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Anthropometric changes caused by hepatitis C treatment with interferon and ribavirin: which patients and which measures are affected?

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Abstract

Background: Chronic hepatitis C causes chronic hepatic inflammation, which can lead to cirrhosis, terminal liver failure, and hepatocellular carcinoma. The treatment aims to achieve viral clearance, but the usage of pegylated interferon and ribavirin is linked to side effects such as severe weight loss, which can lead to complications and treatment discontinuation. The aim of this study was to investigate which anthropometric measures were more affected in patients with chronic hepatitis C during 24 weeks of treatment with pegylated interferon and ribavirin. Then, the influence of age, sex, hepatic fibrosis stage, and ribavirin doses on each measure was also evaluated.

Methods: Seventy-six patients were included and their weight, triceps skin fold thickness, arm circumference, middle-arm muscle circumference, and corrected arm muscle area were measured before and after 24 weeks of treatment. Epidemiological data and liver biopsy findings were obtained from patients' records. The sample was divided into two groups: one with advanced hepatic fibrosis and another group with mild to moderate fibrosis. Comparisons into each group were made using Wilcoxon or paired *t* tests. After that, a linear regression model was applied to estimate the anthropometric changes during the treatment according to age, sex, hepatic fibrosis stage, and ribavirin doses.

Results: The subjects suffered reductions of important anthropometric measures, mainly related to fat mass ($p < 0.001$). Some decrease of fat-free mass was also observed in subjects with advanced fibrosis. The statistic model showed that age and sex were more associated with the anthropometric changes observed.

Conclusions: In conclusion, the antiviral treatment caused loss of relevant anthropometric measures, and the model proposed was able to estimate some of them.

Keywords: Anthropometry, Hepatitis C, Weight loss, Liver fibrosis, Linear regression

Background

Hepatitis C is a worldwide problem that affects 3 to 4 million of people yearly, of which 160 million have developed the chronic disease [1]. The virus can cause complications such as cirrhosis and hepatocellular carcinoma, which are the main causes of liver transplantation [2].

Before the development of non-invasive exams, the gold-standard method for liver fibrosis staging was only liver biopsy [3] by which the METAVIR classification is used to define the stages of fibrosis and inflammation [4]. Fibrosis staging is one of the most important findings associated with outcomes in hepatitis C patients, predicting the occurrence of cirrhosis and its complications [5].

Nowadays, there are many direct-acting antivirals for hepatitis C treatment, achieving remarkable rates of viral clearance. However, until recently the disease was treated only with two drugs: pegylatyed interferon and

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ribavirin, which allowed to achieve sustained virological response in 40 to 50% of the patients [6]. Moreover, they are still used for many patients, and those who accomplish sustained virological clearance achieve a better prognosis [7].

The use of these drugs often leads to malnutrition among patients with hepatitis C submitted to antiviral treatment. Weight loss can be observed in 10–29% of those receiving pegylated interferon and ribavirin [8–10]. Moreover, weight loss at the beginning of hepatitis C treatment is associated with better rates of viral clearance during the therapy [11]. However, there is little information on how body composition can be affected, which is a relevant issue because the loss of lean mass is linked to worse outcomes in cirrhotic patients, which are a significant part of the patients who are treated [12].

Body composition assessment is a difficult task in patients with advanced hepatic diseases, because fluid imbalance is not rare among them. Actually, even some modern methods can be affected by fluid retention in these patients, such as bioimpedance analysis (BIA) and dual-energy X-ray absorptiometry [13]. Hence, anthropometry is still a valuable technique of body composition assessment in this population, because some measures are less influenced by fluid imbalance.

Therefore, the aim of this study was to evaluate which anthropometric measures are affected among hepatitis C patients receiving pegylated interferon and ribavirin, comparing the results obtained from those with advanced liver disease with patients with low grades of hepatic fibrosis. Then, a linear regression model was proposed to estimate the anthropometric changes caused by the antiviral treatment. The model was based on four variables: age, sex, hepatic fibrosis stage, and ribavirin doses.

Methods

This observational study was approved by the local Ethics Committee (protocol number 855.565) and was carried out according to the Declaration of Helsinki and its revisions. Informed consent was obtained from the subjects. The data were obtained from outpatients with chronic hepatitis C receiving pegylated interferon and ribavirin. The interferon dosages received by the subjects were those recommended by the producers.

The inclusion criteria were minimal age of 18 years old, chronic hepatitis C confirmed by polymerase chain reaction test, and liver biopsy, and the usage of antiviral therapy composed by pegylated interferon and ribavirin. The exclusion criteria were coinfection by hepatitis B or human immunodeficiency virus and the presence of any contraindications to interferon-based treatment, such as pregnancy, neoplastic disease, decompensated cirrhosis, severe heart failure, kidney disease, or psychiatric disturbances.

Sample size calculation

The Fisher and Belle formula was applied to estimate the sample size. The adopted confidence interval and precision were 95 and 10%, respectively. According to a previous study, the prevalence of weight loss of 5 kg or more in hepatitis C patients receiving interferon-based treatment was 71% [14]. Therefore, the estimated sample size to achieve the study aims was 80 subjects.

Anthropometric evaluation

Anthropometric measurement was based on weight, triceps skinfold (TSF), and arm circumference (AC). The values obtained from these measures allowed calculating middle-arm muscle circumference (MAMC) and corrected arm muscle area (CAMA). A decimal scale (Filizola®) was used to measure body weight. Arm circumference and TSF were obtained using tape measure and skinfold caliper (Lange®), respectively, as previously described [15]. Middle-arm muscle circumference and CAMA were also calculated as formerly stated [15].

Liver fibrosis staging

The liver material assessment was categorized in accordance to the METAVIR system. In this score, F0 means absence of fibrotic tissue, F1 corresponds to portal liver fibrosis, F2 is used to describe the presence of portal liver fibrosis with few septa, F3 is applied to show the presence of significant fibrosis with many portal septa, and F4 means the presence of cirrhosis with regenerative nodules [4]. Subjects with METAVIR scores between F0 and F2 composed the low stage fibrosis group, and those with F3–F4 scores comprised the advanced fibrosis group.

Statistical analysis

Anthropometric and laboratorial data of each group were registered before the therapy and 24 weeks after beginning the treatment. Parametric variables were depicted by mean and standard deviation, whereas non-parametric data were shown by median and interquartile range. The subjects were allocated according to their liver fibrosis

Table 1 Demographic data, viral genotyping, and ribavirin doses of the sample evaluated

Variable	Values ($n = 76$)
Age (years)	48.28 ± 11.01[a]
Men/women (%, *n*)	56.57%/43.42 (43/33)[b]
Advanced liver fibrosis % (*n*)	56.63% (40)[b]
Genotype 1/3% (*n*)	63.15% (48)/36.84% (28)[b]
Initial ribavirin dose (mg/kg)	17.54 ± 2.82[a]
Ribavirin dose (mg/kg) at the 12th week	18.62 ± 2.72[a]

[a]mean ± standard deviation
[b]percentile and absolute values

Table 2 Comparisons between anthropometric measures before and after 24 weeks of treatment in the low fibrosis group

Variables	Week 0	Week 24	Variation	*p*
Weight (kg)[a]	*71.72 ± 12.85*	*66.95 ± 12.83*	*−6.66 ± 5.78*	*<0.001*
AC (cm)[a]	*32.80 ± 3.29*	*31.28 ± 3.93*	*−4.58 ± 7.61*	*<0.001*
MAMC (cm)[a]	25.40 ± 3.66	25.28 ± 3.50	−0.12 ± 7.39	0.677
CAMA (cm^2)[a]	44.18 ± 13.54	43.59 ± 13.14	−0.67 ± 18.07	0.625
TSF (mm)[b]	*24.00 (16.50 – 30.25)*	*17.00 (12.75 – 26.00)*	*−19.05 (−30.00 – −3.03)*	*<0.001*

AC arm circumference, *MAMC* middle-arm muscle circumference, *CAMA* corrected arm muscle area, *TSF* triceps skinfold thickness
[a]Data showed as mean and standard deviation
[b]Data showed as median and interquartile range
The data in italics achieved the significance level

staging given by liver biopsy analysis found in their medical records. Comparisons into each group at different times were made by paired *t* test or Wilcoxon test. The significance level adopted was 5% ($p < 0.05$).

A linear regression model was applied to estimate the decrease of these measures. In this model, the influence of age, sex, liver fibrosis, and ribavirin doses was analyzed by using the Eq. (1), as follows:

$$Y = \alpha + \beta X1 + \beta X2 + \beta X3 + \beta X4 \quad (1)$$

(X1 = age; X2 = sex; X3 = hepatic fibrosis; X4 = ribavirin dose)

In this equation, the anthropometric measure (Y) is the dependent variable and is estimated by the sum of other variables: α (the point in which the line intersects the y-axis) and the sum of the independent variables multiplied by another constant β (the angular coefficient of the line).

Results

Eighty-six patients were selected to participate but 10 of them missed the nutritional appointments to make the final anthropometric measurement. Thus, 76 subjects were included, of which 56.6% (43) were men and 43.4% (33) were women. Advanced liver fibrosis (F3–F4 according to the METAVIR system) was found in 52.6% (40), whereas 47.4% (36) had low stage liver fibrosis (F0–F2 according to the same system). Most subjects had the genotype 1 virus (63.1% of the sample), and the others had the genotype 3 virus. The mean age was 48.3 years old (Table 1).

Table 2 shows comparisons between anthropometric data in the low fibrosis group before and after 24 weeks of the treatment. Only weight, arm circumference, and triceps skinfold thickness were significantly reduced by the antiviral treatment.

Table 3 shows comparisons between anthropometric data in the advanced fibrosis group before and after 24 weeks of the treatment. Similarly, weight, AC, and TSF thickness were significantly reduced by the antiviral treatment, but MAMC and CAMA were also affected in this group.

The Table 4 shows the results obtained by the appliance of the linear regression model for estimating the variations of each anthropometric measure. The model was tested by residual analysis (using the Shapiro-Wilk test) and by the adjusted coefficient of determination.

Figure 1 presents the comparison between the TSF thickness variations in men and women. The results showed that the decrease of this measure was more significant in women, as also showed by the Table 4.

Discussion

Hepatitis C treatment with pegylated interferon and ribavirin was a landmark against this disease, allowing achieving better virological response rates and avoiding the development of liver cirrhosis and its complications, such as liver cancer. However, many patients faced side effects that preclude the maintenance of interferon-based

Table 3 Comparisons between anthropometric measures before and after 24 weeks of treatment in the advanced fibrosis group

Variables	Week 0	Week 24	Variation	*p*
Weight (kg)[a]	*75.40 ± 16.39*	*69.59 ± 15.86*	*−7.66 ± 5.64*	*<0.001*
AC (cm)[b]	*33.00 (31.50 – 35.00)*	*30.50 (28.00 – 33.87)*	*−6.74 ± 7.02*	*<0.001*
MAMC (cm)[a]	*26.55 ± 3.08*	*25.81 ± 3.00*	*−2.46 ± 7.66*	*0.028*
CAMA (cm^2)[a]	*48.08 ± 12.32*	*44.99 ± 11.75*	*−4.91 ± 17.80*	*0.024*
TSF (mm)[a]	*20.78 ± 10.54*	*15.97 ± 8.30*	*−19.26 ± 26.81*	*<0.001*

AC arm circumference, *MAMC* middle-arm muscle circumference, *CAMA* corrected arm muscle area, *TSF* triceps skinfold
[a]Data showed as mean and standard deviation
[b]Data showed as median and interquartile range
The data in italics achieved the significance level

Table 4 Linear regression model appliance to estimate the variations of each anthropometric measure according to age, sex, hepatic fibrosis stage, and ribavirin doses during 24 weeks of treatment. The effectiveness of this model was tested by residual analysis and by the adjusted coefficient of determination.

Dependent variable: weight				
	β	95% CI		*p*
Advanced liver fibrosis stage (reference = low fibrosis stage)	−0.48	−2.53	1.58	0.647
Male sex (reference = female)	0.06	−1.88	2.01	0.949
Age (years)	*−0.08*	*−0.15*	*0.00*	*0.048*
Initial ribavirin dose (mg/kg)	−0.08	−0.28	0.12	0.415
Residual analysis: p (SW) = 0.349; diagnostic analysis: plot residuals x predict aleatory behavior; R^2 = 61%				
Dependent variable: arm circumference				
	β	95% CI		*p*
Advanced liver fibrosis stage (reference = low fibrosis stage)	−0.30	−1.43	0.84	0.605
Male sex (reference = female)	0.27	−0.80	1.35	0.614
Age (years)	*−0.05*	*−0.10*	*−0.01*	*0.010*
Initial ribavirin dose (mg/kg)	0.04	−0.07	0.15	0.431
Residual analysis: p (SW) = 0.333; diagnostic analysis: plot residuals x predict aleatory behavior; R^2 = 41%				
Dependent variable: middle-arm muscle circumference				
	β	95% CI		*p*
Advanced liver fibrosis stage (reference = low fibrosis stage)	−0.25	−2.77	2.27	0.843
Male sex (reference = female)	−0.42	−2.81	1.96	0.724
Age (years)	*−0.14*	*−0.23*	*−0.05*	*0.003*
Initial ribavirin dose (mg/kg)	0.06	−0.18	0.31	0.620
Residual analysis: p (SW) = 0.485; diagnostic analysis: plot residuals x predict sistematic behavior; R^2 = 59%				
Dependent variable: corrected arm muscle area				
	β	95% CI		*p*
Advanced liver fibrosis stage (reference = low fibrosis stage)	−2.70	−7.84	2.43	0.297
Male sex (reference = female)	0.34	−4.51	5.19	0.888
Age (years)	−0.09	−0.27	0.10	0.342
Initial ribavirin dose (mg/kg)	0.25	−0.24	0.75	0.310
Residual analysis: p (SW) = 0.212; diagnostic analysis: plot residuals x predict aleatory behavior; R^2 = 0%				
Dependent variable:triceps skinfold	β	95% CI		p
Advanced liver fibrosis stage (reference = low fibrosis stage)	0.09	−2.58	2.75	0.948
Male sex (reference = female)	*2.96*	*0.44*	*5.48*	*0.022*
Age (years)	*−0.10*	*−0.20*	*0.00*	*0.043*
Initial ribavirin dose (mg/kg)	−0.08	−0.34	0.18	0.528
Residual analysis: p (SW) = 0.242; diagnostic analysis: plot residuals x predict aleatory behavior; R^2 = 43%				

β regression coefficient, *CI* confidence interval, R^2 adjusted coefficient of determination, *SW* Shapiro-Wilk test. The analysis of the model effectiveness is shown in italic for each dependent variable
Dependent variable= triceps skinfold thickness
The data in italics achieved the significance level

treatments. Infections, fever, dry mouth, depression, anxiety, cough, alopecia, anemia, and weight loss are part of the undesirable effects of these two drugs. Frequently, one or more of these side effects are found in patients receiving these medications, and they are even worse than the prior symptoms caused by the virus, making difficult to assure patients adherence to the treatment and impairing the viral clearance. Of note, the risk of developing severe symptoms is higher in patients with advanced hepatic fibrosis.

Health professionals already expect the occurrence of weight loss and anemia in patients receiving interferon-based regimens. Symptomatic anemia often leads to ribavirin dosing reductions or the need of erythropoietin

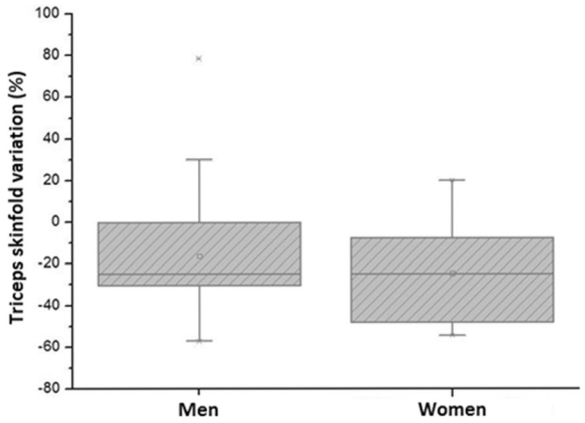

Fig. 1 Triceps skinfold thickness variations. Legend: box plot representing the triceps skinfold thickness variations in men and women throughout the antiviral treatment. Median, 1° and 3° quartiles, mean (square), minimum, and maximum values (multiplication sign) are shown.

prescription [16]. Weight loss can be also worked around by interferon and ribavirin reductions, but sometimes it is not enough to keep the patient receiving an effective therapy. Since weight loss is a known indication of interferon effectiveness, some authors have postulated that it can be a predictor of virological clearance [17]. However, which body components are more committed is still an unanswered question.

The first aim of this work was to identify if those who had advanced hepatic fibrosis could have more severe reductions in anthropometric measures associated to lean mass, such as MAMC and CAMA. The study had some limitations, such as the sample size and the fact that cirrhotic patients can be already stricken by complications that could lead to reductions in food ingestion. It could be a reason to a more severe impact of the treatment in this group.

The mean age was 48 years, the majority of subjects had the genotype 1 virus, and their liver fibrosis was categorized as F3–F4 according to the METAVIR system. Kershenobich et al. (2011) showed that in Brazil the disease is more common in people aging more than 30 years old, achieving the highest prevalence in those between 50 and 59 years old. The genotype 1 was the most prevalent virus in the country (64.9%), followed by the genotype 3 [18]. Thus, the epidemiological data of the sample was in agreement with prior studies. None of the patients was drinking alcohol, which was prohibited during the antiviral treatment.

Since the stage of hepatic fibrosis is one of the most important predictors of virological response to treatments with or without interferon and ribavirin [19], the sample was split in two groups with low or advanced liver fibrosis. Even in the group with low stage of liver fibrosis, reductions of anthropometric measures were significant. Worth mentioning, MAMC and CAMA were lowered in the group with advanced fibrosis. Prior studies have already shown that in cases of liver cirrhosis MAMC has a clear impact on outcomes, as well as TSF thickness, which had a prominent reduction in both groups [12, 14].

Whereas TSF thickness is more related to fat depots, AC, MAMC, and CAMA are also related to lean mass. The results show that fat mass was more affected by the antiviral treatment, but the analysis suggest that some patients were also stricken by lean mass reduction, such as those with advanced liver fibrosis. Gowda et al. showed that even in patients with low stage of liver fibrosis the loss of lean mass measured by AC and MAMC is relevant, proposing that both measures should be part of body composition assessment of these patients, combined to others such as height and weight [20].

Even so, when compared to age and sex, the role of hepatic fibrosis was not so significant. It became clear that age was relevant for the variation of all the anthropometric measures evaluated, showing that old patients lost more weight, AC, MAMC, CAMA, and TSF thickness than the younger ones. In addition, female patients had a more significant decrease in TSF thickness than males. Some prior studies with cirrhotic patients showed that MAMC is more affected in men than in women, whereas TSF thickness is expressively more reduced in women compared to men [13, 21]. Since the sample had a significant amount of subjects with advanced liver fibrosis and TSF thickness was more affected than MAMC, the results were compatible with these prior studies. If the sample was only composed by cirrhotic patients, it would be possible that MAMC reductions were more significant in men.

The linear regression model showed an interesting profile to estimate the variations of some anthropometric measures, such as weight, AC, and TSF thickness. In contrast, the analysis of this model showed that it was not so reliable to estimate the loss of MAMC or CAMA. In fact, the decrease in weight, AC, and TSF thickness were more significant in all subjects, regardless of age, sex, or hepatic fibrosis staging, making possible to estimate variations in this model. On the other hand, Tables 2 and 3 showed that the variations of MAMC and CAMA were very dissimilar between patients with different stages of liver fibrosis, making possible that other variables could have to be considered. For practical purposes, the model could be applied only with age and sex as the main variables because their role on anthropometric variations had a more predictable impact.

Conclusions

In conclusion, the results of this study showed that 24 weeks of antiviral treatment with pegylated interferon and ribavirin lead to severe reductions of weight and

anthropometric measures that are more associated to fat mass. Even so, patients with advanced liver disease also had decreases in measures associated to lean mass. Furthermore, the anthropometric changes registered were more influenced by age and sex than by liver fibrosis stage or ribavirin doses, and the model proposed in this study could be useful to estimate the loss of some important measures caused by the antiviral treatment.

Abbreviations

AC: Arm circumference; β: Regression coefficient; BIA: Bioimpedance analysis; CI: Confidence interval; CAMA: Corrected arm muscle area; MAMC: Middle-arm muscle circumference; R2: Adjusted coefficient of determination; SW: Shapiro-Wilk test; TSF: Triceps skinfold

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LFA and MSD conducted the patients, performed the analysis, and drafted the final article. LAAS and TBL drafted the final article. HRCN performed the statistical analysis and proposed the model applied. SARP, GFS, XQ, and FGR drafted and corrected the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the local Ethics Committee (protocol number 855.565) and was carried out according to the Declaration of Helsinki and its revisions. Informed consent was obtained from the subjects prior to their inclusion in the study.

Consent for publication

This manuscript does not contain individual person's data in any form.

Competing interests

The authors declare that they have no competing interests related to this work.

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