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Retrospective Study

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

Phase angle and liver fibrosis in HIV/HCV coinfected

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Abstract

BACKGROUND

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

AIM

To evaluate the relationship between AP, body composition parameters (fat-free mass and fat mass) with steatosis and hepatic fibrosis in HIV/HCV coinfected patients.

METHODS

A retrospective observational study by convenience sampling with coinfected HIV/HCV patients, where all patients underwent transient elastography (TE) (Fibroscan®) and BIA evaluation. The 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.

RESULTS

Forty-three under antiretroviral therapy met the inclusion criteria, and 23 (53.5%) were under schemes containing protease inhibitors (PI). There was no difference in the PA between those using PI or not (P = 0.635). There was no correlation between the fibrosis grade and the PA (P = 0.355) or with the lean mass (P = 0.378). There was a significant inverse correlation between CAP and lean mass (P = 0.378), a positive correlation between PA and lean mass (P = 0.378), and a negative correlation between PA and fatty

mass (P = 0.378), albeit CAP and PA were not correlated. Also, when evaluated by sex, there were no significant correlations.

CONCLUSION

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

Key Words: Phase Angle; bioelectrical impedance; coinfection; HIV; hepatitis C virus

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Core Tip: Patients living with 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 (BIA) has been a prognostic marker of clinical progression and survival in HIV-infected patients. The aim was to assess the relationship between PA, steatosis and liver fibrosis in HIV/HCV co-infected patients. Forty-three HIV/HCV co-infected patients were included. The PA determines the muscle functionality of patients co-infected with HIV / HCV, and the CAP values reinforce the association with lean mass, suggesting patients who need early nutritional intervention.

INTRODUCTION

Patients living with the human immunodeficiency virus (HIV) are frequently affected by the occurrence of malnutrition, and this may contribute to the emergence of infections[1,2]. Individuals at all stages of HIV disease 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].

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

Strikingly, through bioelectrical impedance (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, a low PA is an independent prognostic marker of clinical progression and survival in HIV-infected patients on 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 since it reflects muscle volume and functionality without the influence of confounding factors [8]. In this context, in the study that evaluated 129 cirrhotic patients 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. patient's

clinic as measured by the Child-Pugh score. Another fact that draws attention to the study is the discrepancy in the percentage of malnourished measured by the methods, corroborating the statement that diagnosing the nutritional status of patients with chronic liver disease is still a challenge. The importance of identifying the nutritional status of the patient is to intervene early and consequently improve their clinical prognosis [8].

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

Hence, to the best of our knowledge, there are no studies that assess the role of PA and its body composition associated with hepatic steatosis and fibrosis in HIV/HCV coinfected patients. The findings of this study can guide future interventions that have 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 Infectology clinic of Hospital Nossa Senhora da Conceição, both are tertiary reference centers at Porto Alegre, RS, Brazil.

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

Diagnosis of HIV/HCV: Serological tests determined chronic HCV and HIV infection. Briefly, a positive serological test for HCV by enzyme-linked immunosorbent assay (ELISA) with a positive reverse transcriptase-polymerase chain reaction (RT-PCR) for HCV-RNA confirming viremia. Also, the ELISA with a confirmatory western blot test confirmed HIV infection.

Anthropometric measurement: Weight and height were measured on a mechanical scale with a Filizola® stadiometer with a weight scale of 100 g and a height scale of 1 cm, previously calibrated. The patients were measured wearing light clothing and barefoot. Height was determined with a fixed stadiometer on the wall, with the patient standing erect and barefoot. Body mass index (BMI) was calculated using weight (in kilograms - kg) divided by the height (in meters) squared[12].

Bioelectrical impedance analysis (BIA): The BIA was performed in all patients, without previous specific preparation for fasting. Patients were evaluated in a comfortable dorsal decubitus position and relaxed, without shoes, socks, or metallic fittings. The legs were spread apart, hands open and supported on the 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, and slightly above the line of the right wrist joint, coinciding with the styloid process. The device used was Biodynamics®, model 450 (multifrequential - 800 A and 50 KhZ and tetrapolar).

To assess cellular functionality and integrity, the PA was measured, which was automatically provided by the equipment from the values of R and Xc[13]. The 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. Through BIA, the lean mass and fat mass of coinfected 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 patient data. A Fibroscan™ device – Echosens (Paris) was used and the results expressed in kilopascals (kPa). The exam was performed after a 4-hour fast. Procedures were considered reliable and included for analysis only when they presented at least 10 valid shots, a success rate of at least 60%, and an interquartile range (IQR) of liver stiffness (LS) value under

or equal to 30%. The cutoff points of 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 way to identify steatosis. The studied population was stratified into two groups considering the staging of fibrosis at TE: with (≥ F3) and without advanced fibrosis (< F3).

Statistical analysis: The normality of the data was assessed using the Kolmogorov–Smirnov test. Parametric variables were described by mean and standard deviation. The categorical variables were described by frequencies and percentages and were. Differences of PA, lean mass and fatty mass percentages between groups considering the staging of fibrosis were analyzed with the Student's t-test. Pearson's chi-square test was used to assess the association between 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 the analyses were performed using the SPSS program version 21.0.

RESULTS

Initially, of a total of 47 patients, 4 were excluded because they did not agree to perform TE or BIA, remaining 43 patients for analysis. The anthropometric and clinical characteristics are observed 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 body mass index 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). Also, using the PA cut-off points, only 2 patients (4.7%) were classified as malnourished.

All patients were taking ART, being 23 (53.5%) using schemes containing protease inhibitors (PI) and 20 (46.5%) not. There was no difference in the PA between these groups using PI or not (7.20° ± 0.70 *vs* 7.06° ± 1.09; t(37) = 0.479, P = 0.635).

Groups were compared in accordance to the fibrosis stage. The value of PA for patients with fibrosis (TE < F3; n = 16) was 7.3° ± 1.0, and for advanced fibrosis (TE ≥ F3; n = 27) was 7.0° ± 0.7 (t(41) = 0.936; p=0.355). No differences were found between the values of percentage of lean mass for patients with fibrosis and advanced fibrosis (73.9% ± 9.7 *vs* 76.5 ± 8.9; t(41) = -0.89; P = 0.378). The values of percentage of fatty mass between patients with fibrosis and advanced fibrosis were also not different (26.1% ± 9.7 *vs* 23.5% ± 8.9; t(41) = 0.886; P = 0.381). There was no correlation between the fibrosis grade and the PA and anthropometric parameters (Table 3).

The mean CAP was 241.1 ± 55.7 (Table 1). As shown in table 3, there was a significant inverse correlation between CAP and percentage of lean mass (Pearson's r^2 = -0.493, P = 0.01). Although no significant correlations between 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, there were no significant correlations (Table 4).

DISCUSSION

The present study evaluated the role of PA in HIV/HCV coinfected patients. Notably, there was no correlation between the fibrosis grade and the PA values. However, there was an inverse correlation between CAP and fatty mass, a positive correlation between PA and lean mass, and a negative correlation between PA and fatty mass, albeit this correlation was not significant when evaluated by sex and age. Even though it is not possible to stratify patients by age due to the small 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 the liver steatosis but several covariates may hamper the analysis, including non-alcoholic fatty liver disease (NAFLD), diabetes, and BMI. However, most studies using CAP evaluated small sample sizes and heterogeneous populations with variable BMI and diabetes prevalence; this may be an

explanation for the differences in proposed cutoffs [16]. The present study observed a mean value that is not considered very high (241.1 ± 55.7 - Table 1), and so we cannot confirm that CAP has demonstrated significant steatosis in the present casuistic. Meanwhile, there was a significant inverse correlation between CAP and lean mass. 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 the ART, or even the greater occurrence of steatosis in some patients with HCV to justify these findings. Nonetheless, we cannot prove the role of each parameter individually. 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, no patients were using schemes containing these ART.

Concomitantly, of the nucleoside analogue reverse transcriptase inhibitors (NRTIs) currently available in Brazil for the treatment of people living with HIV (PLHIV), zidovudine (AZT) is the main drug related to adverse events, being 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 and also prescribed in Brazil, can cause damage due to mitochondrial dysfunction, but to a lesser extent when compared to AZT[17]. Additionally, lipohypertrophy is a common feature in PLHIV treated with first-generation PI, such as indinavir, but it is not possible to prove a direct relationship of this adverse event with this class of drugs[18]. Those with greater total body fat 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 in the study by Schmidt N *et al* [20], which evaluated patients with chronic liver diseases. In this study, the PA was directly proportional to the amount of 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, Teixeira JM *et al* [21], when evaluating the PA in patients with NAFLD also showed an association of this parameter with the muscle mass of individuals, as well as an association with insulin resistance. However, they were not able to demonstrate a correlation between PA and NAFLD staging, as well as the present study when evaluating the PA and the liver fibrosis in coinfected HIV/HCV patients.

Recently, the 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 the use of PA is the possibility of 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 study amongst 539 HIV adults showed that lower BMI, lower PA, and loss of fatty mass were associated with more advanced HIV infection (CD4+ lymphocyte count <200 cells/mm^3) [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 the quality of life of patients [25]. In this context, a cross-sectional study evaluated the nutritional status and dietary intake of fifty-seven HIV/HCV coinfected patients under treatment at a public hospital in Southern Brazil. Regardless of the fact that this study did not evaluate BIA, the prevalence of malnutrition varied between the methods, from 10.5% to 56.2%, and there was a high percentage of patients with an inadequate intake of protein, fat, and energy [26].

As possible limitations of the present study, we highlight the small number of patients. As for strengths, we highlight the originality and importance of the data for early intervention in the clinical/nutritional treatment of patients co-infected with the HIV/HCV virus that guarantee a better quality of life and prognosis. In addition, this

study used an important tool, electrical bioimpedance, which does not depend on the operator. Another important and extremely relevant point is the evaluation of the liver fibrosis by elastography, a non-invasive and promising method in the diagnosis of these patients.

CONCLUSION

In conclusion, 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.

ARTICLE HIGHLIGHTS

Research background

HIV/HCV co-infected 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 the HIV virus and the 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" (eg, 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, there are no studies that assess the role of 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 coinfected HIV/HCV patients, where all patients underwent transient elastography (TE) (Fibroscan®) and BIA evaluation. The 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

43 patients were analysed. 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). 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 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=.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 co-infected with the HIV/HCV virus, such as malnutrition, is of great 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.

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