 of 72 patients (12 patients lacked post-POEM data). Subsequently, weight gain was classified into the following three categories: high response (gain > 4 kg), moderate response (gain > 2 kg), and low response (gain < 2 kg); each group comprised a similar number of patients ($n = 15$, $n = 20$, and $n = 25$, respectively). The results indicated that it is difficult to predict low, moderate, or high response before the procedure (Table 3).

Post-peroral endoscopic myotomy subcutaneous fat area and visceral fat area in patients with achalasia.

Change in bodyweight and body composition before and after POEM are shown in Figure 5. Bodyweight increased from 50.5 ± 7.4 kg to 54.8 ± 7.1 kg ($P < 0.01$). No significant difference in muscle mass and body water content before and after POEM was observed ($P = 0.20$ and 0.18 , respectively). Change in body water content was insignificant from pre-POEM to post-POEM (0.66 ± 0.10 to 0.66 ± 0.11 , $P = 0.33$). SMI significantly increased

from 5.8 ± 0.75 to 6.0 ± 0.66 ($P = 0.02$), although the increase seems slight, and the value after POEM is still low (see section). In contrast, VFA and SFA significantly increased from 15 ± 17.0 cm² to 44.5 ± 15.3 cm² ($P < 0.01$) and from 101 ± 46.3 cm² to 132 ± 40.2 cm² ($P < 0.01$), respectively. Furthermore, the ratio of the visceral to subcutaneous fat area increased significantly from 0.17 ± 0.10 to 0.32 ± 0.08 ($P = 0.02$). In addition, in the previous 50 patients, bodyweight change increased 51.5 ± 10.7 kg to 55.0 ± 10.7 kg ($P < 0.01$), and no difference was observed between weight before ($P = 0.16$) and weight after ($P = 0.24$) in the last 10 patients undergoing dual BIA. Therefore, we considered dual BIA applicable to all patients with achalasia in this study.

Blood biomarker relationship with low bodyweight and low intra-abdominal fat in patients with achalasia.

Controlling nutritional status (CONUT) score was effective in evaluating the daily nutritional status of all inpatients based on laboratory data, including levels of serum albumin, total cholesterol, and total lymphocyte count. CONUT is an easy-to-use screening tool employed for early detection and continuous control of nutrition in hospitals.^{24,25} In this study, seven parameters, including serum total protein, HbA1c, C-reactive protein, and peripheral blood hemoglobin levels, were investigated to determine if serum biomarker reflect low BMI or low intra-abdominal fat condition.

No serum biomarker could predict low BMI or low intra-abdominal fat in patients with achalasia (Table 4).

Table 2 Characteristics of patients with achalasia with low body mass index before treatment

Comparison between patients with achalasia with low and normal body mass index (BMI; $n = 72$)			
	BMI < 18.5 ($n = 20$)	BMI ≥ 18.5 ($n = 52$)	P value
Age, years [†]	53 ± 18.9	54 ± 17.6	NS [‡] (0.70)
Sex (women : men)	10:10	23:29	NS [‡] (0.66)
Symptom duration, years [†]	4.2 ± 6.9	7.6 ± 12.4	NS [‡] (0.18)
Eckardt score	6.5 ± 2.2	6 ± 2.5	NS [‡] (0.29)
IRP (LES pressure) [†]	33.3 ± 15.6	26.6 ± 14.2	NS [‡] (0.47)
Weight gain, kg [†]	2.9 ± 3.5	2.0 ± 2.2	NS [‡] (0.18)

[†]Mean ± SD.

[‡]NS, no significance.

IRP, integrated relaxation pressure; reflecting the pressure of lower esophageal sphincter (LES).

Discussion

To our knowledge, this is the first study to investigate change in bodyweight and body composition in patients with achalasia. In this study, we retrospectively analyzed the characteristics of underweight patients (BMI < 18.5) before POEM. Twenty patients (27.8%) were underweight before treatment, although no specific clinical characteristics associated with being underweight were identified. In Japan, 10.3% of women and 4.0% of men were reported to be underweight in 2017²⁶; therefore, achalasia has a definitive negative impact on bodyweight. Furthermore, in our study,

Table 3 Characteristics of patients with achalasia showing increase in weight after treatment

	Comparison between patients with achalasia showing weight gain (n = 60)				
	Weight gain ≥ 4 kg (n = 15)	P value (vs < 2 kg)	Weight gain ≥ 2 kg (n = 35)	P value (vs < 2 kg)	Weight gain < 2 kg (n = 25)
Age, years [†]	53.0 ± 18.6	NS [‡] (0.64)	53.0 ± 17.6	NS [‡] (0.57)	58.0 ± 15.2
Sex (women : men)	7:8	NS [‡] (0.42)	13:22	NS [‡] (0.08)	15:10
Body mass index, kg/m ^{2†}	19.9 ± 2.8	NS [‡] (0.11)	19.9 ± 2.9	NS [‡] (0.12)	20.5 ± 3.1
Symptom duration, years [†]	4.5 ± 13.5	NS [‡] (0.26)	7.0 ± 10.9	NS [‡] (0.37)	7.7 ± 12.1
Eckardt score [†] (before)	7 ± 2.5	NS [‡] (0.83)	6 ± 2.4	NS [‡] (0.95)	6 ± 2.1
IRP (before)	35.7 ± 12.4	NS [‡] (0.10)	30.8 ± 12.1	NS [‡] (0.15)	24.8 ± 19.1
Eckardt score (after)	1 ± 1.1	NS (0.83)	1 ± 1.0	NS (0.15)	1 ± 0.5
IRP (after)	5.5 ± 4.5	NS (0.96)	7.4 ± 4.5	NS (0.15)	10.6 ± 4.8

[†]Mean ± SD.

[‡]NS, no significance.

IRP, integrated relaxation pressure; reflecting the pressure of lower esophageal sphincter.

48.6% of patients experienced > 2 kg weight gain following POEM. No clinical characteristics were associated with good weight gain. The results indicate that patients with achalasia experience weight loss before POEM and gain weight after POEM because of several underlying factors. Improvement in appetite may be closely related to weight gain; however, it cannot be confirmed.

Dual BIA instruments are generally used for the assessment of excess intra-abdominal fat volume, particularly in patients with lifestyle-related diseases, such as obesity or type II diabetes; however, this study reported that these devices can also be used to determine if a patient has low abdominal fat volume. Therefore,

dual BIA can be useful to assess disease severity and treatment response in other diseases, like anorexia or sarcopenia. Using dual BIA instruments, the second analysis was performed prospectively to determine the body composition of patients with achalasia, and a significant increase in intra-abdominal fat volume was observed in a short time. Before conducting the study, we hypothesized that patients with achalasia reduce bodyweight because of body water loss from conditions such as dehydration. However, body water content in patients in this study was within the normal range before treatment, and no significant increase was observed after treatment. This indicates that patients with chronic-phase achalasia can

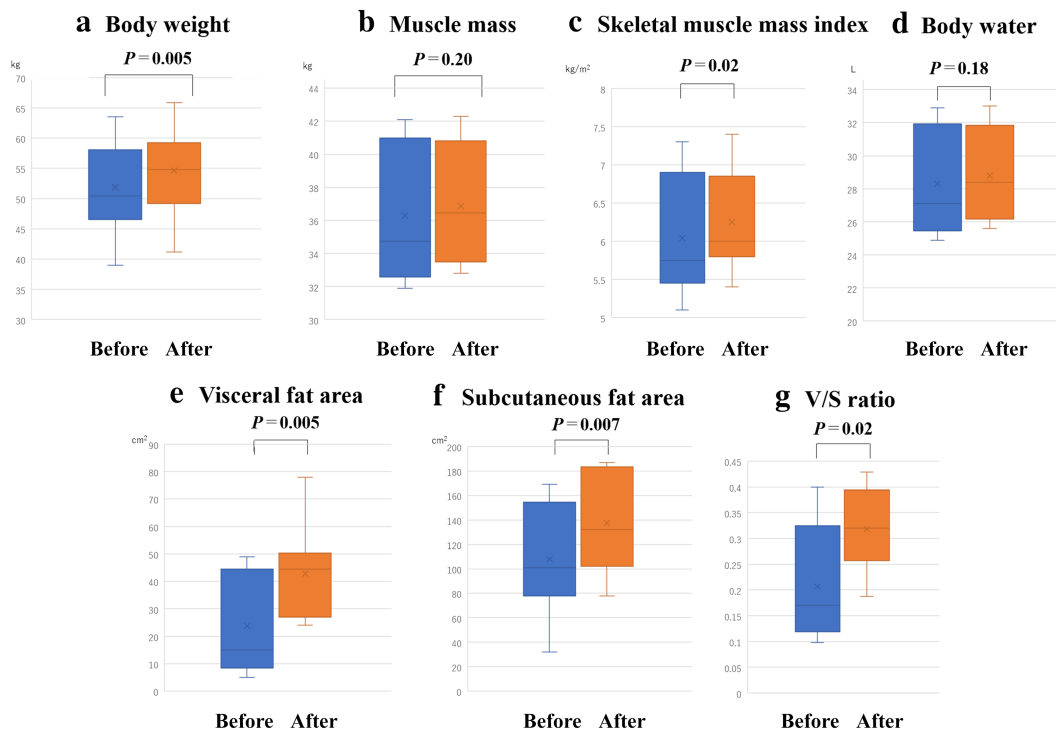


Figure 5 Change in bodyweight (a) and body composition (b, muscle mass; c, skeletal muscle mass index; d, body water; e, visceral fat area; f, subcutaneous fat area; g, ratio of the visceral to subcutaneous fat area [v/s ratio]) in patients with achalasia before and after treatment. As bodyweight increases, visceral fat volume, subcutaneous fat volume, and v/s ratio increase significantly.

Table 4 Investigation of a biomarker of low body mass index and low visceral fat in patients with achalasia

Serum biomarker	Low body mass index (BMI)		Low visceral fat area (VFA)		BMI \geq 18.5 (n = 52)
	BMI < 18.5 (n = 20)	P value	Low VFA (n = 10)	P value	
Total protein (g/dL) [†]	7.5 \pm 0.57	0.13	7.4 \pm 0.42	0.51	7.3 \pm 0.44
Albumin (g/dL) [†]	4.3 \pm 0.32	0.14	3.9 \pm 0.28	0.47	4.2 \pm 0.39
Hemoglobin (g/dL) [†]	14.1 \pm 1.6	0.12	13.9 \pm 1.1	0.46	13.4 \pm 1.3
Total cholesterol (mg/dL) [†]	194 \pm 36.6	0.87	198 \pm 33.4	0.36	199 \pm 34.5
Lymphocyte count (per L) [†]	1670 \pm 320	0.58	1450 \pm 505	0.54	1660 \pm 479
HbA1c (%) [†]	5.5 \pm 0.29	0.22	5.5 \pm 0.26	0.06	5.6 \pm 0.66
C-reactive protein (mg/dL) [†]	0.09 \pm 0.12	0.08	0.14 \pm 0.29	0.16	0.055 \pm 0.49

[†]Mean \pm SD.

HbA1c, glycosylated hemoglobin.

maintain body water content. Body water is exceedingly essential to support life; therefore, humans adjust body water content using an internal regulation mechanism to maximally utilize a limited oral intake or ingested water pass through tight LES area easier than food. The rapid decrease of intra-abdominal adipose tissue to calorie restriction in patients with lifestyle diseases such as obesity has been suggested previously,^{27,28} and this study indicated that VFA and SFA also rapidly increase in response to calorie intake. Yamada *et al.* reported SMI < 6.8 kg/m² in men and < 5.7 kg/m² in women in the presence of sarcopenia.²⁹ Based on that criteria, regarding SMI in our case series, 4 out of 10 were still lower than the cut-off value, and another two were above the cut-line after POEM (Fig. 5c, detailed data not shown). Therefore, although bodyweight increased after POEM, the increase in skeletal muscle mass was considered insufficient for optimal health. In this study, no blood biomarkers were associated with a low BMI or low intra-abdominal fat in patients with achalasia. Parameters, like CONUT score, are used for the assessment of the nutritional status of the patients; however, other biomarkers should be investigated.

This study has several limitations. First, we could not calculate weight loss from baseline because many patients could not remember their baseline weight accurately. Second, the sample size used in this study might be inadequate to show a significant difference.

In conclusion, dual BIA instruments are effective non-invasive tools for the assessment of body composition in underweight patients. In patients with achalasia, weight gain in short-term period could not be a satisfactory outcome; at least maintenance of enough skeletal muscle volume should be confirmed in a further investigation with a longer study period. Additional studies are warranted to understand the pathological implications of low intra-abdominal fat or subcutaneous fat volume and the rapid increase after treatment in patients with achalasia.

Acknowledgment

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