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Phase angle (PhA) in overweight and obesity: evidence of applicability from diagnosis to weight changes in obesity treatment

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Abstract
Phase angle (PhA) is a recently proposed marker of nutritional status in many clinical conditions. Its use in patients with obesity presents different critical concerns due to the higher variability of the two measured parameters (resistance, R, and reactance, Xc) that contribute to the determination of PhA. Controversial is the relation between PhA and BMI that might vary with graded levels of obesity due to the variation in fat and free fat mass. Obesity is frequently associated with metabolic, hepatic, cardiovascular and kidney diseases that introduce variations in PhA values, in relation to multimorbidity and severity degree of these diseases. It is reported that the improvement of clinical condition is associated with a positive change in PhA. Also, the treatment of obesity with weight loss might confirm this effect, but with different responses in relation to the type and duration of the intervention applied. In fact, the effect appears not only related to the percentage of weight loss but also the possible loss of free fat mass and the nutritional, metabolic and structural modifications that might follow each therapeutic approach to decrease body weight. We can conclude that the PhA could be used as marker of health status in patients with obesity supporting an appropriate weight loss intervention to monitor efficacy and fat free mass preservation.

Keywords Obesity · Phase angle · Bioelectrical impedance analysis · BIA · BIVA · Weight loss

1 Introduction

In 2022, the European Regional Office of the World Health Organization (WHO) updated its Report on Obesity in the European region, which highlights overweight and obesity rates that have reached epidemic proportions [1]. The

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document shows that 59% of European adults and almost 1 in 3 children (29% of males and 27% of females) are overweight or suffer from obesity, now considered a disease [1]. Overweight and obesity are in fact among the main causes of death and disability also in the European Region and recent estimates suggest that they cause more than 1.2 million deaths per year, corresponding to over 13% of total mortality. Obesity increases the risk of many non-communicable diseases, including cancer, cardiovascular disease, type 2 diabetes mellitus, and chronic respiratory disease [2]. Additionally, obesity is associated with an increased risk of complications and mortality in the case of SARS-CoV-2 infection [3, 4]. The prevalence of obesity in adults in the European region is higher than in any other WHO region, except the Americas [5]. Over the last five years to 2022, obesity rate among adults aged 18 and older has increased an annualized 1.8% to 33.0 people per 100 individuals [6]. WHO estimates that by 2025, approximately 167 million people (considering adults and children) will become less healthy because of overweight or obesity [1, 6].

Obesity is characterized not only by an increase (from moderate to severe) of body adipose tissue but also by alterations in the metabolic, structural and functional characteristics of skeletal muscle (i.e. low muscle quality) [7]. Surrogate measures, such as the body mass index (BMI) give no indication of fat free mass, muscle mass or nutritional state. Although obesity treatment can begin with a screening threshold of a BMI ≥ 30 Kg/m^2, a proper body composition analysis is important to determine baseline fat mass and fat free mass (lean soft tissue mass). Different methods are used for body composition assessments depending on practicality and feasibility, including bioelectrical impedance analysis (BIA), anthropometry (skinfold thicknesses, body girths) and dual-energy X-ray absorptiometry (DXA) [8–10]. BIA is a simple, inexpensive, quick and non-invasive technique for assessing body composition and its changes over time. BIA is used in various clinical settings due to its safety and cost-effectiveness compared to DXA [11–13]. However, at present, the routinely use of body composition analysis by BIA for obesity treatment is still debated. Concerns include the assumption of constant hydration of the fat free mass and validity of multiple regression prediction models for fat free mass. Importantly, the water content of adipose tissue is appreciable with estimates highly variable (6 to 36%) due to limited samples and diverse anatomical sampling locations [14] with a generally accepted value of 15% [15]. Phase angle is a unique biomarker that discriminates the expanded ECW in adipose tissue [16]. It is a unique bioelectrical impedance variable to overcome these limitations because it accounts for hydration status and cell mass [12]. The PhA has been related to muscle strength, being higher in athletes and lower in sarcopenic obese subjects [17, 18]; low PhA values are associated with impaired quality of life and poor prognosis in various chronic diseases [19]. The European Working Group on Sarcopenia in Older People recently proposed the PhA as a possible indicator of muscle quality [20].

Presently, PhA has limited usefulness in clinical practice because of a lack of reference values for overweight and obese populations. Also, variability exists in responses of PhA to weight loss induced by different diet and physical activity treatments, different types of bariatric surgery and the metabolic impact of reducing inflammatory processes. The aim of this narrative review is to depict the evidence of importance and applicability of PhA in patient with obesity and in the treatment of obesity through weight reduction as well as improvement of metabolic and clinical conditions associated with obesity.

1.1 What is the physiological meaning of "phase angle" in patients with obesity?

The use of PhA and its raw BIA components has gained attention as an alternative to conventional error-prone estimation of body composition. BIA measures whole-body impedance, the opposition of the body to alternating current caused by water and electrolytes and consists of two components: resistance (R) and reactance (Xc) [21]. Resistance is the decrease in voltage reflecting conductivity through ionic solutions. Reactance is the delay in the flow of current measured as a phase-shift, reflecting dielectric properties (i.e. capacitance of cell membranes and tissue interfaces). BIA is not a direct method for body composition assessment and its accuracy in estimating body composition relies on the assumption of constant hydration of the fat free mass sample-specific regression equations [22].

The PhA is calculated with R and Xc values: PhA (°) = arctangent (Xc/R) x (180°/π); it is related to the distribution of intracellular and extracellular fluids and integrity of cells membrane [23, 24]. Importantly, from a strictly mathematical point of view, the values of R differ from those of Xc by an order of magnitude, therefore, the variability of Xc will have a significantly greater effect than those of R in the value of PhA. Biological variations in intracellular or extracellular fluids and cell membrane integrity are reflected on R and Xc values, and consequently on PhA. For this reason, some researchers have already highlighted the need to adjust for hydration status when measuring PhA. For instance, the PhA and the extracellular/total body water (ECW/TBW) ratio were important factors in malnutrition and predictors of clinical outcomes. The excess of ECW, unlike the increase in the relative intracellular water (ICW), is almost always a condition to be avoided. In many scientific studies it is often found that the increase in FM is correlated with an altered distribution of body fluids. Overweight

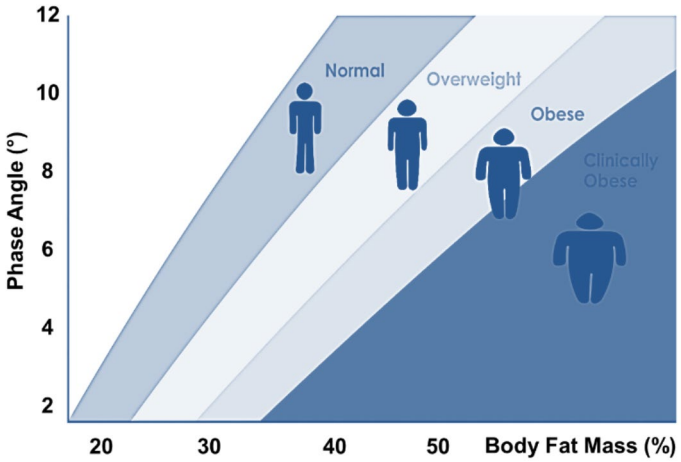

Fig. 1 Phase angle distribution in normal-weight subjects and in patients with overweight/obesity. The PhA ranging from 3.9° to 4.9° and 4.1° to 5.1° in women and men respectively showing a decrease range when compare to normal-weight (6.7°-7.8° in women and 7.2°-8.4° in men)[44]. Multiple reasons might be responsible to this shift including increased adiposity, hyperhydration, body cell mass, FFM, inflammation and malnutrition

and / or obese subjects may have a high percentage of ECW and an ECW/ICW ratio above 0.85, higher than the average for the normal weight population (about 0.70–0.75) [25, 26]. This condition is partly proven by the fact that the adipose tissue itself has a higher ECW / ICW ratio than muscular mass. In fact, while FFM has an average ECW/ICW ratio of about 0.80, adipose tissue can achieve an ECW/ICW ratio of up to about 3.7 [27 Wang J.] Consequently, a high percentage of FM can help increase the percentage of ECW. The ECW/ICW ratio could be particularly altered when the extra adipose tissue is present in the abdominal area or as a result of different mechanisms, such as water retention, total body water (TBW) in excess caused by an altered regulation of the state of hydration, edema (generally present in the lower limbs), hormonal responses related to adipose tissue, insulin resistance, high triglyceride levels, low HDL cholesterol levels, metabolic syndrome, malnutrition [28, 29]. The high ratio of ECW/ICW could also reflect a state of cellular dehydration or any physiological shifts of intracellular towards the extracellular water (such as when an inflammatory state or a stressful condition at the cellular level is present in the body). A high ECW/ICW ratio in overweight and/or obese subjects may also be associated with impaired metabolic regulation, glucose intolerance, reduced lipolysis and increased risk of diabetes. A systemic inflammatory condition, such as that found in obese individuals is responsible for these changes. Research has shown that isotonic and endurance physical activity can promote an increase in ICW, a signal for an increase in cell mass, muscle mass, basal metabolic rate, strength and improvement of the immune system. Conversely, low values of the ECW / ICW ratio (< 0.60) can be used to detect any risk conditions or the presence of dehydration.

The alterations in the PhA associated with disease, malnutrition, and physical inactivity could be justified by modifications in FFM that have been commonly shown in patients with obesity. However, even in situations when FFM loss has not occurred, extracellular fluid expansion can lead to an increase in the ECW/ICW ratio, for example in sepsis and the early phases of malnutrition leading to a decrease in the PhA [30–32]. It is important to note that the resistance measure (R) refers to the compartments of fluid and electrolyte-containing tissues (e.g. soft tissue mass), which offer greater resistance to the passage of this current [33], is higher in obesity and produces a reduction in PhA. On the other side, reactance is decrease for cellular injury, cachectic or inflammatory conditions such as in neoplastic or immunological diseases. Furthermore, it is suggested that BCM in obesity presents modification in selective permeability [34] due to a subclinical inflammation condition by different cytokine production by adipose tissue and also an increased production of reactive oxygen species (ROS) that oxidize lipids and proteins, including those in the cell membrane, which decreases cellularity [35]. All these conditions interfere with phase angle values, as summarized in Fig. 1.

The PhA of healthy individuals can vary between 6º and 7º with a possible cut-off value at a value of 6.96º [24, 32]; in athletes it may reach value > 8.5° [36]. Reported high values may exceed 8° whereas values < 6° reflect a poor clinical prognosis [36, 37]. As reported in a systemic review by DiVincenzo et al. [38], the PhA of individuals with obesity presents a large range of values with no range of normal values. This variability may be explained by a combination of factors including diverse underlying clinical conditions and the different technologies in BIA instruments and electrode placement.

1.1.1 Importance of gender and ethnic differences

Gender is a determinant of PhA values. Women tend to have lower PhA values than men [24] largely due to lesser Xc values attributed to reduced fat free mass [39]. Additionally,

an increased adipose tissue mass, which includes substantial water content (~20%), is associated with larger TBW and reduced R [24]. Ethnic differences reflect the variance in percentage of FM for the same BMI. In a study with 3 ethnic groups, the lower PhA was reported in Japanese compared with Germans in all age groups and it was depended by higher ECW/TBW ratio, with a lower skeletal muscle mass (SMM)/FFM [40]. A higher PhA for Mexicans in comparison with Germans is in accordance with differences in the height, which is highly correlated with fat free mass, in all groups [40].

1.1.2 Age, Height and PhA

A physiological change of PhA occurs with age. Findings indicate a general trend for PhA to decline with aging due to reduction of the parallel reactance with the loss of muscle mass and a concurrent increase in resistance associated with the decline in TBW at the expense of increasing in adipose tissue [19, 41]. The association of a deficit in muscle strength and a reduction in total muscle mass with aging is defined sarcopenia [42]. Phase angle has been associated with functional tests, such as gait speed and hand grip strength, in older women [43], and explained by the decline of Xc and the deleterious changes in electric properties of skeletal muscle with aging [32]. Multiple linear regression analysis revealed that age, skeletal muscle mass index (SMI), and muscle quality (evaluated by handgrip strength, HG) were independently associated with PhA in both sexes [44]. Recently, the cut-off PhA values are reported for predicting sarcopenia: 5.95°, 5.04°, 5.02°, and 4.20° in young male, elderly male, young female, and elderly female participants, respectively [44]. In a recent review, PhA was decreased in sarcopenic subjects [38]. Among different studies, the absolute values of PhA and the frequencies of sarcopenia might depend of gender, age and the clinical condition of the individual (e.g. COPD, cirrhosis, kidney transplant, cancer patients) probably in relation to nutritional state. The cut-off values of PhA varied from 4.05 to 5.05, possible because of the methods used for their identification. A significant association between PhA and functional test performance (e.g. six minutes walking test-6MWT) in older female adults, regardless of the potential confounding effects related to body composition [45]. A direct relation has been found with the muscle mass and strength [17, 18], as physical activity level influences body composition and seems to be positively associated with high PhA values [19]. Nescolarde et al. [46] showed that Xc and PhA decrease after an acute muscle injury.

Excess adiposity is one component of the specific condition termed sarcopenic obesity [42]. These patients present an increased ratio of intramuscular and intermuscular fat infiltration and a decreased ratio of muscle mass to total body mass related with metabolic abnormalities, low strength, and decreased mobility. The frequency of this condition is variable, ranging from 11 to 28%. In women with obesity, PhA was positively correlated with ultrasound-determined muscle area, muscle circumference, muscle echo intensity, serum albumin and total protein concentrations [47]. PhA was shown to be inversely correlated with body fat % ($r = -0.74$; $p < 0.001$), and positively correlated with peak oxygen uptake ($r = 0.50$; $p < 0.001$) and lower- and upper-body maximal strength ($r = 0.65$; $r = 0.70$; $p < 0.001$, respectively). Thus, PhA was proposed as a clinically tool to screen the physical fitness and functional status of adults with obesity [39].

Few studies demonstrated, in multivariate regression analysis, that height exerted largest impact on PhA followed by body weight and muscle mass [40]. Since height and weight are representatives of somatic development reflecting skeletal and muscular growth and collectively they increase percentage of FFM and thus influence resistance and PhA.

1.1.3 Influence of BMI on PhA

Conflicting data describe the relationship between PhA and BMI. Reports indicate a positive [41] and a negative correlation [42] and other findings no effects were evident [43]. Bosy-Westphal et al. [32] showed that PhA tended to increase with BMI up to 35 kg/m^2 and then decreased when BMI was > 35 kg/m^2; in both genders PhA was negatively associated with BMI values > 40 kg/m^2. Our group described in a wide cohort of patients with obesity a progressive decrease in PhA, in men and women both [44]. In particular, a reduction starting from a BMI of 40 kg/m^2 then becoming highly significant for BMI values higher than 50 kg/m^2, demonstrating the effect of adiposity excess and the low cellular integrity in case of extremely increased BMI (high resistance, low reactance). Thus, these data confirm that PhA in obesity is affected by multiple variables: sex, age, FM, FFM, hydration status, and nutritional state that directly influence resistance and reactance and not to BMI alone. It is notable that the increase in % fat, particular visceral FM, was associated with a reduction in PhA [24, 39, 40, 42, 45], probably for the alterations in the cell size, the permeability of the cell membrane, or differences in the distribution of fluids in the tissues, specifically an increase in ECW/ICW [46]. The parameter that most affects the PhA, in normal weight and normally hydrate adults, is FFM [30], in particular the skeletal muscle mass. Skrzypek et al. [45] confirmed, in a normal weight population, that PhA was positively correlated with muscle mass as well as with muscle strength. In fact, not only muscle mass is important, but

also muscle quality due to fibre composition, metabolism, aerobic capacity, insulin resistance, and fat infiltration/fibrosis as in patients with obesity [45].

1.2 Phase angle in patients with obesity and different associated clinical conditions

Phase angle has been studies as a prognostic marker in several clinical conditions (e.g. cancer, kidney and cardiac diseases, HIV infection, etc.) and in diseases frequently associated with obesity such as metabolic dysfunction, insulin-resistance, inflammation and disability, and in the development of chronic diseases such as diabetes, dyslipidaemia and cardiovascular diseases; moreover, the possibility to monitor the progression of metabolic or cardiovascular risk factors with PhA changes is very promising (*see Sect. 4*). The metabolic syndrome (MS) includes risk factors associated with heart disease, obesity, and diabetes. In a recent study [46] only the waist circumference was associated with lower PhA values. For the glucose, non-HDL-C, triglycerides, CRP, HOMA-IR and uric acid levels there was no association with PhA in the adjusted models. Furthermore, women with obesity and a low PhA tertile had high fat mass with high levels of glucose, HOMA, IL-6 and leptin, which are risk factors for atherosclerosis and cardiovascular disease in obese patients [47]. Low values of PhA were found in adults with higher prevalence of hyperuricemia, that increases oxidative stress and a proinflammatory state even after adjustment for waist circumference, hyperglycemia and arterial hypertension but not with physical activity [48].

In patients with diabetes, Buscemi et al. [49] observed a negative correlation between fasting plasma glucose level and PhA that was inversely related to the ECW/TBW ratio because hyperglycaemia induces an osmotic effect and higher resistance value. Pillon et al. [50] showed that in diabetes there is reduced ability to exchange potassium due to a decreased active cell mass. Therefore, the smaller PhA could be considered marker for the catabolic state in people with diabetes [51, 52]. An important application is the evaluation of nutritional state in diabetic chronic kidney disease patients. These patients present a hyper-hydration and a significant association with glomerular filtration rate (eGFR) and albumin level with undernutrition (PhA < 4.17°) [53]. The loss of muscle mass was also significantly related to the eGFR decline [54]. Recently Barrea et al. [55] reported, in a group of patients with PCOs, two significant results: PhA was negatively associated not only with the inflammatory status but also with the hyperandrogenemia in BMI-matched controls than suggest PhA as an endocrine marker of the severity of the PCOs. In the second study [56] the same Authors reported that PhA is significant low in patients with metabolically unhealthy obese (MUO) characterizes by highest percentage of severe obesity, low adherence to the Mediterranean diet, high CRP levels and frequency of MS diagnosis; for this data PhA was considered in the definition of relative prognostic value of MUO-PCOS phenotype [56]. Thus, decreased PhA values apparently are a consequence of metabolic perturbations associated with a pro-inflammatory state and its effects on body composition.

The presence of the metabolic dysfunction-associated fatty liver disease (MAFLD) and non-alcoholic steatohepatitis (NASH) range from 70 to 80% of patients with obesity and diabetes with a possible progression in fibrosis and cirrhosis. The accumulation of hepatic fatty acid within the liver, cause MAFLD and is associated to hepatic insulin resistance and an increase in pro-inflammatory mediators (IL-6, high sensitivity C-reactive protein and TNF-α) [57]. In patients with MAFLD but without fibrosis and severe steatosis, PhA rises proportionally to the increase in fat mass and BMI and decreases in advanced liver fibrosis [58]. A previous study reported that PhA values were significantly higher in well-nourished patients than in malnourished patients, characterized by both increased ECM and decreased BCM, but no statistically significant correlation was found between PhA, R and Xc values and Child-Pugh score [59]. Positive correlation with albumin levels suggested PhA as an indicator of nutritional status [59, 60].

Obesity is associated with a high risk of heart failure (HF) caused by both fluid retention (excessive fat mass) with cardiac overload and also malnutrition ("cardiac cachexia", with loss of muscle mass and systemic inflammatory in adipose tissue). The PhA showed lower values in patients in New York Heart Association (NYHA) classes III-IV than in those in classes I-II and is an independent predictor of mortality in HF patients. Relative Plasma Volume Status ("intravascular" congestion) was the major determinant (20% of PhA variability), while peripheral oedema and BNP plasma levels (markers of congestion) explained 12% and 2% of variability, respectively [61]. High values in central venous pressure (i.e. expansion of plasma volume) were associated to downward displacement of the impedance vector, and lower phase angle value on the R/Xc graph [62].

A direct role of obesity in kidney injury has been demonstrated. The Obesity-Related Glomerulopathy should be defined as a special form of focal-segmental glomerulosclerosis with cellular fat load and perivascular fat depot as well as so-called fatty kidney with fat depot in the perirenal and renal sinus. The clinical consequences are the higher prevalence of urinary albumin excretion, sub-nephrotic syndrome, nephrolithiasis, increased risk of developing CKD. Furthermore, obesity is frequently associated with hypertension, MS, insulin resistance, diabetes and atherogenic dyslipidemia that contribute to renal damage through mechanisms that include inflammation, oxidative

stress, renin-angiotensin-aldosterone system up-regulation, increased sympathetic activity, and endothelial dysfunction [63]. Fluid overload and protein-energy wasting are common in patients with end-stage renal disease and lead to a poor prognosis. The PhA was found to be positively associated with a geriatric nutritional risk index, lean tissue index and albumin while over-hydration/ECW showed an inverse correlation [64].

Obesity and particularly central adiposity are potent risk factors for obstructive sleep apnoea syndrome (OSAS) [65]. The severity of the diseases (measured with AH Index) was positive related with ECW% while negative correlation was demonstrated with PhA and MM%. A possible explanation is an overnight rostral fluid displacement from the legs independent of body weight with an increase of cardiovascular risk again [66].

The aging process and the progression of obesity-related disease are characterized by increased levels of inflammatory mediators such as IL-6, TNF-α, and acute phase CRP as well as increased production of reactive oxygen species (ROS) and inhibition of antioxidant enzymes. It is reported an inverse relation between PhA and inflammatory biomarkers (IL-6, TNFα, and CRP) and the significant positive relation with antioxidant enzymes and the total radical-trapping antioxidant (TRAP), regardless of age, number of diseases, and body composition in older women [67]. A possible explanation is that an increase in inflammatory biomarkers is the first response to tissue and cellular injury while low levels of oxidative stress participate in the regulation of cellular activities such as cell growth [68]. Barrea et al. [69] demonstrated, in both sexes with large range of BMI, that smaller PhA was associated with higher CRP levels, independently of age, physical activity, anthropometric measurements, and adherence to the Mediterranean diet; this indicated PhA as a marker of meta-inflammation. The PhA was assessed in patients with HIV infection in new diagnosis with unintentional weight loss or low percentage of $CD4^+$ T cell. In patients with controlled viremia but decreased in cellular integrity (nutritional decline, or CD4+% < 15%), PhA is used for monitoring intensive nutrition therapy (body protein stores). The combination antiretroviral therapy (cART) regimens, with less toxicity on metabolic parameters, registered an increase in patients with obesity. They present PhA lower than healthy, HIV-uninfected groups, higher percentage of body fat mass and lower percent lean mass but PhA is not correlated with mortality risk. It is also possible that obese individuals with HIV maintain adequate cellular mass for survival even when general cellular degradation that reflects a systemic reaction to infection, results in a declining PhA [70].

Different epidemiologic studies showed, in patients with COVID-19 infection, an association between increased BMI and the severity of the disease and mortality. On the contrary, low PhA (< 3.95°), independent of age, sex, BMI, and comorbidities, is a significant predictor of mortality risk in COVID-19 [71] and is associated with an increase in disease severity, reflected by the need for intensive care unit admission, morbidity and mortality [72]. Low PhA showing a situation of inflammation and cell injury associated with SARSCoV-2 infection, indicating a deteriorating nutritional status with higher state of hydration (ECW and hydration percentage) and decreased BCMI, associated with proinflammatory and immune response (CRP, lymphocytes, CRP/pre-albumin) [71]. In post-Covid rehabilitation, recovery of malnutrition state might be monitoring with the increasing PhA values [73].

1.3 Weight loss and phase angle changes

Weight loss is the main outcome of obesity treatment. It induces an improvement of the clinical condition with a prevention of associated obesity disease appearance and progression, a reduced risk of development of disability and reduction in mortality risk. To induce weight loss, different strategies might be performed, starting from lifestyle modifications to bariatric surgery procedures depending of the obesity grading. In the last years a close attention to the kinetics of weight loss was studied, in order to depict and reduce the risk of sarcopenia (loss of quantity and quality of muscle mass) that could be associated to the loss of body FM. Monitoring PhA change during weight loss appear as a useful marker to evaluate the risk of malnutrition or the recovery of health status (improvement of metabolic parameters and decrease of inflammation).

1.3.1 Nutritional intervention

No data are available on the effects diet-induced (hypocaloric) weight loss alone on PhA in obesity. The PhA has been previously investigated in patients with obesity after three sequential 10-day cycles of ketogenic enteral nutrition (a total of 205–270 calories/daily) with rapid weight loss (-6.4 kg). Results obtained at day 50, after the 3 treatment cycles, evidenced significant decreases in FM. This effect might be due to the reduction in lipogenesis and increased lipolysis typical of ketogenic diets. Lean mass decreased less than expected probably due to the assumption of leucine that stimulate downstream control of protein synthesis. PhA decreased in association with the greater weight loss [74]. On the contrary, Barrea et al. [75] reported that PhA increased during the active stage of VLKCD, very early and independently of weight loss amount (mean weight loss reported as -7.3 kg) and with a significant increase of Xc. We can speculate that ketogenic diet might change different

parameters: reduction in ECW, insulin-resistance on cell surface, interlukine production. These data, and the mechanisms involved, need to be better investigated in wider cohorts and in longer temporal follow-up.

1.3.2 Physical activity

Patients with obesity generally have sedentary behaviour and the body composition and the response to physical activity, cannot be comparable with general population nor athletes, since they present reduced muscle mass and/or functional deficit, "obesity sarcopenia", comparable to elderly patients. The physical activity level influences body composition and seems to be positively associated with PhA values, as found among non-institutionalized physically active elderly subjects with high phase angle values [19]. The application of different weekly resistance training frequencies performed over a 24 weeks exercise program produce a significant reduction in body weight, waist circumference, and FM% in both group but PhA increased only in the group that performed the training program at a higher weekly frequency [76]. The hypothesis suggested is an increase in reactance and a reduction in the ECW/ICW relationship due to weight loss. Ribeiro et al. [77] showed improvements in PhA following resistance training exercises carried out 3 times a week in obese women. In their study, after 8 weeks of training in obese old women, a significant increase in FFM, ICW and PhA were observed [78] as in old normal weight women [79]. This finding is probably reflected in the increase in muscle mass, a tissue that holds a large amount of ICW, resulting in better electrical conductivity and, thus, a concomitant increase in PhA. Others cellular mechanisms might be involved if we considering that exercise results in a greater reduction in CRP, IL-6, and TNF-a when accompanied by a reduction in BMI or FM% in overweight/obese individuals [80]. Furthermore, studies have shown that PhA increases after a training period or is higher in active subjects compared to less active ones, suggesting that many of the exercise-induced systemic adaptations can impact cell integrity and functionality [78, 81, 82].

1.3.3 Lifestyle modification

A comprehensive program of lifestyle modification (diet, exercise, and behaviour therapy) is considered the first option for patients with obesity and overweight. The aim of this program is a 5–10% reduction in initial body weight that is associated with clinically meaningful improvements in several CVD risk factors, including the prevention of type 2 diabetes [83]. No data were available for PhA changes after lifestyle intervention program in patients with obesity. For this reason, we evaluated the PhA changes in a group of patients with obesity (mean age 53yrs) following a lifestyle program for weight management (mean baseline BMI: 29,2 Kg/m^2) that reached a mean body weight loss − 6.3% after six months follow up (Table 1), mean PhA was 5.54° at baseline, and 5.94° after 6 months with a significant increase of Xc values (*unpublished data*).

Table 1 Changes in Body Impedance Analysis before and after 6 months of lifestyle intervention in a cohort (N = 61) of outpatients with overweight and/or obesity

	Before (T0)		After (6 Months)		
	Mean	**SD**	**Mean**	**SD**	***p-value***
BMI (Kg/m^2)	29.24	5.43	27.08	4.99	0.020
Weight (kg)	80.85	17.51	74.81	15.40	0.040
R (Ω)	482.05	70.73	487.72	71.87	ns
Xc (Ω)	46.33	7.57	50.41	8.54	0.006
PhA (°)	5.54	0.89	5.94	0.90	0.010
FM (%)	30.68	9.25	26.81	8.05	0.015
FFM (%)	69.32	9.25	73.19	8.05	0.012
ECW (%)	48.23	4.50	46.28	4.17	0.011
ICW (%)	51.77	4.50	53.72	4.17	0.010
ECW/ICW (L)	0.48	0.09	0.47	0.09	ns

BMI: body mass index; R(resistance); Xc (reactance); PhA (Phase angle); FM (fat Mass); FFM (free fat mass); ECW (extra cellular water); ICW (intra cellular water). Significant p-value < 0.05 (paired T test)

1.3.4 Intensive Rehabilitation program

The combination of nutritional intervention and physical activity in intensive rehabilitation program on PhA was not previously reported. In line with analysis reported in Sect. 4.3 we checked body impedance changes in a cohort of inpatients with obesity and different comorbidities (diabetes, dyslipidaemia, hypertension, heart failure, COPD, OSAS, hepatic steatosis, osteoarticular diseases). Patients were admitted in Clinical Rehabilitation Unit for hypocaloric diet (15% of energy deficit of resting energy expenditure) + physical activity (about 2 h/day of aerobic activity for five days/week) during a mean 28days period. We selected patients that obtained a weight loss over 5% of initial body weight (mean values 6,50%), we have a data setting of 1,081 subjects, mean age 53 ± 13.9yrs (18-50yrs 38%, 51-70yrs 51% and 70 + yrs 10%). Mean PhA was 4.34° at admission and 4.41° at discharge with a significant increase of Xc values (Table 2) (*unpublished data*).

1.3.5 Bariatric surgery

Some studies were performed to evaluated the shift on PhA after bariatric surgery. In a recent review, DiVincenzo O et al. [38] found 8 eligible papers (4 with LSG, 2 RYGB and 1 LGB) comparing values before and from 6 weeks to 2 years

Table 2 Changes in Body Impedance Analysis before and after 28 days of intensive multidisciplinary rehabilitation program in a cohort (N = 1081) of inpatients with obesity

	Before (T0)		After (28 days)		
	Mean	**SD**	**Mean**	**SD**	***p-value***
BMI (Kg/m^2)	44.28	7.25	41.43	6.76	0.0001
Weight (kg)	123.74	24.29	115.79	22.60	0.0001
R (Ω)	453.67	72.85	477.72	72.01	0.0001
Xc (Ω)	34.85	11.57	37.10	11.43	0.0001
PhA (°)	4.34	1.11	4.41	1.07	0.0119
FM (%)	46.23	7.26	46.07	7.49	ns
FFM (%)	53.77	7.26	53.93	7.49	ns
ECW (%)	42.71	3.78	42.68	3.55	ns
ICW (%)	57.29	3.78	57.32	3.55	ns
ECW/ICW (L)	0.76	0.21	0.75	0.14	ns

BMI: body mass index; R(resistance); Xc (reactance); PhA (Phase angle); FM (fat Mass); FFM (free fat mass); ECW (extra cellular water); ICW (intra cellular water). Significant p-value < 0.05 (paired T test)

after surgery and recovery [84–91]. The greatest decrease in PhA values was observed in patients with the highest loss of body weight following RYGB or LSG either after 24 months [89] or after 6 months [87, 88]. Teixeira et al. [91] reported that the decline of PhA after RYGB was negatively associated with weight loss and positively with the decrease of BMI, skeletal muscle mass, FM, and visceral fat area. The authors observed that, in six out of the eight selected papers PhA decreased by 1–20%, independently of the type of surgery (RYGB o LSG) [84–91]. To understand the mean of these changes, raw BIA variables (R and Xc) need to be considered. Unluckily, at present these data are not reported. Previous studies with tritiated or bromide water dilution analysed fluid change distribution after bariatric surgery. Mazariegos M et al. [28] reported that total body water, ECW and ICW decreased in LSG and in RYGB group but the ECW/ICW ratio remained unchanged in the LSG group, and significantly increased in the RYGB. They conclude that malassorbitive surgical procedures cause a further increase in ECW/ICW ratio, possibly through mild malnutrition not detectable by conventional serum markers of nutritional state, which implies that the ECW/ICW ratio might be an early marker of nutritional state worsening. Furthermore, Levitt et al. [92] show that ECW/ICW was significantly increased above normal before surgery (RYGB), and it increased slightly after surgery. These changes are consistent with the expected physiological changes in body composition after surgery. More recently, using impedance analysis, during 6 months of follow-up after RYGB surgery [84], a significant decrease in TBW accounting for a decrease in ICW, mismatching with a non-significant decrease of BCM and body cell mass index, was observed. In another study [87], TBW, ECW and ICW significantly decreased in patients with RYGB and LSG after 6 months but no difference was reported between two groups. In the absence of other measurements of muscle quality, there is no obvious explanation for the involving of FFM or MM; explanations suggested a worsening of nutritional status [86] and another two an increased risk of developing malnutrition [87, 88], with no comments in the others. In other groups of RYGB patients, the reduction in body weight and BMI, body fat mass, FFM as well as BCM, PhA and SM Index were significantly different for follow-up periods of 1–2 or 5years after surgery [93–95]. The reduction of BCM results in an increase of the ECM/BCM Index, indicating malnutrition. According to these results, FFM and skeletal muscle mass reduction occurs frequently after bariatric surgery and mainly during the first year after surgery with an increase risk to develop sarcopenia. In a previous study in RYGB and the LSG treated patients, there was a significant reduction of BMI, FM, FFM, PhA and CPR after 6 months in both groups, not significantly different. Only in RYGB group a decreased in advanced oxidation protein products, was registered. In the interpretation of the results it is suggested that BMI reduction in the RYGB group support a concomitant decrease of lipid oxidative damage, whereas in the LSG group, changes in BIA parameters—PhA, resistance, and reactance—suggest inverse changes in protein oxidative damage [90]. In a small study of women who underwent RYGB, PhA reduction was accompanied by a significant decrease in body weight and BMI after 3 months then PhA remained stable after 6 months.

Friedrich et al. [86] compared one-year changes in body composition following sleeve gastrectomy (LSG) and multidisciplinary weight loss program (MIP). They found a more significant reduction in PhA with LSG than with MIP after 6 months with no significant difference in weight and total water loss between the two groups. Fat mass loss at 6 months was not different in the two groups while BCM was significant higher in MIP and result in an increased also in ECM/BCM index. Cell proportion, which is defined as the percentage of cells within the BCM, is thought to indicate the individual nutritional and training status. This parameter deteriorated significantly in the LSG group, but was preserved in the MIP group within 12 months, whereas both treatments resulted in a decrease in basal metabolic rate. It is suggested that LSG is a risk for worsened nutritional status with notable evidence for protein–energy malnutrition.

Pre-operative PhA values also has prognostic value. Vassilev et al. [85] reported that high admission PhA values before bariatric surgery (127 RYGB and 46 LSG) predicted a successful weight loss reduction with surgery; furthermore, preoperative PhA values were correlated with FM reduction and preservation of FFM in early phase, 6 and 18 weeks, or in follow up, 6-9-12 months after surgery. Gerken et al. [89] similarly reported beneficial effects of increased

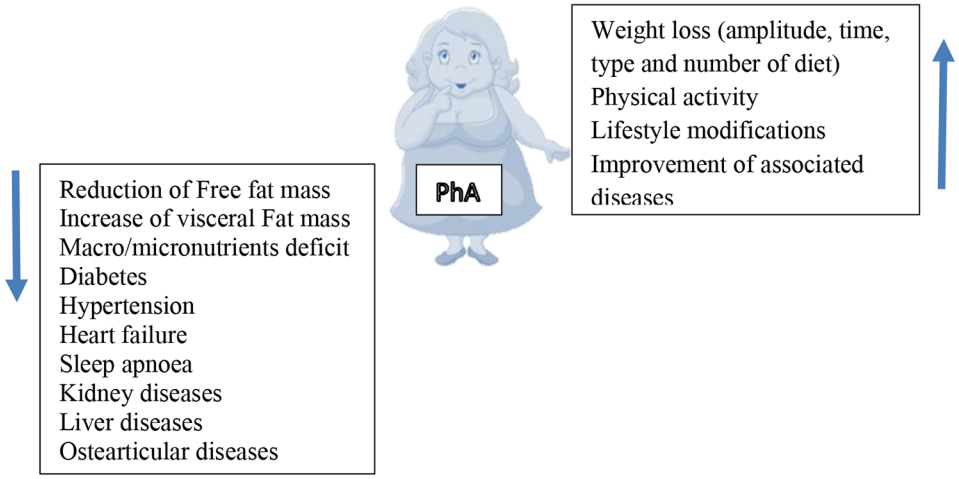

Fig. 2 Cause of change in PhA values in patients with obesity

PhA in 198 patients 24 months after LSG or RYGB interventions. Preoperative PhA had a moderate/weak relation with total weight loss after RYGB and with loss of excess weight after both LSG and RYGB.

2 Discussion

Clinical use of PhA in obesity can be an important marker to describe health status but with some observations. As a screening tool, PhA values vary widely in individual who are overweight and obese but a low PhA value is common compared to healthy gender-matched adults (Fig. 2). Disparities in body composition and hydration status contribute to this variability in PhA values. BMI is a weak moderator of PhA distribution among individuals with excess adiposity with BMI ≥ 35 kg/m^2 indicative of excessive fat accumulation and overhydration. Fat free mass, muscle mass and altered ECW/ICW are the major factors affecting PhA in these patients. It is dubious to define PhA cut-off in obesity due to the multiple factors that contribute to obesity pathophysiology that directly impacts Xc and R. Obesity is a complex metabolic disorder with a multifactorial origin. It is associated with hyperglycaemia and hyperinsulinemia, hyperlipidaemia, hyperleptinemia from adipose tissue, endothelial dysfunction also with alteration in renin–angiotensin system, mitochondrial dysfunction from muscle activity, chronic low grade of inflammation with alteration in cytokines production, vitamins and minerals deficiencies derived from unhealthy eating behaviour that contribute to an increase oxidative stress [96]. Any of these mechanisms can contribute to a pro-inflammatory state that might induce fluid disturbances, adversely affect the integrity of cell metabolism and promote loss of cells. Identification of individuals with low PhA is important for the clinical practice physician to identify individuals at increased risk of morbidity and mortality [97], to treat critical clinical condition.

Monitoring PhA changes during weight loss appear as a useful marker to evaluate the risk of malnutrition (excessive loss of FFM or protein deficit) and recovery of health status (improvement of metabolic parameters, decreased inflammation and oxidative stress). At present inconsistent findings of changes in PhA after surgical interventions for weight loss do not allow any conclusion. We need standardized protocols to well define PhA changes during weight loss and in particular after bariatric surgery.

3 Conclusion

The integrity of the cell membrane and the abundance of lean mass coincide with health and their recovery and conservation constitute the highest goal in all therapies, especially in obesity. The data here reported demonstrate that the PhA is a good indicator of health, because it measures the integrity of the cells and, therefore, their functionality. In general, high PhA values indicate a good healthy state, while low values should be investigated, in relation to the clinical history of the patient. In pathological subjects, the PhA tends to have low values and is actually used as an indicator of poor nutritional status, prognosis and increased mortality risk. Phase angle values are influenced by age, gender, height, ethnicity and BMI. The data in the literature highlight the possibility of using the PhA as new cellular health markers during weight loss phases. Furthermore, the PhA could be used as a prognostic marker for clinical conditions associated with obesity (such as fluid overload as in HF, worsening of diabetes and its complications, inflammatory state etc.) and to monitor some diagnoses linked to inflammatory, metabolic or endocrine alterations. It is essential to increase research on PhA to develop new therapeutic strategies for obesity and obesity complication treatment in the near future. For instance, when studying body composition it is now crucial to well define the population used (from

overweight to obesity and morbid obesity, and taking into account age and sex, inflammation degree and therapies), monitoring and reporting the PhA values and its variations with weight loss, to well define the effects of new pharmacological treatments (such as GLP-1 agonists), lifestyle and physical activity program (aerobic exercise combined with short bouts of resistance training), nutritional intervention and bariatric surgery procedures on body composition. The focus on PhA and body composition is of utmost importance also for the establishment of weight maintenance protocols after weight loss.

Abbreviations

6MWT	Six minutes walking test
BCM	Body cell mass
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BNP	B-type natriuretic peptide
cART	Combination antiretroviral therapy
COVID-19	Corona Virus Disease-2019
CAT	Catalase
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CVD	Cardiovascular diseases
DXA	Dual energy X-ray absorptiometry
ECW	Extracellular water
eGFR	Glomerular filtration rate
FM	Fat mass
FFM	Free fat mass
HF	Heart failure
HG	Hand grip
HOMA-IR	Homeostatic model assessment of insulin resistance
ICW	Intracellular water
IL-6	Interleukin-6
LSG	Laparoscopic sleeve gastrectomy
LGB	Laparoscopic gastric banding
MAFLD	Metabolic-associated fatty liver disease
METs	Metabolic equivalent of task
MS	Metabolic syndrome
MIP	Multidisciplinary weight loss program
MHO	Metabolic health obesity
MUO	Metabolic unhealth obesity
NASH	Non-alcoholic steatohepatitis
OSAS	Obstructive sleep apnea syndrome
PCOS	Polycystic ovary syndrome
PhA	Phase angle
R	Resistance
RYGB	Roux-en-Y gastric bypass
ROS	Reactive oxygen species
SMI	Skeletal mass index
SMM	Skeletal muscle mass
TBW	Total body water
TNF	α, Tumor necrosis factor-α
TRAP	Total radical-trapping antioxidant
TWL	Total weight loss
VLKCD	Very low caloric diet
VO_2	Oxygen consumption
WHO	World Health Organization
Xc	Reactance

Declarations

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Conflict of interest All the authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported.

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