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Phase angle is associated with advanced fibrosis in patients chronically infected with hepatitis C virus

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ABSTRACT

Aims: The objective of this study was to evaluate the association of phase angle (PhA) with advanced liver fibrosis in patients chronically infected with hepatitis C virus (HCV).
Main methods: One hundred sixty consecutive patients chronically infected with HCV were treated at the Hepatitis C outpatient care setting of our hospital from April 2010 to May 2011 and prospectively evaluated. Bioelectrical impedance analysis measurements were performed during the first hospital visit. Biochemical measurements and liver biopsy data were collected from the patients' medical records and included in the analysis only if they were performed within three months of the inclusion of the patient in the study.
Key findings: One hundred sixty consecutive patients were evaluated and 25 patients were excluded. A total of 135 patients with 49.8 ± 11.4 years old were studied. Among these patients, 60% were male and the PhA was 6.5 ± 0.8°. Regarding the stage of fibrosis, patients with advanced fibrosis were older and had more insulin resistance and more inflammation compared with patients that had mild fibrosis. Logistic regression analysis revealed that PhA was a predictor of advanced fibrosis even when adjusted for gender, age, HOMA-IR, HDL-cholesterol and AST (OR: 0.227; CI 95%: 0.090–0.569; p: 0.013). The best PhA cut-off points associated with advanced fibrosis for the combined data, for females and for males were 6.43°, 5.94° and 6.72°, respectively.
Significance: PhA was predictor of advanced liver fibrosis in patients chronically infected with HCV. In the sample evaluated, for each one-degree decrease in PhA, the risk of advanced fibrosis increased more than four-fold.

1. Introduction

The hepatitis C virus (HCV) was discovered more than 20 years ago, and it is still a major public health problem [1,2]. HCV affects approximately 3% of people worldwide, and the progression to advanced liver fibrosis occurs silently and over decades. The data from the literature suggest that between 10 and 40% of patients chronically infected with HCV develop cirrhosis, and among these patients, up to 4% per year develop hepatocellular carcinoma (HCC) [3,4].

In addition, there is a lack of a gold-standard nutritional assessment method for patients with liver cirrhosis. However, several studies have suggested that bioelectrical impedance analysis (BIA) could be used to evaluate nutritional status in these patients [5,6]. BIA has been used for more than 20 years as a tool for body composition assessment. It has become popular because it is a portable, non-invasive and easy-to-use bedside method. Whole body impedance is measured mainly by the opposition of the body to an alternating current based on two components: resistance (R) and reactance (Xc) [7,8]. The phase angle (PhA) obtained from BIA is estimated by the direct ratio between R and Xc.

More recently, the use of PhA in clinical practice has increased. PhA analysis has been used as a prognostic tool in several clinical situations, such as advanced cancer, liver diseases and malnutrition [5,8,9–12]. Selberg and Selberg showed that low PhA values were associated with reduced survival in patients with liver cirrhosis [5]. In addition, in a small study, Antaki et al. determined that BIA could not distinguish between mild and advanced fibrosis in patients chronically infected with HCV [13].

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Table 1
Demographic and laboratorial data of 135 patients chronically infected with HCV.

Variable	N = 135
Age (years)	49.8 ± 11.4
Male, n (%)	81 (60)
Phase angle (°)	6.5 ± 0.8
BMI (kg/m^2)	26.5 ± 4.8
TSF (mm)	21 (13−30)
HOMA-IR	2.8 (1.7–5.1)
AST (NxULN)	1.4 (0.8–2)
ALT (NxULN)	1.2 (0.8–1.9)
GGT (NxULN)	1.6 (0.9–2.8)
TC (mg/dL)	160.5 ± 34.7
LDL (mg/dL)	85.2 ± 29.8
HDL (mg/dL)	50.6 ± 17.2
TG (mg/dL)	105.0 (179.0–142.0)

BMI: Body Mass Index; TSF: Triciptal Skinfold Thickness; HOMA-IR: Homeostasis Model of Assessment of Insulin Resistance; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; NxULN = number of times above upper limit of normal; TC = total cholesterol; TG = triglycerides; (°): degrees. The data are expressed as the mean SD± or median (lower-upper quartiles).

These studies suggest that PhA could be used as a prognostic tool in patients with HCV. Despite this finding, the association of PhA with disease severity in HCV patients requires further elucidation. Thus, the objective of this study was to evaluate the association of PhA with advanced liver fibrosis in patients chronically infected with HCV.

2. Materials and methods

2.1. Study design

This study was approved by the Ethics Committee of Botucatu Medical School. Written informed consent was obtained from all patients. One hundred sixty consecutive patients chronically infected with HCV who had attended the hepatitis C outpatient care setting of our hospital from April 2010 to May 2011 were prospectively evaluated. Inclusion criteria were treatment naïve patients or no treatment with PEGylated interferon and ribavirin for at least one year and the presence of liver biopsy. Exclusion criteria were ascites, hepatitis B virus infection, HIV infection, chronic kidney disease (CKD), heart failure (HF), carriers of electronic devices and metallic implants, physically disabled and pregnancy.

The Fisher and Belle formula was used to estimate the required sample size using the following variables: 25% prevalence of HCV infected patients who were evaluated for liver fibrosis; 95% confidence interval and 7.5% sample error. A total of 128 patients were included [14].

Bioelectrical impedance analysis measurements were performed during the first hospital visit. Biochemical tests and liver biopsy data were collected from the patients' medical records and included in the analysis only if they were performed within three months of the inclusion of the patient in the study.

2.2. Liver biopsy

Percutaneous liver biopsies were performed. Liver samples were considered adequate if there were at least eight complete portal tracts or if the fragment was larger than 1 cm in length. A single pathologist performed the histological analyses, and the Metavir scoring system was used to identify the amount of fibrosis or scarring: Score F0: no scarring; F1: minimal scarring; F2: scarring has occurred and extends outside the areas of the liver that contain blood vessels; F3: bridging fibrosis has spread and connected the areas that contain fibrosis; or F4: cirrhosis or advanced scarring of the liver [15,16].

2.3. Biochemical analysis

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), total cholesterol (TC), triglycerides (TG), HDL-cholesterol and fasting glucose were measured as previously described [17]. LDL-cholesterol was calculated using the Friedewald formula. Fasting insulin levels were measured using a chemiluminescence immunoassay. The Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR) index was calculated using the following formula: [fasting glucose (mmol/L) * fasting insulin (μU/mL) / 22.5] [18].

2.4. Bioelectrical impedance analysis

BIA was performed using tetrapolar and single-frequency equipment (Biodynamic-450, 800 μA; 50 kHz) applied to the skin using 4 adhesive electrodes on the right side of the body, with the subject lying in a supine position. All measurements were performed in the morning. The PhAs derived from the BIA were determined as previously described [19], and their values were calculated as follows: PhA = (arc tangent reactance / resistance * (180° / π)).

2.5. Statistical analysis

The data are expressed as the means ± SD or the medians (including the lower and upper quartiles). The Spearman correlation was used to evaluate the association between continuous variables with a normal distribution. Based on the liver biopsy results, the subjects were categorised into 2 groups: mild fibrosis (F0–F2) or advanced fibrosis (F3–F4). Univariate and multiple logistic regressions were used for advanced fibrosis prediction. The PhAs were included in the models as continuous independent variables and adjusted by gender, age, HOMA-IR, HDL and AST. The receiver operator characteristics (ROC) curves were used to determine the best phase angle cut-off points associated with advanced fibrosis. The data analysis was performed using Sigma Stat 3.5 for Windows (Systat Software, Inc., San Jose, CA, USA) and MedCalc (7.2). p-Values lower than 0.05 were considered statistically significant.

3. Results

One hundred sixty consecutive patients were evaluated, and 25 were excluded. The patients were assessed before nutritional evaluation, and ten patients were excluded due to uncompleted data; four due to absence of liver biopsy; eight due to the presence of ascites;

Table 2
Demographic and laboratorial data of 135 patients chronically infected with HCV according to fibrosis stage.

Variable	Mild fibrosis (F0–F2) n = 54	Advanced fibrosis (F3–F4) n = 81	p value
Age (years)	44.20 ± 11.27	53.58 ± 9.92	<0.001
Male, n(%)	31 (57.4)	50 (61.7)	0.747
PA (°)	6.81 ± 0.80	6.27 ± 0.74	<0.001
BMI (kg/m^2)	25.65 ± 4.42	27.12 ± 4.98	0.082
TSF (mm)	22.20 ± 10.46	21.74 ± 10.84	0.803
HOMA-IR	2.08 (1.38–2.93)	4.17 (2.47–6.58)	<0.001
AST (NxULN)	1.07 (0.74–1.67)	1.58 (0.82–2.09)	0.036
ALT (NxULN)	0.84 (0.58–1.23)	1.50 (0.99–2.12)	<0.001
GGT (NxULN)	1.01 (0.49–2.09)	1.81 (1.12–3.43)	<0.001
TC (mg/dL)	162.4 ± 35.3	159.2 ± 34.4	<0.001
LDL (mg/dL)	87.14 ± 29.69	83.91 ± 29.97	0.542
HDL (mg/dL)	52.69 ± 17.20	49.20 ± 17.20	0.254
TG (mg/dL)	98.0 (74.5–129)	111.5 (85.0–147.0)	0.099

PhA: phase angle; BMI: Body Mass Index; TSF: Triciptal Skinfold Thickness; HOMA-IR: Homeostasis Model of Assessment of Insulin Resistance; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; NxULN = number of times above upper limit of normal; TC = total cholesterol; TG = triglycerides; (°): degrees. The data are expressed as the mean SD± or median (lower-upper quartiles).