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Original article

Bioimpedance phase angle is associated with serum transthyretin but not with prognostic inflammatory and nutritional index during follow-up of women submitted to bariatric surgery

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SUMMARY

Background & aims: Phase angle (PhA) has been used as a prognostic indicator in several clinical situations. However, the use of PhA as a prognostic tool in bariatric patients is less known. The aim of this study was to evaluate PhA as a prognostic index and its correlation with the prognostic inflammatory and nutritional index (PINI) during follow-up of women subjected to bariatric surgery.
Methods: Twenty female volunteers were studied. Body weight, body mass index (BMI), PhA, and biochemical components of PINI [serum C-reactive protein, alpha-1-acid glycoprotein, albumin, and transthyretin (TTR) concentrations] were evaluated at three time points: before (T0) and approximately 2–3 (T1) and 6 (T2) months after surgery. One-way repeated measures ANOVA or the Friedman test with Tukey's *post hoc* test was used depending on data normality. The associations between PhA and the other parameters were evaluated using Spearman's (nonparametric data) or Pearson's (parametric data) correlation coefficient.
Results: Phase angle reduction was accompanied by a significant decrease in body weight and BMI at T1 ($P < 0.05$), but not at T2 ($P > 0.05$). PINI indicated low-risk complications during the preoperative period and no risk during the postoperative period (T1 and T2). No significant correlation was observed between PhA and PINI ($P > 0.05$). Regarding its association with the biochemical components of PINI, lower PhA values were significantly correlated with lower serum TTR concentrations ($r = 0.633$, $P < 0.001$).
Conclusions: Phase angle was not associated with PINI, although lower values were correlated with lower serum TTR, suggesting that PhA reduction is associated with an increased nutritional risk.

1. Introduction

Bioelectrical impedance analysis (BIA) is an indirect method for the estimation of body composition through the measurement of two bioelectrical parameters: body resistance and reactance. Resistance is the opposition of the body to the flow of an alternating electrical current, while reactance refers to the capacitance properties of the cell membrane [1]. Since body composition assessment

Abbreviations: PhA, phase angle; BIA, bioelectrical impedance analysis; BS, bariatric surgery; CRP, C-reactive protein; AGP, alpha-1-acid glycoprotein; TTR, transthyretin; PINI, Prognostic Inflammatory and Nutritional Index; RYGB, Roux-en-Y gastric bypass.

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is limited in several clinical conditions, the use of raw data from BIA has gained increasing attention. The phase angle (PhA) is a BIA-derived parameter that is calculated directly from reactance and resistance [2]. This parameter primarily reflects changes in cellular membrane integrity and alterations in fluid balance [3] and can be considered a suitable indicator of health status [4]. The PhA has been used as a prognostic indicator in various clinical situations such as malnutrition, cancer, and HIV infection [5] to predict clinical outcomes, including survival and mortality [5,6]. However, the use of PhA as a prognostic index and health status indicator in the follow-up of bariatric patients is less known [7].

Many biochemical parameters have also been used to predict the prognosis of patients in several clinical conditions. Whereas the prognostic value of each individual parameter is questionable, their combination may increase the prognostic power [8–10]. The prognostic inflammatory and nutritional index (PINI) combines two inflammatory (C-reactive protein - CRP and alpha-1-acid glycoprotein - AGP) and two nutritional markers (serum albumin and transthyretin - TTR). This index was originally proposed to classify the risk of complications or death in critically ill patients [11], and has been applied to identifying patients at risk in the perioperative period [9]. In addition, the CRP/albumin ratio has been reported as an independent prognostic marker in patients with severe sepsis [12] and different types of cancer [13,14], and is correlated with inflammation severity and mortality [15,16]. The usefulness of these prognostic indices in bariatric patients has not yet been assessed. In addition, it is unknown whether PhA is correlated with PINI in bariatric patients. Our hypothesis is that lower PhA values are associated with a higher prognostic inflammatory and nutritional risk in bariatric patients. Therefore, the aim of the present study was to evaluate PhA as a prognostic index and the correlation with PINI and its components during follow-up of women subjected to bariatric surgery (BS).

2. Materials and methods

2.1. Study design and subjects

A prospective study was conducted on female volunteers enrolled in the Bariatric and Metabolic Surgery Program of the University Hospital of the Federal University of Espírito Santo, Brazil. Twenty-six women (>18 years), who met the criteria for RYGB of the Program, agreed to participate in the study. However, only 20 volunteers completed the three data collections established in the study and composed the final sample.

The subjects were evaluated at three time points: before surgery (T0) and about 2–3 (T1) and 6 (T2) months after surgery. Between April 2016 and August 2017, data of the subjects (blood sample, anthropometric variables, and BIA measurements) were collected at each time point during the standard clinical follow-up consultations at the university hospital. The study was approved by the Ethics Committee on Research Involving Humans of the University Hospital, and all procedures were performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All subjects signed a consent form.

2.2. Anthropometric and PhA measurements

Body weight was measured on a platform scale to the nearest 0.05 kg, with the subject barefoot and wearing light clothing. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. The BMI was calculated as body weight in kilograms divided by height in meters squared. BIA was performed at a single frequency of 50 kHz with a Biodynamics 450® analyzer (Biodynamics Co., Shoreline, WA, USA). The measurements were made according to recommendations for the clinical application of BIA reported in the European Society of Clinical Nutrition and Metabolism guidelines [17].

2.3. Blood samples and biochemical parameters

The blood samples were collected at the Clinical Analyses Laboratory of the University Hospital between 7 and 10 am after 10–12 h of fasting. Venous blood (5 mL) was drawn into tubes containing gel and clot activator. Serum was separated within 1 h by centrifugation at 3500 rpm for 5 min. Serum ultrasensitive CRP, AGP, albumin, and TTR concentrations were measured by trained technicians. CRP, AGP, and TTR were analyzed by an immunoturbidimetric method and albumin by a colorimetric method in a Wiener Lab CMD 800i® chemistry analyzer using commercial kits (Wiener Lab, Santa Fé, Argentina). The reference ranges of the biochemical parameters provided by the Laboratory were: CRP (<5 mg/L), AGP (500–1200 mg/L), albumin (34–50 g/L), and TTR (200–400 mg/L). PINI was calculated according to Ingenbleek and Carpentier [11]: PINI = CRP (mg/L) × AGP (mg/L)/albumin (g/L) × TTR (mg/L). The results were stratified as follows: <1, no risk of complications; 1–10, low risk; 11–20, medium risk; 21–30, high risk; >30, life risk. The CRP/albumin ratio was calculated based on their serum levels.

2.4. Statistical analyses

The normality and homogeneity of variances of all variables were tested by the Shapiro–Wilk test and Levene test, respectively ($P > 0.05$). Depending on data normality, one-way repeated measures ANOVA (parametric data) or Friedman test (nonparametric data) followed by Tukey's *post hoc* test were applied. The associations of PhA with the prognostic indices and biochemical parameters were evaluated using Spearman's (nonparametric data) or Pearson's (parametric data) correlation coefficient. The strength of the association was classified as null for $r < 0.25$, weak for $0.25 \leq r < 0.5$, moderate for $0.5 \leq r < 0.75$, or strong for $r \geq 0.75$ [18]. The results are reported as mean ± standard deviation (SD) for parametric variables or as median (interquartile range) for nonparametric variables. The Statistical Package for the Social Sciences 21.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. A P-value <0.05 was considered statistically significant.

3. Results

The participants had a mean age of 40.2 ± 7.7 y and a mean height of 1.59 ± 0.07 m before surgery. The women were evaluated on average (mean ± SD) at 24.0 ± 20.5 d (T0), 72.0 ± 19.5 d (T1), and 189.0 ± 12.2 d (T2).

The results of the anthropometric and PhA measurements at each time point are shown in Table 1. Body weight, BMI, and PhA decreased significantly over time ($P < 0.001$). The reduction in PhA was accompanied by a decrease in body weight and BMI at T1 ($P < 0.05$), but not at T2 ($P > 0.05$). PhA values at T1 and T2 were significantly lower than at T0 ($P < 0.05$). However, body weight and BMI were significantly lower at T2 compared to T1 ($P < 0.05$).

The biochemical parameters and prognostic inflammatory and nutritional indices are described in Table 2. Serum concentrations of TTR, CRP and AGP decreased significantly over time, with lower values at T1 and T2 compared to T0 ($P < 0.05$). Serum TTR concentrations below the reference values were observed in 15% ($n = 3$) of the subjects at T0, in 75% ($n = 15$) at T1, and in 70% ($n = 14$) at T2. Albumin concentrations did not change significantly over time ($P > 0.05$). The PINI risk classification indicated a low risk of complications at T0 and no risk at T1 or T2. PINI values between 1

Table 1
Pre- and postoperative body weight, body mass index (BMI) and phase angle (PhA) of women submitted to bariatric surgery.

Variable	T0	T1	T2
Body weight (kg)	106.5[a] (96.2–120.2)	87.9[b] (80.7–100.5)	77.7[c] (69.7–84.7)
BMI (kg/m^2)	42.9[a] (39.1–46.5)	35.2[b] (32.6–39.9)	30.8[c] (28.7–33.8)
PhA (°)	7.1[a] (6.6–7.6)	5.7[b] (5.3–6.3)	5.9[b] (5.3–6.4)

Values are the median (interquartile range) (n = 20). Data were analyzed by the Friedman test followed by Tukey's *post hoc* test. Median values in the same row followed by different letters differ significantly (P < 0.05). T0: 24.0 ± 20.5 d before surgery; T1: 72.0 ± 19.5 d after surgery; T2: 189.0 ± 12.2 d after surgery.

Table 2
Pre- and postoperative serum transthyretin (TTR), albumin, C-reactive protein (CRP) and alpha-1-acid glycoprotein (AGP), prognostic inflammatory nutritional index (PINI), and CRP/albumin ratio of women submitted to bariatric surgery.

Variable	Reference values	T0	T1	T2
TTR (mg/L)*	200–400	246.55 ± 43.63[a]	177.60 ± 30.15[b]	178.80 ± 41.67[b]
Albumin (g/L)*	34–50	40.88 ± 2.30[a]	40.94 ± 1.68[a]	41.40 ± 2.03[a]
CRP (mg/L)**	<5	12.00[a] (2.32–20.52)	4.50[b] (1.45–8.20)	2.45[b] (0.85–4.80)
AGP (mg/L)**	500–1200	961.00[a] (753.00–1087.00)	808.00[b] (651.50–913.50)	702.00[b] (644.00–854.50)
PINI**	–	1.01[a] (0.17–2.42)	0.51[a] (0.15–0.99)	0.26[b] (0.08–0.54)
CRP/albumin ratio**	–	0.28[a] (0.06–0.49)	0.11[a] (0.04–0.20)	0.06[b] (0.02–0.12)

Mean or median values in the same row followed by different letters differ significantly (P < 0.05) (n = 20). T0: 24.0 ± 20.5 d before surgery; T1: 72.0 ± 19.5 d after surgery; T2: 189.0 ± 12.2 d after surgery.
* Values are the mean ± SD. One-way repeated measures ANOVA followed by Tukey's *post hoc* test.
** Values are the median (interquartile range). Friedman test followed by Tukey's *post hoc* test.

and 10 (low risk) were found in 45% of the subjects at T0, but in only 25% at T1 and in 10% at T2. There was a significant reduction in the CRP/albumin ratio, with lower values at T2 compared to T0 and T1 (P < 0.05).

Considering all values of PhA, PINI, CRP/albumin ratio, and biochemical parameters at the three time points (n = 60), there was no important and significant correlation of PhA with PINI (r = 0.067; P = 0.618) or CRP/albumin ratio (r = 0.153; P = 0.241), nor with the inflammatory biomarkers CRP (r = 0.168; P = 0.203) and AGP (r = 0.153; P = 0.251). Regarding nutritional markers, PhA was not significantly associated with serum albumin (r = 0.236; P = 0.069), but a significant positive correlation was observed with serum TTR (r = 0.633, P < 0.001) (Fig. 1).

4. Discussion

In this study, body weight, BMI and PhA were lower during the postoperative period than during the preoperative period. PINI indicated either a low risk of complications before BS and the absence of risk during the first 6 months after surgery, or a period of rapid weight loss [19,20]. No significant correlation was found between PhA and PINI or CRP/albumin ratio, although PhA values were significantly correlated with serum TTR concentrations.

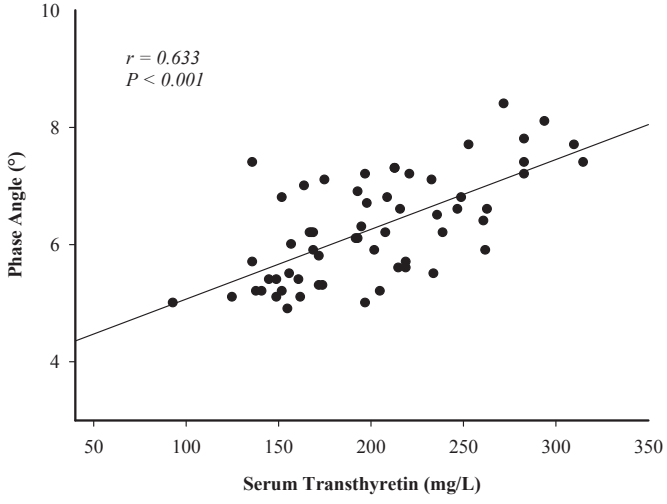

Fig. 1. Correlation between phase angle and serum transthyretin in the pre- and postoperative period of women submitted to bariatric surgery.

The lower PhA values observed after BS might suggest an interpretation different from that indicated by PINI and CRP/albumin, explaining in part the lack of a significant association between PhA and prognostic indices. To support our hypothesis, lower PhA values should be associated with higher PINI values and CRP/albumin ratios. Although women subjected to RYGB had lower PhA values after BS, PINI indicated no risk of complications. Moreover, the CRP/albumin ratio was also reduced after BS.

PINI indicated a low prognostic risk for obese women before surgery that did not persist after BS (no risk at T1 or T2). Obesity is related to chronic low-grade inflammation [21,22] that increases the synthesis of positive acute-phase proteins [23]. Here, higher concentrations of CRP were also found before BS, albeit not enough to produce higher PINI values, as observed in other clinical conditions [11,24]. In fact, PINI was initially developed to evaluate critically ill patients in whom serum CRP levels are about ten times higher than the reference values [11]. PINI has been described as a reliable prognostic indicator in different clinical conditions, such as burn, renal and cancer patients [24,25]. The results of this study suggest that the reduction in the inflammatory state was crucial to improve PINI at T1 and T2, since serum albumin concentrations did not differ and there was even a decrease in TTR levels at these time points. Similarly, the results also showed that the decrease in the CRP/albumin ratio, which is a simplified indicator of PINI [16], occurred at the expense of CRP level reduction.

Although PhA did not correlate significantly with PINI or CRP/albumin ratio, a moderate and significant correlation was observed between PhA values and serum TTR concentrations. Many biochemical markers have been used for nutritional purposes. Although none of them is entirely reliable [26,27], TTR seems to be the most useful one, not as a tool to diagnose malnutrition, but to identify patients at risk of developing malnutrition [26,28], especially when an inflammatory state is absent (CRP <15 mg/dL) [26]. Proinflammatory cytokines may induce the liver to prioritize the synthesis of positive acute-phase proteins, mainly CRP, over TTR

synthesis [26]. In this study, both serum CRP and AGP were significantly reduced to reference levels after BS, suggesting that liver priority in favor of CRP and AGP synthesis at the expense of TTR did not occur. Hence, it seems that TTR synthesis was affected by nutritional causes. In fact, TTR itself can reflect alterations in the amount of visceral protein and lean body mass [29,30] resulting from acute low calorie-protein intake, and has been used to predict poor short-term outcome, severity of diseases and even mortality [31,32]. In this study, the women showed loss of lean body mass and a low protein intake at T1 and T2 (data not shown). Mushnick et al. [33] observed a similar correlation between PhA and serum TTR concentrations in peritoneal dialysis patients and concluded that PhA is an independent predictor of survival in these patients. Here, the lower PhA values after BS were also correlated with serum TTR levels below reference values, suggesting that the reduction in PhA after BS might be associated with the risk of developing malnutrition, and could reflect a reduction in visceral protein and lean body mass.

Nevertheless, the effectiveness of BS, especially RYGB, for the treatment of severe obesity has been well established [34,35]. After surgery, the majority of body weight loss occurs during the first 6 months, the period of rapid weight loss [19,20]. In this study, as expected, women subjected to RYGB also exhibited a significant reduction in body weight and consequently in BMI (27%), a known morbidity and mortality indicator [36]. This significant body weight loss was not accompanied by a significant reduction in PhA at T2 compared to T1. Thus, differences in PhA over time cannot be explained only by differences in body mass. One possible explanation are differences in hydration and fluids in the extracellular compartments of obese individuals, which could increase the extracellular:intracellular water ratio [37]. The body weight loss observed after BS may alter this ratio and contribute at least in part to the stabilization of PhA values at T2. In addition, other factors such as nutrient intake and exercise alter cell function [38,39] and could also affect PhA values at the time points studied.

BIA measurements could be advantageous compared to biochemical analysis, since aside from estimating body compartments (lean body mass and fat mass), PhA is a noninvasive, low-cost and easily obtainable BIA parameter that could assist in indicating the right nutritional strategy for bariatric patients. The main limitations of this study are the sample size ($n = 20$) which may have affected the statistical power, the difficulty in carrying out all data collection procedures near the expected moments, and a possible excessive reduction in calorie-protein intake by the subjects close to the clinical follow-up consultations (days), which could affect serum TTR levels.

In conclusion, the results of the present study showed that PhA was not associated with PINI or CRP/albumin ratio, but lower PhA values were correlated with lower serum TTR concentrations. These findings suggest that lower PhA values are associated with a risk of developing malnutrition in women during follow-up after BS.

Statement of authorship

Koehler KB: conception and design of study; acquisition of data; analysis and interpretation of data; drafting the manuscript; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published; **Moraes RAG:** conception and design of study; acquisition of data; analysis and interpretation of data; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published; **Rodrigues JB:** acquisition of data; analysis and interpretation of data; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published; **Portela BSM:** acquisition of data; analysis and interpretation of data; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published; **Miguel GPS:** conception and design of study; acquisition of data; analysis and interpretation of data; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published; **Pedrosa RG:** conception and design of study; analysis and interpretation of data; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published; **Haraguchi FK:** conception and design of study; analysis and interpretation of data; drafting the manuscript; revising the manuscript critically for important intellectual content; approval of the version of the manuscript to be published;

Conflict of interest statement

The authors declare no conflict of interest.

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