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Retrospective Study

Relationship between phase angle, steatosis, and liver fibrosis in patients coinfecting with human immunodeficiency virus/hepatitis C virus

Sabrina Alves Fernandes, Cristiane Valle Tovo, André Luiz Machado da Silva, Letícia Pereira Pinto, Randhall B Carteri, Angelo A Mattos

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Abstract**BACKGROUND**

Malnutrition, lipodystrophy, and dyslipidemia are prevalent characteristics in patients with human immunodeficiency virus (HIV) infection with or without previous treatment. Such a clinical condition can lead to the hypothesis of the presence of hepatic steatosis with possible progression to fibrosis and the risk of hepatocellular carcinoma. Notably, a low phase angle (PA), evaluated by bioelectrical impedance analysis (BIA), is an independent prognostic marker of clinical progression and survival in HIV-infected patients.

AIM

To evaluate the relationship between PA and body composition with steatosis and hepatic fibrosis in HIV/hepatitis C virus (HCV)-coinfecting patients.

METHODS

A retrospective observational study by convenience sampling of coinfecting HIV/HCV patients, in which all patients underwent transient elastography

(Fibroscan) and BIA evaluation. Student's *t* test was used for group comparisons, and Spearman's or Pearson's correlation test was used when appropriate. The significance level was set at 5%, and analyses were performed using SPSS version 21.0.

RESULTS

Forty-three patients who received antiretroviral therapy met the inclusion criteria, and 23 (53.5%) were under treatment with protease inhibitors (PIs). There was no difference in PA between those who used PIs and those who did not ($P = 0.635$). There was no correlation between fibrosis grade and PA ($P = 0.355$) or lean mass ($P = 0.378$). There was a significant inverse correlation between the controlled attenuation parameter (CAP) and lean mass ($P = 0.378$), positive correlation between PA and lean mass ($P = 0.378$), and negative correlation between PA and fatty mass ($P = 0.378$), although the CAP and PA were not correlated. When evaluated by sex, no significant correlations were found.

CONCLUSION

PA determines the muscle function of HIV/HCV-coinfected patients, and the CAP values reinforce the association with lean mass, suggesting that patients require early nutritional interventions.

Key Words: Phase angle; Bioelectrical impedance; Coinfection; Human immunodeficiency virus; Hepatitis C virus; Nutrition

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Core tip: Patients living with human immunodeficiency virus (HIV) are often affected by malnutrition, which may be related to the progression of liver disease. A low phase angle (PA), assessed by bioelectrical impedance analysis, is a prognostic marker of clinical progression and survival in HIV-infected patients. This study aimed to assess the relationship between PA, steatosis, and liver fibrosis in HIV/hepatitis C virus (HCV)-coinfected patients. Forty-three HIV/HCV-coinfected patients were included in this study. PA determines the muscle functionality of patients coinfecting with HIV/HCV, and the controlled attenuation parameter values reinforce the association with lean mass, suggesting that patients require early nutritional interventions.

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INTRODUCTION

Patients living with human immunodeficiency virus (HIV) are frequently affected by malnutrition, which may contribute to the emergence of infections[1,2]. Individuals at all stages of HIV are at risk of nutritional deficiency, and nutritional status is a strong predictor of disease progression, survival, and functional status during the course of the disease, showing a direct relationship with cell integrity and function[3,4].

Furthermore, in patients coinfecting with HIV and hepatitis C virus (HCV), physicians must consider not only the natural history of the disease, but also the patient's clinical treatment and previous clinical conditions, which significantly compromise physiological homeostasis[3]. One of the physiological mechanisms of lean mass increase is the role of anabolic hormones, mainly testosterone and insulin-like growth factor-1[3]. The associated mechanisms are responsible for catalyzing protein synthesis and enhancing the replication and differentiation of muscle cells. In HIV patients, testosterone levels decrease, which negatively affects the healthy body composition of this population. This modification of the physiological architecture causes these patients to present with lipodystrophy and malabsorption of nutrients, compromising their nutritional status[3]. Owing to the strong association between muscle mass loss and liver disease, regardless of obesity or metabolic syndrome, identifying a method that indicates these physiological impairments is of paramount importance.

Strikingly, through bioelectrical impedance analysis (BIA), it is possible to measure the phase angle (PA); defined as the relationship between two vectors of resistance and reactance, and a parameter

widely used and established as a prognostic factor in several diseases. Currently, low PA is an independent prognostic marker of clinical progression and survival in HIV-infected patients receiving antiretroviral therapy (ART)[5,6].

Nevertheless, nutritional assessment in patients with chronic liver disease has limitations due to body asymmetry (for example, ascites and edema) that these patients may present as a result of complications from liver cirrhosis, in addition to the lack of a gold standard method[7]. Therefore, PA is the nutritional assessment method with the best performance because it reflects muscle volume and functionality without the influence of confounding factors[8]. In this context, in a study that evaluated 129 patients with cirrhosis using different nutritional assessment methods, including body mass index (BMI), skin folds, subjective global assessment, handgrip strength, and PA, the authors concluded that PA was the only method associated with the condition. Another fact that draws attention to this study is the discrepancy in the percentage of malnourished patients measured by the methods, corroborating the statement that diagnosing the nutritional status of patients with chronic liver disease remains challenging. Identifying the nutritional status of patients is important to intervene early and consequently improve their clinical prognosis[8].

Moreover, coinfecting HIV/HCV patients may also have a poor prognosis, as evidence suggests that HIV infection negatively impacts the progression of liver diseases, particularly increasing risks for fibrosis and hepatocellular carcinoma development[9,10], although this may be controversial[11].

Hence, to the best of our knowledge, no studies have assessed the role of PA and its body composition associated with hepatic steatosis and fibrosis in HIV/HCV-coinfecting patients. The findings of this study can guide future interventions with a positive impact on the prognosis and quality of life of this population.

MATERIALS AND METHODS

This was a retrospective study by convenience sampling conducted between January and July/2019 at the outpatient Gastroenterology and Hepatology Clinic of Santa Casa Hospital and the Infectiology Clinic of Hospital Nossa Senhora da Conceição, both tertiary reference centers in Porto Alegre, RS, Brazil.

Subject selection criteria

The study included coinfecting HIV/HCV patients. Patients with hepatitis B virus infection, significant alcohol consumption (> 14 drinks *per week* for women and > 21 for men), and hepatocellular carcinoma were excluded.

Diagnosis of HIV/HCV

Serological tests were used to determine chronic HCV and HIV infections. A positive serological test for HCV by ELISA with a positive reverse transcription polymerase chain reaction for HCV RNA confirmed viremia. An ELISA with a confirmatory western blot test confirmed HIV infection.

Anthropometric measurements

Body weight and height were measured on a mechanical scale using a Filizola stadiometer with a weight scale of 100 g and a height scale of 1 cm, which was previously calibrated. The patients were evaluated while wearing light clothing and barefoot. Height was determined using a fixed stadiometer on the wall, with the patient standing upright and barefoot. BMI was calculated as weight (kg) divided by height (in meters) squared[12].

BIA

BIA was performed in all patients without previous specific preparation for fasting. The patients were evaluated in a comfortable dorsal decubitus position and relaxed without shoes, socks, or metallic fittings. The legs were spread apart, hands opened, and supported on a stretcher. The electrodes were positioned as follows: One was placed at the base of the middle toe on the right foot, and another slightly above the line of the ankle joint between the medial and lateral malleoli. Another pair of electrodes was distributed at the base of the middle finger of the right hand, slightly above the line of the right wrist joint, coinciding with the styloid process. The device used was Biodynamics® model 450 (multifrequency-800 A and 50 KhZ, and tetrapolar).

To assess cellular functionality and integrity, PA was measured, which was automatically provided by the equipment based on the values of R and Xc[13]. PA was classified according to the cut-off point of 5.4°, based on the reference parameters of the study by Fernandes *et al*[8], in which values below this point are considered predictive of poor prognosis, and the values above are predictors of good prognosis. Using BIA, the lean mass and fat mass of the coinfecting patients were also measured.

Staging of liver fibrosis

Liver fibrosis was evaluated by transient elastography (TE) (Fibroscan), performed by a specialized physician experienced in the procedure (at least 500 examinations performed). The physician was blinded to the patient's data. A FibroScan device (Echosens, Paris, France) was used, and the results were expressed in kPa. The examination was performed after a 4-h fast. Procedures were considered reliable and included in the analysis only when they presented at least 10 valid shots, a success rate of at least 60%, and an interquartile range of liver stiffness value $\leq 30\%$. The cutoff points for TE were established according to the Brazilian Society of Hepatology and Brazilian College of Radiology practice guidance for the use of elastography in liver diseases for HCV patients (7.1 kPa for F2, 9.5 kPa for F3, and 12.5 kPa for F4)[14]. The controlled attenuation parameter (CAP) was evaluated in all TE in a complementary manner to identify steatosis. The study population was stratified into two groups based on the stage of fibrosis at TE: With (\geq F3) and without ($<$ F3) advanced fibrosis.

Statistical analysis

The normality of the data was assessed using the Kolmogorov–Smirnov test. Parametric variables are described as means and standard deviations. Categorical variables were described by frequencies and percentages. Differences in PA, lean mass, and fatty mass percentages between groups considering the staging of fibrosis were analyzed using Student's *t*-test. Pearson's χ^2 test was used to assess the association between the CAP and PA, and Spearman's correlation coefficient was used to assess the association between fibrosis and PA. The significance level adopted was 5%, and analyses were performed using SPSS version 21.0.

RESULTS

Initially, of a total of 47 patients, four were excluded because they did not agree to perform TE or BIA; the remaining 43 patients were included in the analysis. Anthropometric and clinical characteristics are shown in [Table 1](#). Male sex was more frequent (22; 51.2%), mean age was 46.2 ± 8.5 years, the HCV genotype 1 was the most frequent ($n = 30$; 69.7%), and 27 (62.8%) presented advanced fibrosis (F3/F4). The mean BMI was 25.9 ± 4.9 kg/m², and participants showed a mean percentage of lean mass of 75.5 ± 9.2 and a mean percentage of fatty mass of 24.5 ± 9.2 ([Table 1](#)). In addition, using the PA cutoff points, only two patients (4.7%) were classified as malnourished.

All patients were taking ART, with 23 (53.5%) using schemes containing protease inhibitors (PIs), and 20 (46.5%) did not. There was no difference in PA between these groups using PIs [$7.20 \pm 0.70^\circ$ vs $7.06 \pm 1.09^\circ$; $t(37) = 0.479$, $P = 0.635$].

The groups were compared according to the fibrosis stage. The value of PA for patients with fibrosis (TE $<$ F3; $n = 16$) was $7.3 \pm 1.0^\circ$, and for advanced fibrosis (TE \geq F3; $n = 27$) was $7.0 \pm 0.7^\circ$ [$t(41) = 0.936$; $P = 0.355$]. No differences were found between the percentages of lean mass for patients with fibrosis and those with advanced fibrosis [$73.9\% \pm 9.7$ vs 76.5 ± 8.9 ; $t(41) = -0.89$; $P = 0.378$]. The values of the percentage of fatty mass between patients with fibrosis and those with advanced fibrosis were also similar [$26.1\% \pm 9.7$ vs $23.5\% \pm 8.9$; $t(41) = 0.886$; $P = 0.381$]. There was no correlation between fibrosis grade, PA, and anthropometric parameters ([Tables 2 and 3](#)).

The mean CAP was 241.1 ± 55.7 ([Table 1](#)). As shown in [Table 3](#), there was a significant inverse correlation between the CAP and the percentage of lean mass (Pearson's $r^2 = -0.493$, $P = 0.01$). Although no significant correlations between the CAP and PA were found, there was a positive correlation between PA and lean mass (Pearson's $r^2 = 0.373$, $P = 0.014$) and a negative correlation between PA and fatty mass (Pearson's $r^2 = -0.373$, $P = 0.014$). Additionally, when evaluated by sex, no significant correlations were found ([Table 4](#)).

DISCUSSION

The present study evaluated the role of PA in HIV/HCV-coinfecting patients. Notably, there was no correlation between the fibrosis grade and PA values. However, there was an inverse correlation between the CAP and fatty mass, a positive correlation between PA and lean mass, and a negative correlation between PA and fatty mass, although this correlation was not significant when evaluated according to sex and age. Although it is not possible to stratify patients by age because of the limited number of patients allocated to the study, the patients' mean represents the age group that presents the physiological degradation of skeletal muscle mass[15].

Importantly, the CAP quantifies liver steatosis; however, several covariates may hamper the analysis, including nonalcoholic fatty liver disease, diabetes, and BMI. However, most studies using the CAP evaluated small sample sizes and heterogeneous populations with variable BMI and diabetes prevalence, which may explain the differences in the proposed cutoffs[16]. The present study observed a mean value that was not considered high (241.1 ± 55.7 , [Table 1](#)), and thus we cannot confirm that the

Table 1 Anthropometric and clinical characteristics of the evaluated patients (n = 43) (mean ± SD)

Characteristic	
Male sex, n (%)	22 (51.2)
Age, yr	46.2 ± 8.5
Body mass index	25.9 ± 4.9
Phase angle	7.1 ± 0.8
Lean mass, %	75.5 ± 9.2
Fatty mass, %	24.5 ± 9.2
Genotype HCV, n (%)	
1	30 (69.7)
2	02 (4.7)
3	09 (20.9)
Missing data	02 (4.7)
Fibrosis, n (%)	
F0	05 (11.6)
F1	10 (23.3)
F2	01 (2.3)
F3	10 (23.3)
F4	17 (39.5)
CAP	241.1 ± 55.7

CAP: Controlled attenuation parameter; HCV: Hepatitis C virus.

Table 2 Relationship between hepatic fibrosis and controlled attenuation parameter vs phase angle and lean mass (n = 43)

	Fibrosis ¹		CAP ²	
	rho	P value	r ²	P value
Phase angle	0.075	0.634	0.016	0.918
Lean mass	0.095	0.543	0.493 ³	0.001

¹Spearman's rho test.

²Pearson test.

³Correlation is significant at the 0.05 level (2-tailed).

CAP: Controlled attenuation parameter.

CAP has demonstrated significant steatosis in this case. Meanwhile, we demonstrated a significant inverse correlation between the CAP and lean mass. To justify these findings, we could consider the role of lipodystrophy, a common issue in patients with HIV, as well as the greater chance of steatosis in these patients related to ART, or even the greater occurrence of steatosis in some patients with HCV. Nonetheless, we could not prove the individual role of each parameter. Accordingly, moderate-to-severe steatosis in people living with HIV without viral hepatitis or excessive alcohol intake is associated with cumulative exposure to stavudine, elvitegravir, and raltegravir[17]. In the present study, none of the patients used schemes containing ART.

Concomitantly, of the nucleoside analog reverse transcriptase inhibitors currently available in Brazil for the treatment of people living with HIV (PLHIV), zidovudine (AZT) is the main drug related to adverse events, with para effects due to mitochondrial damage, such as myopathy, lipoatrophy, peripheral neuropathy, hepatic steatosis, and lactic acidosis[17]. Similarly, lamivudine and abacavir, other representatives of this class prescribed in Brazil, can cause damage due to mitochondrial dysfunction, but to a lesser extent than AZT[17]. Additionally, lipohypertrophy is a common feature in PLHIV patients treated with first-generation PIs such as indinavir, but it is not possible to prove a direct relationship between this adverse event and this class of drugs[18]. Those with greater total body fat

Table 3 Comparison between groups in accordance with fibrosis staging

	Fibrosis (TE < F3; n = 16)	Advanced fibrosis (TE ≥ F3; n = 27)	t-test	P value
Phase angle°	7.3° ± 1.0	7.0° ± 0.7	t (41) = 0.936	0.355
Lean mass (%)	73.9% ± 9.7	76.5 ± 8.9	t (41) = -0.89	0.378
Fatty mass (%)	26.1% ± 9.7	23.5% ± 8.9	t (41) = 0.886	0.381

Values are represented as mean ± SD. TE: Transient elastography.

Table 4 Relationship between phase angle and lean mass, fatty mass and controlled attenuation parameter

	Total (n = 43)		Males (n = 22)		Females (n = 21)	
	r²	P value	r²	P value	r²	P value
Lean mass (%)	0.373 ¹	0.014	0.208	0.353	0.189	0.412
Fatty mass (%)	-0.373 ¹	0.014	-0.208	0.353	-0.189	0.411
CAP	0.016	0.918	0.035	0.878	0.102	0.659

¹Spearman’s rho test. Correlation is significant at the 0.05 level (2-tailed).

CAP: Controlled attenuation parameter.

before ART and a positive energy balance may have an additional increase in trunk fat, including visceral, breast, and dorsocervical adiposity[19].

Accordingly, the findings of the present study corroborate those observed by Ruiz-Margáin *et al*[20], which evaluated patients with chronic liver disease. In this study, PA was directly proportional to skeletal muscle mass. Therefore, it is possible to observe that the skeletal muscle mass significantly guarantees the improvement of the physiological performance of patients.

Likewise, Osuna-Padilla *et al*[21], when evaluating PA in patients with HIV, also showed that this parameter could be a predictor of malnutrition. In addition, they identified PA cut-off points for men and women of 5.45° and 4.95°, respectively, with specificity and sensitivity > 70%, similar to the present study when evaluating PA, body composition, and the degree of hepatic fibrosis in patients coinfecting HIV/HCV.

Recently, PA has gained importance as a nutritional status marker, with low values associated with malnutrition and nutritional risk at the time of hospital admission[22]. The main advantage of using PA is the possibility of its application even under unstable tissue hydration conditions, such as edema and ascites[23]. This fact deserves recognition since patients with HIV may have reduced muscle mass and increased fat mass.

Furthermore, a previous study of 539 adults with HIV demonstrated that lower BMI, lower PA, and loss of fatty mass were associated with more advanced HIV infection (CD4⁺ lymphocyte count < 200 cells/mm³)[24]. Hence, BIA is a good tool for detecting body cell mass loss in HIV and compares favorably with gold-standard methods. Nevertheless, one of the main clinical complications of advanced liver disease is protein-calorie malnutrition, which has a prevalence ranging from 10% to 100%, regardless of the stage and etiology of the disease. Thus, it is evident that the general prognosis of the disease worsens in the presence of malnutrition, contributing negatively to patients’ quality of life [25].

A possible limitation of the present study was the small number of patients. As for strengths, we highlight the originality and importance of the data for early interventions aimed towards the clinical/nutritional treatment of patients coinfecting with HIV/HCV, offering improved quality of life and prognosis. In addition, this study implemented an important tool, namely electrical bioimpedance, which does not depend on the operator. Another important and extremely relevant point is the evaluation of liver fibrosis by elastography, a noninvasive and promising method for the diagnosis of these patients.

CONCLUSION

PA determines the muscle function of HIV/HCV-coinfecting patients, and the CAP values reinforce the association with lean mass (both show a relationship with muscle mass, PA, and the CAP), suggesting that patients require early nutritional interventions.

ARTICLE HIGHLIGHTS

Research background

Human immunodeficiency virus/hepatitis C virus (HIV/HCV)-coinfected patients may have a poor prognosis, as evidence suggests that HIV infection negatively impacts the progression of liver disease, particularly increasing the risks of developing fibrosis and hepatocellular carcinoma, although this can be controversial. Both HIV and HCV negatively affect the nutritional status of patients, regardless of the stage of the disease. In addition, nutritional assessment in patients with chronic liver disease has limitations due to the body asymmetry (*e.g.*, ascites and edema) that these patients may experience as a result of complications from liver cirrhosis, in addition to the lack of a standard method.

Research motivation

There is a strong association between muscle mass loss and liver diseases, regardless of obesity or metabolic syndrome, and identifying a method that indicates these physiological impairments is of paramount importance.

Research objectives

To the best of our knowledge, no studies have assessed the role of phase angle (PA) and its body composition associated with hepatic steatosis and fibrosis in HIV/HCV-coinfected patients.

Research methods

A retrospective observational study by convenience sampling with coinfecting HIV/HCV patients, where all patients underwent transient elastography (Fibroscan) and bioelectrical impedance analysis evaluation. Student's *t*-test was used for group comparisons and Spearman's or Pearson's correlation tests were used when appropriate. The significance level adopted was 5% and the analyses were performed using the SPSS version 21.0.

Research results

Of 43 patients who were analyzed, male sex was more frequent (22; 51.2%), mean age was 46.2 ± 8.5 years, HCV genotype 1 was the most frequent ($n = 30$; 69.7%), and 27 (62.8%) presented with advanced fibrosis (F3/F4). There was no correlation between the fibrosis grade and the PA ($P = 0.355$). Also, there was no correlation between the fibrosis grade and the lean mass ($P = 0.378$). The mean controlled attenuation parameter (CAP) was 241.1 ± 55.7 , and there was a significant inverse correlation between CAP and percentual of lean mass ($P = 0.01$). Although no significant correlations between CAP and PA were found, there was a positive correlation between PA and lean mass ($P = 0.014$), and a negative correlation between PA and fatty mass ($P = 0.014$). Additionally, when evaluated by sex, there were no significant correlations.

Research conclusions

The PA determines the muscle function of the HIV/HCV-coinfected patients, and the CAP values reinforce the association with lean mass (both show a relationship with muscle mass, the PA and the CAP), suggesting patients who need early nutritional intervention.

Research perspectives

Identifying clinical factors that potentiate a poor prognosis of patients coinfecting with HIV/HCV, such as malnutrition, is of relevance. With this information, it is possible to act early in the management of these patients and increase the effectiveness of the therapeutic response, with a consequent improvement in the prognosis and quality of life of this population.

FOOTNOTES

Author contributions: Fernandes SA was responsible for the conception and design, data collection, statistical analysis, and manuscript writing; Tovo CV was responsible for the conception and design, statistical analysis, manuscript writing, and critical revision; da Silva ALM was responsible for data collection, manuscript writing, and critical revision; Pinto LP was responsible for data collection, statistical analysis, and critical revision; Carteri RB was responsible for the statistical analysis, manuscript writing, and critical revision; Mattos AA was responsible for conception and design, statistical analysis, manuscript writing, and critical revision.

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