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Influence of Omega 3 Fatty Acid Supplementation on Phase Angle Values of People Living with HIV/AIDS with Lipodystrophy Secondary to Antiretroviral Therapy: A Randomized Clinical Trial

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Abstract

Objective: The measurement of phase angles is an important monitoring parameter and supplementation with omega-3 could promote benefits by modulating the electrical potential of membranes and increasing body cell mass. This study aimed to evaluate the effectiveness of omega-3 fatty acid supplementation on the phase angle of people living with HIV/AIDS. **Methods:** In this study, 63 individuals of all genders who were undergoing outpatient follow-up and showed lipodystrophy due to highly active antiretroviral therapy were analyzed. Our sample consisted of two groups, one that received supplementation containing 2550 mg of omega-3/day (1080 mg of eicosapentaenoic acid and 720 mg of docosahexaenoic acid) for three months (n = 32) and another that underwent nutrition guidance (n = 31). Phase angle and body cell mass were assessed for both groups and compared at the beginning of research (T0) and after our intervention (T1) for each group separately. **Results:** Phase angle averaged 6.45˚ ± 1.06 SD. The comparison between T0 and T1 showed a significant increase in phase angle and body cell mass, whereas the guidance group showed a decrease in body cell mass at T1 in relation to T0, with a significant p-value. Variance in phase angle between moments showed significant values between T0 and T1 in the supplementation group for all genders. **Conclusion:** Omega-3 positively modulated patients phase angle and body cell mass, but we emphasize the need for other studies that

can solidify knowledge about supplementation dosage and intervention time.

Keywords

HIV, Lipodystrophy, Omega-3, Phase Angle

1. Introduction

The use of combined antiretroviral therapy (ART) to treat HIV cases directly increased patient survival. Drug associations enabled the minimization of the deleterious effects of the disease, interfering, for example, in the observed viral load [1]. Previous studies have shown that using these drugs caused some metabolic an nutritional changes, such as redistribution of body fat, elevation of blood lipids, and increase of glucose levels, which characterize ART-associated lipodystrophy [2].

This disease has an unknown real prevalence in Brazil, but estimates suggest that about 50% of patients who use highly active antiretroviral therapy manifest its classic clinical symptoms. Diagnosis is made, in most cases, by clinical anamnesis and semiological observations. However, bioimpedance techniques and imaging methods can assess body composition [3].

Electrical bioimpedance has been used to evaluate body composition as it is based on non-invasive, portable, and easy-to-handle equipment with good reproducibility [4]. This exam can quantify phase angles, a linear measurement applied in clinical practice, obtained by the relation of resistance and reactance variables associated with the integrity of the cell membrane and, consequently, with the prognosis of patients [5].

Fatty acids in the omega-3 family, such as linolenic, eicosapentaenoic (EPA), and docosahexaenoic acid (DHA), favor the formation of mediators with anti-inflammatory characteristics by producing eicosanoids of the odd series. The literature has consolidated the benefits of using omega-3 regarding the reduction of cardiovascular risk and triglyceride rates. Note that this supplementation can positively impact individuals with other chronic diseases [6].

The dietary consumption of omega-3 fatty acids promotes satisfactory cell membrane results as they modify its composition, increasing its fluidity, electrical potential, and cell growth [7]. Thus, studies, including a systematic, showed a reduction in triglycerides by – 77.55 mg (CI from 121.85 to 33.25) in the group that received omega-3, showing that EPA/DHA supplementation reduces serum triglycerides in patients with HIV/AIDS-associated hypertriglyceridemia who regularly used antiretroviral therapy [8].

Phase angle is a variable related to some aspects of the cell membrane, such as quality, size, and integrity. Higher phase angle values are associated with high capacitance and body cell mass and lower resistance, resulting in favorable prognoses. On the other hand, lower values are linked to lower capacitance and high resistance due to cell death, increased membrane permeability, and worsened general condition [9] [10].

In a study with administration of 1800 mg/day of omega-3 to patients, who showed an increase in phase angle (p = 0.01) and body cell mass percentage (p = 0.03) and reduction in pain intensity (p = 0.00), fundamental for the evolution of these individuals' general clinical picture a treatment response [6].

Based on previous studies that point to the immunomodulatory role of omega-3, the question arises whether omega-3 fatty acid supplementation effectively improves the phase angle of patients with lipodystrophy associated with antiretroviral therapy. Given the above, we hypothesized that omega-3 supplementation would change the phase angle of patients with ART-associated lipodystrophy.

Thus, this study aims to evaluate the possible influence of omega-3 fatty acid supplementation on the phase angle and body cell mass of patients with ART-associated lipodystrophy.

2. Objective

To evaluate the effectiveness of omega-3 fatty acid supplementation in relation to phase angle in patients with lipodystrophic syndrome secondary to phase angle antiretroviral therapy.

3. Methods

This study was approved by the ethics and research committee at Belém-PA, under CAAE: 02576318.0.0000.5172.

3.1. Casuistry and Study Design

This is a non-blinded clinical trial that evaluated individuals with ART-associated lipodystrophy by clinical follow-ups of those who met the inclusion/exclusion criteria of this study. Evaluations were carried out in a Reference Hospital. The research took place during the pandemic period when we experiencing a great scarcity of resources and inputs, it was decided not to blind, maintaining the diet therapy guidelines for both study groups, we aim to promote positive impacts and homogenize as much as possible concomitant changes in eating behavior, which could be biases in the research, it is highlighted that the participants do not have links with each other or explicit relationships that could facilitate communication of the type of intervention that was carried out.

This study was carried out from January 2020 to June 2022 and was supported by Resolution 251 of 1957 of the Brazilian National Council of Ethics and Research as a phase IV Research. Good clinical research practices and due submission to the Brazilian registry platform of clinical trials-ReBEC were followed. The study period described comprised the time for standardization of collection instruments, aiming to favor quality in data collection and results obtained (January 2020 to June 2022), in addition to the time for effective research (July 2021 to June 2022), period necessary so that the benefits of omega-3 supplementation could be identified. Furthermore, it is worth highlighting that because it is a reference hospital related to the single health system, in which patients attend the endocrinology outpatient clinic once a week, on Fridays, in a controlled quantity, with return visits every three months, there was their inclusion in the study gradually, according to prior scheduling by the hospital. The study period included the COVID pandemic, therefore, in some interventions, it was necessary to redo the study with 6 patients, due to problems with returning to carry out the return consultation, as they lived in other interior municipalities, where travel was affected and replacement of 1 patient who died during the period.

Sample calculation was performed considering a 5% alpha level, 95% confidence intervals, and two groups (intervention/control) followed for three months. The group selection plan, to guarantee the randomization process, included the allocation of all patient names, which was obtained from the hospital database, in a Microsoft Excel spreadsheet, from which random numbering was assigned, generated by the program, we sequentially separated individuals from 1 - 50 as select for the supplementation groups and from 51 - 100 for the guidance groups. In this way, ensuring that the researcher does not interfere with the allocation of patients into the different groups.

Sample size was calculated for each treatment group based on a previous study [11]. The mean of the studied variable, a 6.45˚ mean phase angle, a 1.09 SD, a 0.645 magnitude of effect (10% × 6.45˚); a 0.645/1.09 = 0.59 standardized effect magnitude; a 0.05 alpha level; and a 0.20 Beta error were considered, totaling 32 individuals in the supplementation/guidance group and 32 individuals in the guidance group (sample calculation for T-test) [12]. In our assessment of body composition using the bioimpedance technique, BioDynamics 450 equipment was used with an electric current intensity of 800 μA and a fixed frequency of 50 kHz (kilohertz), which ran through patients' entire body, using four electrodes, The equipment used is a certified by the National Health Surveillance Agency (ANVISA)/Ministry of Health and used at international scientific research level. The electrical current and frequency used by the device allow it to partially cross the cell membrane to measure resistance and reactance, in order to estimate the fat-free mass, in addition to accurately providing the phase angle, the main object of the research. A study by Back, 2020, which compared three devices that measure bioimpedance components, highlighted that all three can be used in the clinical management of patients, but highlighting the BioDynamics 450, due to its cost-benefit, size of the equipment and the fact that it is portable, making transport easier, compared to octopolar models, for example [13].

The technique included comfortably positioning individuals on a hospital stretcher without shoes, socks, watches, bracelets, or the like in the dorsal decubitus position and affixing two electrodes on their feet (the distal electrode at the base of their middle finger and the proximal electrode a little above their ankle joint line between their medial and lateral malleoli) and two electrodes on their right hand (the distal electrode at the base of their middle finger and the proximal electrode a little above their wrist joint line, coinciding with their styloid process), which were connected to a monitor by a sensor cable. The portion of participants' skin used to attach these electrodes showed no injuries and was previously cleaned with alcohol to remove their oiliness. Electrodes were placed at least five cm apart. After recording the necessary data regarding individuals' age, gender, height, phase angle and body cell mass results were provided in less than one minute, recorded, and subsequently analyzed.

The variables extracted from the bioimpedance test for analysis were phase angle; muscle mass; fat mass; and body cell mass.

The individuals who participated in this study were instructed to fast for four hours before the exam and to refrain from drinking coffee or tea the night before and from drinking alcohol or performing physical activities for eight hours before the exam.

3.2. Participant Safet and Informed Consent

The guarantee of ethical aspects was based on the principles described in the Declaration of Helsinki and the Nuremberg Code, respecting the standards for research involving human beings (Resolution n 466/2012) of the National Health Council, guaranteeing confidentiality with regard to identification of the researched, with signature of Free and Informed Consent Form (TCLE), presented in two copies, one of the copies was given to the participant and the other remained with the researcher for control. Through the ICF, the participant was informed that the research could generate some benefits for individuals with lipodystrophy, in terms of treatment guidance, in addition to contributing to the development of a nutritional assessment and treatment protocol. On the other hand, there were clarifications about the possible risks and discomforts resulting from the study, such as embarrassment, physical damage resulting from the use of assessment equipment such as radiometer and bioimpedance, in addition to possible allergies or gastrointestinal discomfort resulting from the use of supplementation, highlighting as a measure of mitigating risks and ensuring confidentiality in relation to identity, with the use of data only fulfilling the objectives described in the study, calibration and maintenance of the equipment to be used, with a detailed explanation of the preparation criteria for carrying out the tests, exposed through language clear and accessible, making periodic calls to check possible gastrointestinal discomforts, such as vomiting and diarrhea, in the supplementation groups. It is noteworthy that the privacy of the participants was respected, that is, the name or any other data or element that could identify the individual in any way was kept confidential, with no financial loss as a research participant. They were also informed that the individual could refuse to participate in the study, or withdraw consent at any time, without the need for justification, and if they wished to leave the research, they would not suffer any harm to the care they received at the outpatient clinic.

3.3. Inclusion Exclusion Criteria

This study included people living with HIV/AIDS; adults of all sexes, over the age of 18 years, who were undergoing outpatient monitoring and antiretroviral therapy (ART).

All individuals who were intolerant to omega-3 were excluded from our sample, as were those with vulnerabilities and/or associated diseases that negatively interfered with the predilected phase angle values (such as severe obesity, *i.e.*, BMI ≥ 40 Kg/m^2), with edema or ascites, neurological diseases that compromised their understanding of this study, use of a pacemaker or metal prostheses/or theses, kidney diseases, use of diuretics, and Indigenous people, pregnant or lactating women, and those in the supplementation group who failed to adhere to treatment.

3.4. Data Collection

Based on the positive opinions of the ethics and research committee, a brief pilot study was developed with six participants in two consecutive consultations to standardize and adjust the measurement instruments to be adopted. Then, our research took place in three stages by elective consultations at a lipodystrophy outpatient clinic.

In the first stage, an initial consultation between the researcher and patients took place, consisting of the proper guidelines of this study, informed consent form signing, completion of patients' sociodemographic and clinical protocol, and transfer of these guidelines for the second consultation with the supply of printed material, in addition to comments on the preparation criteria for the bioimpedance exam.

In the second consultation, the Guidance (GC) and Supplementation Groups (SG) were randomly defined. Then, the bioimpedance test was carried out for SG and their anthropometric measurements were recorded. These participants were given dietary guidance + supplementation – adapted from Cortes (2014) [6] containing 2100 mg of omega-3 (1270 mg de EPA and 840 mg of DHA) [6], divided into three capsules/day (to be taken two after lunch and one after dinner) for three months. For this intervention, VITHA© omega-3, duly certified by IFOS—an international quality and safety certification (FSSC 22000)—was used, containing 10 mg of vitamin E, which helps to prevent lipid peroxidation. The bioimpedance exam, anthropometric measurements and dietary guidelines were provided to this group.

Every month during treatment, patients were contacted by phone for monitoring, during which possible adverse effects in the intervention group were followed up. SG participants were told to take their supplementation packages for the next consultation so we could evaluate their adherence to the proposed treatment.

In the last consultation, three months after the beginning of treatment, post-treatment biochemical and anthropometric data were collected and bioelectrical impedance was reassessed.

3.5. Statistical Analysis

To compile and analyze our results, a database was built in Microsoft Excel 2010 and analyzed using the statistical package BioEstat 5.0 and Jamovi 2.3.18.

The overall phase angle was averaged. Phase angle per group and at different moments (T0 and T1) were described in a table with means and standard deviations. The T-test for independent samples was used to assess possible statistically significant differences between groups at T0, whereas the Wilcoxon test was applied to evaluate the significance at T0 and T1 of each group.

Body composition variables were displayed in tables. The Guidance (GC) and Supplementation Groups (SG) at T0 were compared by the T-test. The related T0 and T1 samples for each group were evaluated by the T-test.

Phase angle according to gender was displayed in a table and the T test for independent samples was applied to it.

4. Results

4.1. Sociodemographic Profile

Our sample consisted of 63 individuals of all genders divided into groups, one received a supplementation intervention with omega-3 and the other, only dietary guidance.

As for the sociodemographic profile of the supplementation group (n = 32), we found a 56.25% prevalence of women (n = 18) and a 43.75% (n = 14) of men. Most men fell into the 60 - 70 age group (n = 7/50%), whereas most women into the 50 - 60 age group (n = 7/38.89%).

Regarding the guidance group's sociodemographic profile (n = 31), we observed that most individuals were men (n = 19/61.29%), rather than women (n = 12/38.71%). Most men were aged 50 - 60 (n = 5/26.32%) and 60 - 70 years (n = 5/26.32%), whereas women showed a higher prevalence of the age group between 50 - 60 years (n = 5/41.67%).

4.2. Assessment of Body Composition

Table 1 describes our analysis of phase angle in the supplementation group at T0 and T1, with a significantly higher body cell mass at T1 (22.71% ± 6.12 SD) than at T0 (21.79% ± 5.98 SD) (p-value = 0.01). We found no significant differences in fat and lean mass values between T0 and T1.

Table 2 shows our analysis of the body composition variables for the guidance group at T0 and T1, with a significantly lower body cell mass at T1 (21.78% ± 4.24 SD) than at T0 (22.89% ± 4.30 SD) (p-value = 0.01). We found significant differences in fat and lean mass between T0 and T1.

4.3. Phase Angle Evaluation

We calculated phase angle values for the entire sample. We obtained a mean initial value of 6.45˚ ± 1.06 SD.

Evaluation of Phase Angles before and after the Intervention

After comparing phase angles before and after the intervention, we compared the initial phase angle of our groups, finding no significant difference between them (p = 0.316). Our analysis of phase angles at T0 and T1 for the guidance group showed no statistically significant differences between phase angles at T0 (6.70˚ ± 1.2˚), and T1 (6.50˚ ± 1.4˚) (p-value = 0.108). However, when we evaluated the phase angle in the supplementation group, we observed a significantly higher phase angle at T1 (6.65˚ ± 1.67˚) than in T0 (6.5˚ ± 1.02˚) (p-value = 0.006). Table 3 shows these data.

4.4. Phase Angle According to Gender

Regarding our phase angle analysis by gender, Table 4 shows the mean phase angle for men (6.87˚ ± 1.06 SD), significantly higher (p-value = 0.001) than for women (6.01˚ ± 0.88 SD).

Table 1. Comparison of body composition at T0 and T1 in the supplementation group – patients living with HIV/AIDS and ART-associated lipodystrophy who were treated at a reference hospital in Belém-PA, 2022.

Body composition variables	**T0** supplementation		**T1** supplementation		**p-Value**
	Mean	**SD**	**Mean**	**SD**	
Lean mass **(%)**	47.01	10.94	47.88	10.75	0.15*
Fat mass **(%)**	20.06	5.92	19.29	6.37	0.07*
Body cell mass **(%)**	21.79	5.98	22.71	6.13	0.01*

T-test*. Source: Field Research – 2022.

Table 2. Comparison of body composition in the guidance group at T0 and T1 for patients living with HIV/AIDS and ART-associated lipodystrophy who were treated at a referral hospital in Belém-PA, 2022.

Body composition variables	T0 Guidance		T1 Guidance		**p-Value**
	Mean	**SD**	**Mean**	**SD**	
Lean mass **(%)**	47.62	7.07	47.12	7.87	0.27*
Fat mass **(%)**	18.62	6.16	18.82	6.46	0.65*
Body cell mass **(%)**	22.89	4.31	21.78	4.24	0.01*

T-test*. Source: Field Research – 2022.

Table 3. Overall mean phase angle of patients living with HIV/AIDS and ART-associated who were treated at a referral hospital in Belém-PA, 2022.

	Groups		**Guidance Group**		Supplementation **Group**	
	Guidance **T0**	Supplementation **T0**	**T0**	**T1**	**T0**	**T1**
Phase angle	6.60 ± 1.02	6.33 ± 1.11	6.70 ± 1.2	6.50 ± 1.4	6.5 ± 1.02	6.65 ± 1.67
p (value)	0.316*		0.108**		0.006**	

*T-test for independent samples ** Wilcoxon test. Source: Field Research - 2022.

Table 4. Mean phase angle for the guidance group with patients living with HIV/AIDS and ART-associated lipodystrophy who were treated at a referral hospital in Belém-PA, 2022.

Gender	Phase angle		
	Mean	SD	p-VALUE
Women	6.01	0.88	0.001*
Men	6.87	1.07	

T-test*. Source: Field Research - 2022.

5. Discussion

Clinical practice has increasingly disseminated the use of phase angles given its applicability as a tool to diagnose cell integrity and disease severity and prognosis (which may also serve as an instrument to assess for individuals' general health).

Silva and Libonati, 2020, analyzed the phase angle of patients treated at lipodystrophy, finding that it ranged from 4.4˚ to 8.55˚, with a median of 6.45˚ ± 1.09˚, which the authors considered as their cutoff point [14]. Pimentel, 2012, evaluated phase angles in 58 patients with chronic kidney diseases undergoing hemodialysis, finding an average of around 5.7˚ before dialysis and 6.5˚ after dialysis [15].

Higher phase angles are correlated with greater cell membrane integrity and cell size. In healthy individuals, phase angle may show values of approximately 4˚ to 15˚ degrees. Mean expected phase angle values for a healthy population vary between 4˚ and 10˚, depending on gender and age [16].

Lower phase angle values may be associated with worsening health conditions and/or diseases, in addition to suggesting the probability of cell apoptosis or membrane changes [17].

Cortes *et al.*, 2014 studied the relationship between phase angle values and supplementation to identify how omega-3 fatty acids (daily supplementation with 1.800 mg of omega-3 – 1.080 mg de EPA and 720 mg of DHA for 84 days) affected the clinical nutrition characteristics of 40 volunteers of all genders, of which 20 individuals had myofascial pain syndrome (group I) and 21 showed no pain (group II). After bioelectrical impedance, participants who received supplementation showed increased phase angle ($p = 0.01$) and body cell mass ($p = 0.03$) and reduced pain intensity ($p = 0.00$), suggesting greater cellular integrity due to phase angle and visceral deposits and somatic proteins (evinced by body cell mass percentages) that directly affected these individuals' general clinical picture and treatment response [6].

Cell membrane composition, regarding the fatty acids in its phospholipid bilayer, directly influences the electrical potential of membranes, but the exact mechanism of influence on phase angle remains poorly understood [18].

Polyunsaturated fatty acids (the group to which omega-3 belongs) have their first double bond on carbon 3 from the methyl radical of the fatty acid. The main representatives in the class are EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Present mainly in fish oils, they seem to act in cell signaling, enzymatic regulation, eicosanoid synthesis, neuronal migration regulation, and modulation of neuromodulating and neurotransmitting cytokines [19].

Another important characteristic of omega-3 fatty acids relates to increased cell membrane fluidity as it interferes with the composition of membranes and could contribute to increasing the phase angle of individuals supplemented with this fatty acid, reducing tissue resistance and improving physicochemical properties [20].

Regarding body cell mass, serious consequences relate to changes in nutritional status, such as decreased strength and functional capacity, which worsens individuals' quality of life [18]. Thus, improving this bioimpedance indicator significantly and positively affects the nutritional status of patients with HIV. The improvement of these indicators is associated with the functions omega-3 performs regarding lipid composition modification.

Baptista, 2018, measured several parameters (including the phase angle of patients after surgery) and found that phase angle decreases after stressful situations, such as cardiac surgery. Values decreased from 5.5˚ before surgery to 5.7˚ shortly after, shifting to 4.7˚ weeks later. This fact indicates that phase angle varies according to several factors, including morbidities that cause inflammatory alterations and cytokine increases. It is essential to use elements that have antioxidant action, such as omega-3 [21].

Omega-3 acts precisely on immune response modulation, balancing inflammatory responses or increasing protein synthesis, maintaining the integrity of intestinal mucosa, and thus improving patients' clinical and nutritional status [22].

Cell membrane composition, regarding the presence of fatty acids in this phospholipid bilayer, directly influences the electrical potential of membranes, but the exact mechanism of influence on phase angle is yet to be well explained [18].

6. Study Limitations

The limitations of this study include the non-blinding of the sample, a fact that was related to the circumstances related to the COVID-19 pandemic, a shortage of resources and inputs, there was a need to adapt the research protocol, ceasing to carry out the crossover study, the what was the initial design of the project, this way it is known that there are possibilities of biases related to aspects that are associated with the treatment, in the current research, in which blinding was not carried out, in order to minimize differences we carried out standardization of dietary guidelines for both groups, where the researcher was restricted to describing only the described in the list previously prepared and given to the participants.

Limitations of this study also include the COVID-19 pandemic, which demanded non-face-to-face, follow-ups via phone.

Another limitation was the difficulty patients had in storing the bottles of supplements they took, making it difficult for us to assess their adherence to supplement use.

7. Conclusion and Recommendation

This study indicates the benefits omega-3 supplementation may have on phase angle and body cell mass by improving cell composition and offering better prognoses, relevant facts in the face of the inflammatory condition and metabolic alterations observed in individuals using ART.

The results of this study are very relevant as they contribute to the incorporation of omega-3 to the range of non-pharmacological care for patients with ART- associated lipodystrophy as it increases body cell mass, positively mediates lipid profiles, reduces inflammatory process, and increases phase angle (which is an important predictor of cell integrity). Further studies evaluating different dosages and times of use may generate greater robustness for the incorporation of omega-3 in clinical practice and diet therapy in cases of HIV/AIDS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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