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Association between phase angle and blood biomarkers in community-dwelling older adults: The role of BDNF and oxidative stress

Walter SEPÚLVEDA-LOYOLA[1], Yshoner Antonio SILVA-DIAZ[2,3], Cintya Elisabeth ODAR-ROJAS[2,3], Ruth Clarivel VEGA-ROJAS[2,3], Andressa KEIKO MATSUMOTO[4], Denilson TEIXEIRA[5], Vanessa SUZIANE PROBST[5]

1 Faculty of Health and Social Sciences, Universidad de Las Americas, Santiago.
2 Instituto de Salud Integral Intercultural (ISI), Facultad de Ciencias de la Salud (FACISA), Universidad Nacional Toribio Rodríguez de Mendoza (UNTRM).
3 Centro De Investigación Plantas Medicinales, Terapias Alternativas Y Comunidades Nativas Y Rurales (CIPMAYCOM).
4 Department of Pharmaceutical Sciences, State University of Londrina (UEL), Londrina, Paraná, Brazil.
5 Center for Research and Postgraduate Studies in Health (CEPPOS), Center for Health Sciences (CCS), State University of Londrina (UEL), Londrina, Paraná, Brazil.

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ABSTRACT

Introduction: The association among important blood biomarkers with Phase angle (PhA) has not yet been specifically explored.

Objective: To analyze the association between PhA and blood biomarkers, including BDNF, oxidative stress, metabolism, and vitamins, in community-dwelling older adults.

Methods: The study was cross-sectional, involving 169 older adults from the community (Londrina-Brazil). The PhA was measured using bioimpedance with a single frequency. The following blood biomarkers from peripheral blood test were analyzed in all individuals after 10 hours of overnight fasting: Brain-derived neurotrophic factor (BDNF), Nitric Oxide (NO); Advanced Oxidation Protein Products (AOPP), Ferrous Oxidation in Xylenol orange (FOX); Glutathione Transferase (GSH); Total Plasma Antioxidant Potential (TRAP); Total Plasma Sulfhydryl (SH); Catalase (CAT); Superoxide Dismutase (SOD), Vitamin D and Vitamin B12. A linear regression model was developed to analyze the association between blood biomarkers and PhA, verifying values such as BDNF and FOX through assumption checks, considering Model 1 (unadjusted analysis) and Model 2 (adjusted for age and sex). Statistical significance was considered at $p < 0.05$.

Results: 169 older adults were included (age= 70.17 ± 7.14 years; woman= 81%, PhA =5.33 ± 1.46 degree; BDNF= 1576.35 ± 812.75 pg/mL and FOX=0.71 ± 0.35 µ/L). Significant associations were observed between PhA and both BDNF ($\beta=3.43x10^{-4}$, $p=0.04$) and FOX ($\beta = -8.01x10^{-1}$, $p=0.03$) in Model 1 ($R^2=0.15$). After adjustment for age and sex in Model 2 ($R^2 = 0.16$), the associations remained significant for BDNF ($\beta=3.51x10^{-4}$, $p =0.04$) and FOX ($\beta= 7.60x10^{-1}$, $p=0.04$). No significant associations were found between PhA and the other blood biomarkers.

Conclusions: BDNF and FOX are the main blood biomarkers associated with PhA in community-dwelling older adults.

KEYWORDS

Healthy Aging, Body Composition, Sarcopenia, Aged, Vitamin D.

INTRODUCCION

Phase angle (PhA) is a physiological indicator of body composition derived from the values of resistance and reactance of bioelectrical impedance[1]. PhA also reflects the integrity of cell membranes and the proportion of reactive body tissue relative to body fluids and it has been associated with sarcopenia, nutritional status, disability, and risk of mortality in older adults[2]. Several biological biomarkers, including oxida-

Correspondencia:
Walter Sepúlveda-Loyola
wsepulveda@udla.cl

tive stress markers, metabolic biomarkers, and vitamin levels may influence PhA in this population[3,4]. Understanding the modulation of PhA by these biomarkers could provide new insights into the biological mechanisms underlying aging and help prevent age-related complications, reinforcing its relevance in clinical practice[5].

Different blood biomarkers play a crucial role in muscle protein synthesis and tissue regeneration[6]. A notable example is brain-derived neurotrophic factor (BDNF), which promotes muscle fiber regeneration, by modulating reactive oxygen species (ROS), an increase in ROS causes an imbalance between skeletal muscle protein synthesis and degradation, leading to muscle atrophy[7]. Additionally, markers related to oxidative stress, such as nitric oxide (NO)[7] and glutathione (GSH), play a role in vasodilation, promoting blood flow to muscle tissues[8]. On the other hand, vitamins B and D stand out due to their involvement in musculoskeletal stimulation and the conversion of amino acids into neurotransmitters, this significantly improves muscle strength and quality[9].

Scientific evidence suggests that PhA is positively associated with level of antioxidants blood biomarkers[10] and vitamin D[4]. However, although previous research has analyzed the relationship between some blood biomarkers and body composition parameters, such as body mass index (BMI)[11] and body fat, the association between BDNF and other blood biomarkers with PhA has not yet been specifically explored. Therefore, the aim of this study was to analyze the association between PhA and blood biomarkers, including BDNF, oxidative stress, metabolism, and vitamins, in community-dwelling older adults.

MATERIALS AND METHODS

Study design

The present study is a cross-sectional analysis from the study registered on the Brazilian Registry of Clinical Trials platform (RBR-2HJJ7G/UTN: U1111-1254-3147). The study included a non-probabilistic sample of 169 older adults recruited via social media, social networks and community healthcare centers from Londrina, Brazil. The study was approved by the ethics committee from the State University of Londrina (Approval Number 2.788.802). Participation in the study was voluntary and all participants provided written informed consent. The study also followed the principles of the Declaration of Helsinki.

Participants

The inclusion criteria were: (1) woman aged 60 years or more; (2) physically independent (capable of performing basic and instrumental activities of daily living without assistance); (3) had not participated in regular physical exercise programs during the last three months. The exclusion criteria comprised diseases and/or conditions that could interfere in the performance of the tests, such as neurological, vestibular, orthopedic, psychiatric, and decompensated respiratory or cardiac diseases.

Procedures

The following variables were measured: phase angle (PhA), brain-derived neurotrophic factor (BDNF), oxidative stress biomarkers, metabolic biomarkers, and vitamin biomarkers.

Phase Angle

The PhA was measured using bioelectrical impedance (Biodynamics 310TM, Biodynamics Corp. USA) after 10 hours of fasting, in the morning. Patients were asked to urinate before the test. The values and percentages of fat mass and lean body mass were obtained directly from the device.

Blood Biomarkers

Peripheral blood tests were performed in all individuals after 10 hours of overnight fasting. Approximately 40 mL of blood sample were obtained by venipuncture into vacuum tubes (Vacutainer®, Franklin Lakes, NJ USA). Collections were carried out in the morning after an eight-hour fast and volunteers were asked not to exercise on the previous day. Blood samples were centrifuged at 3000 rpm for 10 min and the extracted plasma was stored at -80°C until use[12,13].

Blood biomarkers were measured following previous studies[12,13]. The BDNF levels were determined using a multiplex immunofluorimetric assay with microspheres (ProcartaPlex™ Multiplex Immunoassay, Thermo Fisher Scientific, Waltham, MA, USA) for the Luminex platform (MAGPIX™, Luminex Corp., Austin, TX, USA), and the procedures were performed according to the manufacturer's instructions. Nitric Oxide (NO) was quantified using a microplate reader (EnSpire, Perkin Elmer®, USA) at a wavelength of 540 nm, allowing the concentration of nitrite and nitrate to be obtained (reference values ranging from 5.9 to 8.5 µmol/L). The Advanced Oxidation Protein Products (AOPP) values were determined using the microplate reader at 340 nm (cutoff value of 89 mmol/L)[14]. The Ferrous Oxidation in Xylenol orange (FOX) was used through lipid extraction method to quantify lipid hydroperoxides (normal range between 0.22 and 7.8 µM). Glutathione Transferase (GSH) levels were measured on the same microplate reader at 412 nm, with results expressed in µM. Total Plasma Antioxidant Potential (TRAP) was evaluated on a microplate reader (Victor X-3, Perkin Elmer, USA) and results were presented in mM Trolox[15]. Sulfhydryl groups (SH) were evaluated in a microplate reader (EnSpire, Perkin Elmer, USA) at a wavelength of 412 nm and results were expressed in µmol/L. Catalase (CAT) parameters were measured in microplates (EnSpire, Perkin Elmer®, USA) at a wavelength of 240 nm (normal ranges between 64,700 and 169,300 U/min/gHb). Superoxide Dismutas (SOD) in erythrocytes was analysed through a method based on the inhi-

bition that this enzyme promotes in the auto-oxidation of pyrogallol in aqueous solution. The SOD reaction was read on a microplate reader (EnSpire, Perkin Elmer, USA) with a wavelength of 420 nm and the results were expressed in U/mL. Finally, Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), vitamin D, and vitamin B12 were analyzed according to conventional procedures previously documented in prior protocols[12,13].

Statistical Analysis

Continuous variables were presented as the mean and standard deviation (SD) and categorical variables are presented as the number and percentage. The parametric distribution of the continuous variables was checked using the Kolmogorov Smirnov test. A linear regression model was performed to analyze the association between Blood biomarkers and PhA, considering Model 1 (unadjusted analysis) and Model 2 (adjusted for age and sex). The adjustment variables (sex and age) were selected due to their recognized influence on blood biomarkers. Collinearity diagnostics were performed by calculating the Variance Inflation Factor (VIF), and no multicollinearity was detected (VIF < 2.0 for all variables). The model fit was evaluated using the coefficient of determination (R^2), and the assumptions of linear regression were verified through standardized residual plots, analysis of homoscedasticity, and normality of residuals. In addition, the independence of residuals was confirmed by the Durbin–Watson statistic. Statistical significance was assessed with a p-value < 0.05. No corrections for multiple comparisons were applied to avoid increasing type II error (false negative), which allowed for the identification of potentially relevant associations. Statistical analyses were performed using the software IBM SPSS 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of 169 older adults were presented in Table 1. The average age is 70.17 ± 7.14 years, and 81% (n=137) of individuals were women. Regarding body composition, the PhA was 5.33 ± 1.46 degrees. The average BDNF value is 1576.35 ± 812.75 pg/mL. The oxidative stress biomarkers evaluated were: NO (7.18 ± 4.89 5.9 µmol/L), AOPP (101.11 ± 85.83 mmol/L), FOX (0.71 ± 0.35 µM), GSH (5.20 ± 0.66 µmol/L), TRAP (897.38 ± 152.83 µmol TE/L), SH (219.04 ± 50.88 µmol/L), CAT (71.31 ± 18.53 U/mL), and SOD (68.10 ± 19.77 U/mL). Additionally, metabolic biomarkers such as glucose (108.07 ± 20.47 mg/dL), LDL (125.51 ± 42.89 mg/dL), HDL (53.31 ± 16.81 mg/dL), and triglycerides (133.44 ± 81.09 mg/dL) were analyzed. Finally, the vitamin biomarkers were evaluated, yielding the following results: vitamin D (21.77 ± 29.38 µg) and vitamin B12 (489.66 ± 1251.57 µg).

The linear regression analysis between blood biomarkers and PhA was reported in Table 2. BDNF showed a significant association with PhA in unadjusted analysis model (β coefficient of $3.43x10^{-04}$;p-value = 0.04) and in adjusted model for age and sex (β = $3.51x10^{-04}$, p=0.04). Additionally, the FOX biomarker also showed a significant association in both mod-

Table 1. Demographic Data and Blood Biomarker Values of Older Adults in the Community

Variables	**Total (N= 169)**
Age (years)	70.17 ± 7.14
Female, n (%)	137 (81.07%)
Body composition	
PhA (degree)	5.33 ± 1.46
Neurotrophic factors	
BDNF (pg/mL)	1576.35 ± 812.75
Oxidative stress biomarkers	
NO (µmol/L)	7.18 ± 4.89
AOPP (mmol/L)	101.11 ± 85.83
FOX (µM)	0.71 ± 0.35
GSH (µmol/L):	5.20 ± 0.66
TRAP (µmol TE/L)	897.38 ± 152,83
SH (µmol/L)	219.04 ± 50.88
CAT (U/min/gHb)	71.31 ± 18.53
SOD (U/mL)	68.10 ± 19.77
Metabolic biomarkers	
Glucose (mg/dL)	108.07 ± 20.47
LDL (mg/dL)	125.51 ± 42.89
HDL (mg/dL)	53.31 ± 16.81
Triglycerides (mg/dL)	133.44 ± 81.09
Vitamin biomarkers	
Vitamin D (µg)	21.77 ± 29.38
Vitamin B12 (µg)	489.66 ± 1251.57

Data are expressed as mean § standard deviation; BDNF: Brain-Derived Neurotrophic Factor; PhA: Phase angle; NO: Nitric Oxide; AOPP: Advanced Oxidation Protein Products; FOX: Ferrous Oxidation in Xylenol orange; GSH: Glutathione Transferase; TRAP: Total Plasma Antioxidant Potential; SH: Total Plasma Sulfhydryl; CAT: Catalase; SOD: Superoxide Dismutase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein.

Table 2. Associations Between Blood Biomarkers and Phase Angle in Older Adults: Unadjusted and Adjusted Models

Blood Biomakers	Model 1		Molde 2	
	β (IC 95%)	p-value	β (IC 95%)	p-value
BDNF	$3.43x10^{-04}$ ($1.54x10^{-05}$ - $6.71x10^{-04}$)	0.04*	$3.51x10^{-04}$ ($1.67x10^{-05}$ - $6.84x10^{-04}$)	0.04*
NO	$8.11x10^{-03}$($-3.87x10^{-02}$ - $5.49x10^{-02}$)	0.73	$8.61x10^{-03}$ ($-3.93x10^{-02}$ - $5.65x10^{-02}$)	0.72
AOPP	$1.49x10^{-04}$($-4.49x10^{-03}$ - $4.79x10^{-03}$)	0.95	$6.21x10^{-05}$ ($-4.76x10^{-03}$ - $4.88x10^{-03}$)	0.98
FOX	$-8.01x10^{-01}$($-1.51x10^{0}$ - $8.85x10^{-02}$)	0.03*	$-7.60x10^{-01}$ ($-1.50x10^{0}$ - $-2.56x10^{-02}$)	0.04*
GSH	$9.67x10^{-02}$($-2.72x10^{-01}$ - $4.65x10^{-01}$)	0.61	$8.96x10^{-02}$ ($-2.88x10^{-01}$ - $4.67x10^{-01}$)	0.64
TRAP	$1.12x10^{-03}$ ($-4.66x10^{-04}$ - $2.71x10^{-03}$)	0.17	$1.09x10^{-03}$ ($-5.48x10^{-04}$ - $2.72x10^{-03}$)	0.19
SH	$4.54x10^{-03}$ ($-9.82x10^{-05}$ - $9.19x10^{-03}$)	0.06	$4.35x10^{-03}$ ($-3.75x10^{-04}$ - 9.08 $x10^{-03}$)	0.07
CAT	$-9.01x10^{-03}$ ($-2.21x10^{-02}$ - $4.13x10^{-03}$)	0.18	$-9.23x10^{-03}$ ($-2.27x10^{-02}$ - $4.21x10^{-03}$)	0.18
SOD	$5.20x10^{-03}$ ($-6.45x10^{-03}$ - $1.68x10^{-02}$)	0.38	$6.73x10^{-03}$ ($-5.41x10^{-03}$ - $1.89x10^{-02}$)	0.28
Glucose	$-5.38x10^{-03}$ ($-1.71x10^{-02}$ - $6.38x10^{-03}$)	0.37	$-5.34x10^{-03}$ ($-1.73x10^{-02}$ - $6.63x10^{-03}$)	0.38
LDL	$3.60x10^{-03}$ ($-1.97x10^{-03}$ - $9.17x10^{-03}$)	0.20	$3.20x10^{-03}$ ($-2.64x10^{-03}$ - $9.05x10^{-03}$)	0.28
HDL	$-7.09x10^{-03}$ ($-2.23x10^{-02}$ - $8.10x10^{-03}$)	0.36	$-6.56x10^{-03}$ ($-2.22x10^{-02}$ - $9.08x10^{-03}$)	0.41
Triglycerides	$9.23x10^{-04}$ ($-4.24x10^{-03}$ - $6.08x10^{-03}$)	0.72	$1.05x10^{-03}$ ($-4.28x10^{-03}$ - $6.37x10^{-03}$)	0.70
Vitamin D	$-2.10x10^{-02}$ ($-4.38x10^{-02}$ - $1.91x10^{-03}$)	0.07	$-1.96x10^{-02}$ ($-4.30x10^{-02}$ - $3.76x10^{-03}$)	0.10
Vitamin B12	$-6.91x10^{-05}$ ($-2.52x10^{-04}$ - $1.14x10^{-04}$)	0.46	$-7.32x10^{-05}$ ($-2.59x10^{-04}$ - $1.13x10^{-04}$)	0.44

BDNF: Brain-Derived Neurotrophic Factor; PhA: Phase angle; NO: Nitric Oxide; AOPP: Advanced Oxidation Protein Products; FOX: Ferrous Oxidation in Xylenol orange; GSH: Glutathione Transferase; TRAP: Total Plasma Antioxidant Potential, SH: Total Plasma Sulfhydryl; CAT: Catalase; SOD: Superoxide Dismutase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein.
Model 1: Unadjusted analysis.
Model 2: Adjusted model by age and gender.

els, unadjusted (β = $-8.01x10^{-01}$; p-value = 0.03) and adjusted model (β = $-7.60x10^{-01}$; p-value= 0.04). The coefficient of determination (R^2) was 0.15 for Model 1 and 0.16 for Model 2. On the other hand, the biomarkers NO, AOPP, GSH, TRAP, SH, CAT, SOD, glucose, LDL, HDL, triglycerides, vitamin D, and vitamin B12 did not show significant associations in either model.

DISCUSSION

This study identified an association between phase angle and the blood biomarkers BDNF and FOX. Specifically, PhA was positively correlated with BDNF levels and negatively associated with FOX levels. These findings suggest that a higher PhA may reflect better metabolic and cognitive health in older adults.

The positive association between PhA and BDNF levels remained significant even after adjusting for age and sex. PhA is widely recognized as a marker of cellular integrity[16] and is closely related to body composition parameters[17]. BDNF, in turn, plays a crucial role in synaptic plasticity and cognitive function[18]. Previous studies have shown that lower BDNF levels in older adults are associated with higher BMI[11] and increased body fat, both of which are are key components of body composition, as is PhA. This relationship may be attributed to BDNF's involvement in cellular mechanisms that support muscle maintenance[19], and energy homeostasis[20]. In this context, PhA emerges as a valuable body composition variable in both scientific research and clinical practice[21], providing a comprehensive assessment of health status and functional capacity in older adults.

Aging is characterized by a range of physiological changes[22], largely driven by an imbalance between the production of reactive oxygen species and the body's antioxidant defense

mechanisms[23]. Oxidative stress can be assessed using biomarkers such as FOX, which measures lipid peroxidation[24]. Our study observed a negative association between FOX and PhA, aligning with prior research that links PhA with oxidative stress levels[10]. A lower PhA, which is often indicative of reduced muscle mass and poor nutritional status[25] has been associated with elevated oxidative stress and increased free radical production[26].

PhA is widely used in clinical settings to monitor muscle function, sarcopenia, and frailty[27]. Moreover, it serves as an effective parameter for evaluating therapeutic interventions and guiding personalized rehabilitation strategies for older adults[3]. The biomarkers analyzed in this study fluctuate in response to various clinical conditions, including chronic diseases, acute exacerbations, and hospitalizations. Some, such as metabolic and vitamin biomarkers, are already routinely used in clinical practice for the management of chronic diseases in older adults[28]. Understanding their influence on PhA may enhance the early detection of health risks and improve disease monitoring in aging populations[29]. These findings reinforce the relevance of PhA as a key biomarker in the comprehensive management of geriatric health[30].

Despite the strengths of this study, it is important to acknowledge certain limitations. This is a cross-sectional analysis that limits the ability to establish causal relationships. In addition, the use of non-probability sampling via social networks may introduce selection bias, potentially favoring the participation of individuals with greater access to technology and better functional or cognitive status, thereby limiting the generalizability of the findings. Nonetheless, efforts were made to include a broad panel of blood biomarkers and to ensure standardized, high-quality data collection procedures. Future studies should incorporate longitudinal designs to explore associations between these and other biomarkers with PhA and additional body composition variables.

CONCLUSION

In conclusion, brain-derived neurotrophic factor and ferrous oxidation in xylene orange demonstrated significant associations with phase angle in older adults living in the community. These findings provide new insights into the biological mechanisms underlying phase angle and highlight its potential role as a valuable biomarker for aging and health monitoring. However, these results should be interpreted with caution due to the cross-sectional design and the use of convenience sampling. Future research should further investigate these associations through longitudinal studies to better understand their clinical implications and contributions to healthy aging.

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