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REVIEW

Measurement of body composition as a surrogate evaluation of energy balance in obese patients

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Abstract

In clinical practice obesity is primarily diagnosed through the body mass index. In order to characterize patients affected by obesity the use of traditional anthropometric measures appears misleading. Beyond the body mass index, there are overwhelming evidences towards the relevance of a more detailed description of the individual phenotype by characterizing the main body components as free-fat mass, muscle mass, and fat mass. Among the numerous techniques actually available, bioelectrical impedance analysis seems to be the most suitable in a clinical setting because it is simple, inexpensive, noninvasive, and highly reproducible. To date, there is no consensus concerning the use of one preferred equation for the resting energy expenditure in overweight and/or obese population. Energy restriction alone is an effective strategy to achieve an early and significant weight loss, however it results in a reduction of both fat and lean mass therefore promoting or aggravating an unfavourable body composition (as sarcobesity) in terms of mortality and comorbidities. Therefore the implementation of daily levels of physical activity should be simultaneously promoted. The major role of muscle mass in the energy balance has been recently established by the rising prevalence of the combination of two condition as sarcopenia and obesity. Physical exercise stimulates energy expenditure, thereby directly improving energy balance, and also promotes adaptations such as fiber type, mitochondrial biogenesis, improvement of insulin resistance, and release of myokines, which may influence different tissues, including muscle.

Key words: Obesity; Body composition; Bioelectrical impedance analysis; Energy expenditure; Sarcobesity

Core tip: There are overwhelming evidences towards the relevance of a more detailed description of the individual phenotype by characterizing the main body components as free-fat mass, muscle mass, and fat mass. Among the numerous techniques actually available, bioelectrical impedance analysis seems to be the most suitable in a clinical setting because it is simple, inexpensive, noninvasive, and highly reproducible. To date, there is no consensus concerning the use of one preferred equation for the resting energy expenditure in overweight and/or obese population.

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INTRODUCTION

Obesity, defined by excessive adipose tissue, has been shown several deleterious effects on many body organs through thrombogenic, atherogenic, oncogenic, hemodynamic and neurohumoral pathways and has been linked to several chronic diseases, as diabetes, ischemic heart, and musculo-skeletal disorders, together with malignancies. Overweight and obesity represent the fifth leading risk for global death by The World Health Organization on March 2013[1]. At least 2.8 million adults die each year as a result of overweight/obesity. Moreover the 44% of diabetes and 23% of ischemic heart disease burden can be attributable to an abnormal adipose tissue accumulation[1].

Obesity is diagnosed accordingly to the body mass index (BMI). This index has been strongly recommended for use in clinical practice[2,3]. Multiple studies have shown a U or J-shaped relation between BMI, all causes and/or cardiovascular mortality, thus identifying the best survival rate for BMI values in overweight (25-27 kg/m^2) followed by a dramatic increase in risk profile out of these values[4-9].

In a cross-sectional study enrolling 13601 subjects (45.5 ± 17 years; 48% men) from the Third National Health and Nutrition Examination Survey (NHANES)[10], the BMI cut-off of $\geqslant$ 30 kg/m^2 shown an overall low sensitivity and an high specificity to identify obesity such as defined by an excessive body fat percentage at bioelectrical impedance analysis (> 25% in men and > 35% in women, respectively, thus according to the gold standard definition proposed by the World Health Organization[2]. The BMI-based definition of obesity has important limitations on diagnostic performance, particularly in men and elderly, missing more than 50% of people with excessive fat mass. In men, BMI showed a more reliable association with lean mass than with total body fat. In contrast, in women BMI appears to be more accurate to estimate fat-mass, thus explaining why overweight women have been reported as more consistently related to increased mortality compared to overweight male individuals. Furthermore, there is significant inter-subject variability in body fat percentage in individuals with similar BMI values. About 30% of obese subjects do not show any metabolic complications such as diabetes, hypertension, dyslipidemia, *etc*.), then they can be defined metabolically healthy obese patients[11]. On the other hand, in subgroups of BMI-based normal weight individuals an increased cardiometabolic risk profile and an insulin resistant condition could be described and strictly related to fat mass accumulation[12,13].

Further studies have pointed out the association between visceral adiposity, better than BMI, mortality and cardiovascular disease. Waist circumference as a marker of abdominal adipose tissue, has been placed as one of the main contributors to the Metabolic Syndrome by the National Cholesterol Education Program Adult Treatment Panel Ⅲ in 2001[14], then as the core feature of the diagnostic criteria proposed by the International Diabetes Federation in 2005.

In the International Day for Evaluation of Abdominal adiposity cross-sectional study, enrolling 168.000 patients in 63 countries, waist circumference showed a higher adjusted odds ratio (95%CI) for diabetes than BMI in overall sample population [1.35 (1.30-1.40) *vs* 1.23 (1.19-1.27) for men and 1.55 (1.50-1.60) *vs* 1.23 (1.19-1.27) for women, respectively) such as for cardiovascular disease [1.24 (1.19-1.28) *vs* 1.13 (1.09-1.17) for men and 1.21 (1.17-1.25) *vs* 1.20 (1.16-1.24) for women, respectively)[15].

In the NHANES Ⅰ and NHANES Ⅱ longitudinal prospective cohort studies, performed in 10169 male subjects a continuous positive relationship between fat-mass and all-cause mortality rate (HR = 1.033, 95%CI: 1.005-1.063, P = 0.0213) have been reported, together with a preponderant significantly negative relationship between free-fat mass and all-cause mortality (*i.e.*, protective; HR = 0.923, 95%CI: 0.906-0.941, P < 0.0001)[16].

Furthermore, BMI and weight loss rate may not be linked to clinical improvement of health-related outcomes, in comparison to different body composition measures by simple and non-invasive methods, which demonstrated a strong relationship between mortality, body lean mass and adipose tissue[17-24].

In conclusion beyond the BMI, there are overwhelming evidences towards a more detailed description of the individual phenotype by characterizing the main body components as free-fat mass (FFM), muscle mass (MM), and fat mass (FM).

BODY COMPOSITION MEASUREMENTS: TECHNOLOGICAL ADVANCES AND CURRENTLY AVAILABLE NON INVASIVE TECHNIQUES

Numerous techniques for body composition analysis are currently available: anthropometry, including the 4-skinfold method, hydrostatic weighing, *in vivo* neutron activation analysis, anthropogammametry from total body ^{40}K, nuclear magnetic resonance, dual-energy X-ray absorptiometry (DEXA), computerized tomography (CT), and bioelectrical impedance analysis (BIA). Evaluating complexity, invasiveness, and cost only DEXA, CT, and BIA may represent the methods of choice to assess body composition in clinical practice whereas the other techniques are limited to scientific

purposes.

DEXA estimates body fat and lean mass percentage through a tissue-specific model (fat, lean tissues, and bone) based on X-ray (dose 1-3 mrad) tissue-dependent attenuation[25]. The largest sample (*n* = 22000 partecipants) have been analyzed by the NHANES[26]. DEXA systems currently available for scanning whole-body tissue composition are capable to analyze a wide range of weights including severe obese subjects (> 150 kg). DEXA scans can be subdivided into different body regions, *i.e.*, trunk, arms, and legs, thus identifying and estimating both android and gynoid fat distribution. DEXA can detect only abdominal adipose tissue accumulation without any distinction between visceral and subcutaneous fat because of their similar X-ray attenuation properties and tissue overlapping[27]. DEXA is the gold standard technique for the evaluation of body composition in clinical research[28-30], although limited in clinical practice by the radiation exposure, availability and cost. The use of the same DEXA instruments and analysis software are of relevant importance for longitudinal studies, since they could influence body composition measurements[31].

In patients affected by malignancies, the analysis at the level of the 3rd lumbar vertebra by CT strongly predicted whole body fat and FFM as compared with DEXA[32]. CT provided an accurate evaluation of body composition, not provided by DEXA or BIA and a X-ray exposition similar to a chest radiography. Although not validated, also CT images of the right thigh halfway showed to be significantly related to overall mortality rate in chronic obstructive pulmonary disease patients[33]. Despite its wide use at diagnosis and follow-up in severely ill patients, CT scan at the 3rd lumbar vertebra cannot be considered a feasible method to assess body composition in obese population requiring expensive equipment, trained operators and exposure to ionizing radiation.

BIA is based on the capacity of hydrated tissues to conduct electrical energy. The BIA methodology have been described in two ESPEN position papers[34,35]. The analysis of total body impedance is based on the estimation of total body water. From total body water, prediction equations allow the calculation of FFM and FM. BIA equations have been validated for chronic obstructive pulmonary disease, AIDS, transplant patients and elderly individuals[36]. A prediction equation for FFM estimation by BIA in adults (age: 20-94 years; BMI: 17.0-33.8 kg/m^2) has been proposed[37] as well as reference values of FFM and FM for a Caucasian population[38]. Previously reported data showed no significant differences between DEXA and BIA for the assessment of fat mass in overweight and/or obese patients with a significantly good linear correlation[39,40]. However several factors could limit the validity of BIA in severe obesity[41].

ENERGY BALANCE IMPLICATIONS FOR ADDRESSING OBESITY: AVAILABLE ENERGY EXPENDITURE MEASUREMENTS

Energy balance is constituted by three major components including energy intake, energy expenditure (EE) and energy storage. Energy expenditure is expressed by resting energy expenditure (REE), as the amount of energy required for the endogenous metabolic activity separated from the metabolic effects of food and physical activity, the food-related thermic effects (TEF), as energy need to absorb and metabolize ingested food, and energy expenditure associated to physical activity (EE_{PA}). EE_{PA} is the most inter-individual variable component of energy expenditure and consists of the amount of physical activity performed multiplied the energy requirement of that activity. The REE is proportional to body mass, particularly to the FFM[42]. The REE prediction equations evaluate the energy expenditure of 2 different body compartments as the adipose tissue or FM and the lean mass or FFM. FFM is the main source for REE and is commonly considered as a surrogate measure of metabolically active tissues. Brain, liver, heart, and kidney account for approximately the 60% of REE, despite a combined weight < 7% of FFM. In comparison to the skeletal muscle, the metabolic rate of heart and kidney is approximately 30-fold higher, and the later approximately 2-fold higher in comparison to brain and liver. The skeletal muscle represents the major contributor to the FFM (50%), but accounts for only the 21% of the REE. Adipose tissue has a low energy expenditure, however its body rate varies significantly according to the dramatic increase of overweight and obesity. Then it is notable that FM represent an important source for the REE in all prediction models. Among adults, REE is lower in elderly, almost in part explained by the change in body composition[27].

Advantage and limitations of currently available non invasive techniques for the estimation of EE are summarized in Table 1.

Indirect calorimetry represents the gold standard technique to evaluate REE. This method used the rates of oxygen consumption (V_{O2}) and/or carbon dioxide production (V_{CO2}) to calculate EE according to the Weir predictive equation, derived from studies comparing indirect calorimetry with direct calorimetry[43]. The complexity and cost, together with the requirement of the patient isolation for at least 24 h limit the feasibility of the direct calorimetry in humans.

The indirect calorimetry consists in a gas collector, a canopy and a system that measures the volume and concentrations of O_2 and CO_2 minute by minute. Through a unidirectional valve located in the ventilated canopy, the calorimeter collect and quantify the volume and concentration of O_2 inspired and of CO_2 expired. A systematic literature review aimed to determine the

Table 1 Advantages and limitations of available techniques the measurement of Energy Expenditure

Technique	Advantages	Limitations
Direct calorimetry	The gold standard method for measure EE in animal models	High complexity, high cost, need to confine the subject for almost 24 h
Indirect calorimetry	The gold standard to measure REE in humans. Non invasive, adequately accurate, highly reproducible	High cost, relatively complex, need of trained personnel
Bioelectrical impedance analysis	Non invasive, simple, adequately accurate for body composition analysis, relatively inexpensive	The estimation of EE is limited by the need of obesity-specific predictive equations
Multi-sensor device	Easy and practical to use	The estimation of EE is limited by the need of obesity-specific predictive equation

EE: Energy expenditure; REE: Resting energy expenditure.

optimal conditions for obtaining reliable measures of REE by indirect calorimetry recommends fasting for at least 6 h, avoiding caffeine during the night, nicotine and alcohol for at least 2 h, moderate physical activity for at least 2 h, and vigorous physical activity for 14 h before[44]. Despite methodological, environmental and individual limitations indirect calorimetry represents a non-invasive and very accurate method to estimate REE[45]. However this method is widely limited in most of clinical settings by the requirement of expensive equipment, and trained operators, then many efforts are spent to identify the most accurate predictive equation to determine REE in overweight and obesity.

Predictive equations have generally been calculated from experimental studies performed in healthy subjects on the basis of regression analysis of bodyweight, height, sex, and age as independent variables and REE by indirect calorimetry as a dependent variable. On the basis of a review of available evidences from Harris and Benedict[46], FAO/WHO/UNU weight or weight and height equations[47], and the equations of Mifflin *et al*[48] and Owen *et al*[49], Frankenfield *et al*[50] proposed the use of the Mifflin equation both for overweight and obese subjects. All the available predictive equations have been further validated with indirect calorimetry from adults aged 18-65 years with a BMI of 25 to 40 kg/m^2 in order to identify the most accurate and precise REE predictive equation in specific overweight and obese groups of United States and Dutch subjects: the results of this study were similar to the data of Frankenfield *et al*[50], then supporting the use of Mifflin equation in the United States. However for overweight and obese Dutch adults, there appears to be no accurate equation[51]. This discrepancy for the Dutch than for the United States adults could be explained by the difference about weight and height values, even within sex and BMI subgroups, thus limiting the validity of this equation in similar taller populations. Numerous studies contributed to further evaluate the currently available predictive equations in overweight and obese subjects[52-55] and/or in extremely obese subjects[56-61]. There is some evidences supporting the Mifflin[59], the FAOw[56,58] and the Harris Benedict[60], the Siervo equations[61] in extremely obese subjects. More recently a new equation, using FFM, Horie-Waitzberg, and Gonzalez equations, have been validated and proposed in Brazilian severely obese subjects[62]. The most commonly proposed equation for the measurement of REE have reported in Table 2.

To date there is no consensus about the use of one REE equation compared to others, in overweight and/or obese population. This might be related to differences about group composition, methods, or statistical analysis, at least in part.

In order to estimate EE including EE_{PA}, a practical multi-sensor device, the SenseWear Armband (BodyMedia, Inc., Pittsburgh) has been recently developed. This device contains four sensors to detect heat flux, accelerometry, galvanic skin reaction, skin temperature. Despite excellent results by comparison with energy expenditure measured using the doubly labeled water in overweight/obese children[63] and lactating women[64], other evidences underline the need of obesity-specific equations[65,66].

A meta-analysis of randomized clinical trial suggest that pedometer use is associated with a significant decrease of body weight and blood pressure[67]. However a recent review assessing different accelerometers to measure daily physical activity as a surrogate of EE in comparison with the doubly labeled water only few available devices have been proven to adequately correlate with the reference method[68].

BEYOND THE ADIPOSE TISSUE EXCESS: THE IMPORTANCE OF MUSCLE MASS IN OBESITY

Skeletal muscle plays a critical role in the glucose metabolism and peripheral insulin sensitivity as well as musculoskeletal performance. The importance of lean mass on energy balance has been widely recognized by the rising prevalence of the combination of two condition as sarcopenia and obesity[69]. Two major consensus documents provide different definition of sarcopenia. The European consensus, the Working Group on Sarcopenia in Older People, defines sarcopenia as generalized loss of skeletal muscle mass and strength[70]. The International consensus, the International Working Group on Sarcopenia, requires a decline in muscle mass and walking speed to diagnose sarcopenia[71]. Although sarcopenic obesity is commonly used to define the coexistence of diminished muscle mass and increased adipose tissue, a standard

Table 2 Most commonly proposed predictive equations for the estimation of the resting energy expenditure

	Age	Sex	Equation
Harris and Benedict (kcal/d)	15-74	Male	66.4730 + 13.7516 (W) + 5.0033 (H) – 6.7550 (A)
	15-74	Female	655.0955 + 9.5634 (W) + 1.8496 (H) – 4.6756 (A)
Schofield (MJ/die)	10-17	Male	0.074 (W) + 2.754
	10-17	Female	0.056 (W) + 2.898
	18-29	Male	0.063 (W) + 2.896
	18-29	Female	0.062 (W) + 2.036
	30-59	Male	0.048 (W) + 3.653
	30-59	Female	0.034 (W) + 3.538
	⩾ 60	Male	0.049 (W) + 2.459
	⩾ 60	Female	0.038 (W) + 2.755
FAO/ WHO/ UNU (MJ/d)	10-17	Male	0.0732 (W) + 2.72
	10-17	Female	0.0510 (W) + 3.12
	18-29	Male	0.0640 (W) + 2.84
	18-29	Female	0.0615 (W) + 2.08
	30-60	Male	0.0485 (W) + 3.67
	30-60	Female	0.0364 (W) + 3.47
	> 60	Male	0.0565 (W) + 2.04
	> 60	Female	0.0439 (W) + 2.49
Mifflin-St Jeor (kcal/d)	19-78	Male	10 × W + 6.25 × H – 5 × A + 5
	19-78	Female	10 × W + 6.25 × H – 5 × A – 161
Owen (kcal/d)	18-65	Male	879 + 10.2 × W
	18-65	Female	795 + 7.18 × W

To convert MJ into kcal, multiply the result by 239. W: Body weight (kg); H: Height (cm); A: Age (years).

definition of sarcopenic obesity is still lacking. Several clinical studies have indicated that obesity and/or insulin resistance may underlie the development of sarcopenia[72]. A possible role of vitamin D in sarcopenia has been postulated in two studies demonstrating that serum 25-hydroxy vitamin D was negatively correlated with appendicular (legs and arms) fat mass and positively associated with appendicular muscle mass, both evaluated through DEXA analysis[73,74].

Fat mass excess may induce and/or worsen sarcopenia because the increase of lipid depot reduces both amino acid utilization and protein synthesis in muscle fibers. Evaluating 3132 elderly male subjects without diabetes the highest quartile of homeostasis model assessment of insulin resistance showed the highest risk for a decrease in lean body mass and appendicular mass[75]. On the counterpart, skeletal muscle is the main target of insulin, then loss of muscle mass may cause insulin resistance. A previous study identified sarcopenia as a risk factor for exacerbating insulin resistance in obese subject with dysglycemia[76].

Skeletal muscle fibers can be classified into different categories: from slow (type Ⅰ) fibers with low contractile abilities, numerous mitochondria and high oxidative energy metabolism, to type Ⅱa and type Ⅱd/x, and eventually fast (type Ⅱb) fibers able to contract rapidly and predisposed toward glycolytic processes. In obese and diabetic population skeletal muscle commonly contains more type Ⅱb fibers, while slow muscle fiber percentage and skeletal muscle glucose transport are significantly reduced. Sarcopenic individuals have been shown to be associated with a further impairment of muscle fiber content, predominantly of type Ⅰ [77]. Recent studies have shown that exercise is able to increase the content of type Ⅰ and type Ⅱa fibers[78]. Furthermore, in skeletal muscle with ageing both the number and morphology of mitochondria are changed with an impaired function and an associated reduced oxidative capacity[79]. In particular since the primary role of mitochondria is to maintain the cellular energy balance, shifts in mitochondria respiratory activity can lead to a reduced maximal capacity of the tricarboxylic acid cycle and the electron transport chain together with an incomplete lipid-induced upregulation of β-oxidation rates, thus inducing a significant accumulation of intramyocellular lipids and further impairing whole body insulin resistance[79]. Physical exercise has been demonstrated to induce mitochondria biogenesis, upregulates skeletal muscle gene expression and protein synthesis, and increases skeletal muscle oxidative capacity both in older and sedentary populations[80].

Moreover, recent evidences promote the hypothesis of cross talk between muscle and different tissues mediated by cytokines and other peptides called myokines[81] which are involved both in acute exercise-induced metabolic reactions, as well as in the long-term metabolic benefits induced by exercise[82]. Irisin is one of the most recently identified myokines. Following regular physical activity, Irisin increases two-fold its circulating levels and promotes the shift of white adipocytes into "brite" cells: white adipocytes with a brown-fat-like phenotype. Brown adipocytes activate thermogenesis *via* the mitochondria uncoupling protein UCP-1 (Figure 1). Overexpression of irisin

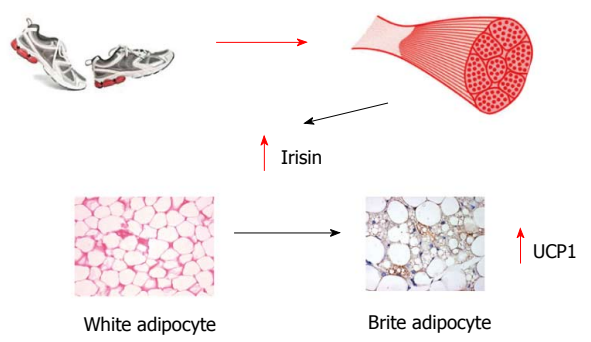

Figure 1 Physical activity increases the intramuscular expression of the membrane protein fibronectin type III domain containing 5 (FNDC5) which is cleaved to form Irisin, a myokin. Irisin may stimulate the transformation of white adipocytes into brite cells, thus suggested by a marked increase in the expression of uncoupling protein 1 (UCP-1). Adapted from Pedersen[82].

determined through a gene therapy approach mediated by adenoviral particles, and leading to a modest approximately 3 fold increase in circulating levels, induced browning of subcutaneous white adipose tissue, stimulating a 10-20 fold increase in UCP1, thus increasing energy expenditure and improving glucose tolerance of high fat fed mice[83]. Despite more recent *in vitro* evidences against the possible translation of the beneficial effects observed in mice to humans, the major role of muscle mass in the energy balance has been definitively established.

In conclusion, physical exercise increases EE and stimulates muscle adaptation mechanisms with potential benefits on different tissues.

ENERGY BALANCE, PHYSICAL ACTIVITY AND DIETARY RESTRICTION

Analysis from the NHANES database describes an average daily intake increase of 168 kcal/d for men and of 335 kcal/d for women, from 1971 to 2000[84]. On the counterpart, examining in 2004, the physical activity patterns in a typical agrarian population in the United States through pedometers an average of about 18000 steps per day in men and of about 14000 steps per day have been reported[85], whereas an average American adult walked about 5000 steps per day[86].

An energy balance flipping point between energy intake and energy expenditure could be recognized in United States around 60' years, thereafter followed by energy intake continuously driving energy expenditure, together with a worldwide burden in the incidence of obesity and type 2 diabetes[87].

The most frequently proposed strategy for treating obesity is food restriction. Energy restriction alone is an effective strategy to achieve a rapid and substantial weight loss, however it results in a reduction of both fat and muscle mass therefore promoting or aggravating an detrimental body composition (as sarcobesity) in terms of mortality and comorbidities. Specifically, approximately 25% of weight loss obtained through short-term low energy diets is lean muscle mass[88-92]. Moreover, the lack of success in weight loss maintenance after low-energy regimen and the subsequent weight regained comprising of up to 80% fat mass compound a further detrimental body composition impairment[93,94]. Weight loss should not be considered the sole focus of therapeutic approach aimed to decrease obesity-related disease risk profile. A systematic review by Chaston *et al*[95] demonstrates that very low calories regimens (VLCD) result in significant greater loss of FFM (lean) in comparison to low-calories diets[95]. Current evidences sustained that the most beneficial long-term outcomes are achieved with a modest energy deficit (2000-4000 kJ/d)[96]. Therefore increased levels of daily physical activity should be simultaneously promoted. Although resistance training retains or improves the relative percentage of lean mass to total body, current evidence failed to detect a loss of fat mass of a similar magnitude to aerobic training which promotes fat mass loss together with beneficial changes in muscle tissue[97-99].

Studies evaluating efficacy of dietary restriction together with exercise program showed more favorable results (as weight loss rate and body composition improvement) compared to diet or exercise prescription alone[69]. Emerging data suggest that the combination of resistance and aerobic exercise with a modest energy restriction was successful for preserving skeletal muscle concomitantly with a significant decrease of fat mass[100].

CONCLUSION

In order to characterize patients affected by obesity the use of traditional anthropometric measures appears misleading. A systematic and deep phenotyping of these patients, thus integrating data from body composition analysis and energy expenditure should be used in a dynamic rather than only basal approach to define and periodically verify the efficacy of the therapeutic regimen proposed. Among the numerous techniques evaluated in this paper, BIA seems to be the most suitable in a clinical setting because it is simple, inexpensive, noninvasive, and highly reproducible. Moreover, a recent paper by our research group showed that the FM and MM percentage estimated by BIA at baseline should be considered as predictors of success (weight loss > 5% at 6 mo from baseline) in a individual cognitive-behavioral program[40].

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