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ASSOCIATION OF THE NUTRITIONAL PROFILE WITH HISTOLOGICAL FINDINGS OF PATIENTS WITH GENOTYPE 1 CHRONIC HEPATITIS C INFECTION

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ABSTRACT - ***Background*** **-** Different factors are responsible for the progression of hepatic fibrosis in chronic infection with hepatitis C virus, but the role of nutritional factors in the progression of the disease is not clearly defined. This study aimed to evaluate the nutritional status and dietary profile among patients with chronic hepatitis C who were candidates for treatment and its association with histopathological features. ***Methods*** **-** A crossectional study was conducted on treatment-naïve patients with chronic hepatitis C genotype 1, between 2011 and 2013. The following assessments were performed before treatment: liver biopsy, anthropometric measurements and qualitative/quantitative analysis of food intake. ***Results*** **-** Seventy patients were studied. The majority of patients was classified as obese (34%) or overweight (20%) according to body mass index [BMI] and as at risk for cardiovascular diseases by waist circumference (79%). Unhealthy food intake was presented by 59% according to qualitative parameters and several patients showed an insufficient intake of calories (59%), excessive intake of protein (36%) and of saturated fat (63%), according to quantitative analysis. With respect to histology, 68% presented activity grade ≥2, 65% had steatosis and 25% exhibited fibrosis stage >2. Comparative analysis between anthropometric parameters and histological features showed that elevated waist circumference was the only variable associated to hepatic steatosis (P=0.05). There was no association between qualitative and quantitative food intake parameters with histological findings. ***Conclusion*** **-** In this study, most of the patients with hepatitis C presented inadequate qualitative food intake and excessive consumption of saturated fat; in addition, excess of abdominal fat was associated to hepatic steatosis. Therefore, nutritional guidance should be implemented prior to treatment in patients with chronic hepatitis C, in order to avoid nutritional disorders and negative impact on the management of patients.

HEADINGS - Liver cirrhosis. Chronic hepatitis C. Fatty liver. Nutritional status. Eating.

INTRODUCTION

Infection with hepatitis C virus (HCV) is a leading cause of chronic diseases in the world. Estimated data from the World Health Organization (WHO) show that about 170 million people are infected with HCV, corresponding to 3% of the world population[26, 30, 32, 40]. In Brazil, this number varies according to region, with 1.38% of the population carrying the virus[25]

Nutritional evaluation is very important in chronic liver diseases, since inadequate nutritional parameters can be the result of advanced stages of disease or can even influence the progression of the disease. In cirrhosis, protein-energy malnutrition, when present[7], is the result of metabolic alterations caused by the disease, as well as of a reduction in food intake related to factors such as anorexia, nausea, vomiting, non-palatable salt-restricted diets for the control of ascites, and dysgeusia caused by zinc and magnesium deficiency, among others[21, 24].

The nutrition status is also involved in the progression of liver disease in patients with chronic hepatitis C, especially, obesity that plays an unfavorable role in the progression of the disease as a consequence of hepatic steatosis[11, 23].

The prevalence of obesity has increased expressively, affecting about 500 million people worldwide[36-38]. In Brazil, the prevalence of obesity

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in the adult population is 17,4%[31]. This increase is, among other factors, associated with physical inactivity and with dietary changes that have occurred over the last two decades, with the adoption of a diet rich in saturated fats, sugars and sodium and low in fibers[4]. Data from Brazilian Survey on Family Budgets conducted between 2008 and 2009 showed that carbohydrate intake decreased while the consumption of saturated and monounsaturated fats and proteins of animal origin increased[5].

Although studies evaluating nutritional factors in patients with chronic hepatitis C are scarce, it is reasonable to suggest that adequate quantitative and qualitative food intake and also adequate body weight are particularly important for this population. Therefore, the objective of the present study was to evaluate nutritional status and dietary profile and its association with histopathological features in patients with chronic hepatitis C who were candidates for treatment.

METHODS

Patients and study design

A study was conducted on treatment-naive patients with chronic hepatitis C genotype 1 candidates to antiviral treatment, seen between 2011 and 2013 at the Hepatitis Center of the Department of Clinical Gastroenterology, Federal University of São Paulo-Brazil.

Treatment-naive patients infected with genotype 1 older than 18 years, who had an adequate biopsy for analysis and had not undergone previous nutritional intervention, were included in the study. Patients with decompensated cirrhosis, co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), alcoholics, presence of chronic kidney disease or in the absense of liver biopsy, all were excluded from the analysis.

Data were collected after approval of the study by the Research Ethics Committee Federal University of São Paulo-Brazil.

Serological and virological analysis

Anti-HCV antibodies were detected by a third-generation enzyme immunoassay (Abbott Laboratories, Germany) using antigens against the core, NS3 and NS4 regions.

Virological analysis for the detection of HCV RNA was performed by qualitative and quantitative real-time polymerase chain reaction (PCR), with detection limits of 50 and 200 IU/mL, respectively[8, 9]. Genomic sequencing of the 5'-untranslated region (5'UTR) of the PCR products was used to identify HCV genotypes[28].

Histopathological analysis

Histological analysis was used to evaluate activity grade and fibrosis stage, according to the METAVIR[2] system. Hepatic steatosis was also evaluated. For comparative analysis, patients were divided according to inflammatory activity (A) into grades 0-1 vs 2-3 and according to fibrosis (F) into grades 0-2 vs 3-4.

Assessment of nutritional status

Nutritional assessment was divided into anthropometric evaluation and qualitative/quantitative analysis of food intake.

Anthropometric evaluation

The body mass index (BMI) was evaluated as proposed by the World Health Organization for adults (normal range: 18.5–24.99 kg/m²)[35] and by the Survey on Health, Well-Being and Aging in Latin America and the Caribbean of the Pan American Health Organization for older adults ≥60 years (normal range: 23-28 kg/m²)[18].

Waist circumference (WC, expressed in cm) was measured with the patient standing, using a tape measure at the midpoint between the anteroposterior iliac crest and the last rib. Patients were classified according to WHO criteria[34] as being at risk for cardiovascular diseases (men ≥94 cm and women ≥80 cm).

Arm circumference (AC, expressed in cm) was measured with a tape measure on the right arm in a relaxed position, at the midpoint between the acromion and humero-radial joint. Triceps (TST) and subscapular (SST) skinfold thickness was measured with a Lange® caliper and was expressed in mm.

Arm muscle circumference (AMC) was calculated using the formulae proposed by Frisancho (1990)[13]: AMC = AC – (TST x 0.314), whereas AC = arm circumference and TST = triceps skinfold thickness.

Arm muscle area (AMA) was calculated using the following formulae: $AMC^2/12.57$. Corrected arm muscle area (CAMA) was calculated from AMA, subtracting a value of 10 cm^2 for men and of 6.5 cm^2 for women, which corresponds to the area occupied by bone.

The classification of AC, TST, SST, AMC and CAMA was based on the values proposed by Frisancho[13]. For comparison with the histological parameters, all anthropometric variables were categorized into adequate and inadequate (patients above and below the normal range).

Qualitative and quantitative analysis of food intake

Food intake was evaluated before treatment using a 24-hour food recall applied by a nutritionist in weekly visits over a period of one month and calculated mean intake from these data for comparison. The 24-hour recall method was used because of the characteristics of the population, which mainly consisted of illiterate adults with difficulties in filling out the 3-day food diary that was applied at the beginning of the study. Multiple 24-hour recalls are a reasonable choice according to other authors[27]. Qualitative analysis was performed according to the Healthy Eating Index, proposed by Fisberg et al.[12] composed by 10 components. For comparison, diet was classified as healthy (score ≥65 points) or unhealthy (score <64 points).

The quantitative content of dietary calories, carbohydrates, proteins and fat was analyzed using the Nutriquanti® software. The intake of macronutrients was classified as adequate when it was within the recommended intake levels, or insufficient and excessive; it was based on criteria proposed by DRI, 2002/2005[15]. Proteins were also classified as gram per kilogram weight according to FNB/NCR[22]; cholesterol

and saturated fat was classified according to Brazilian Society of Cardiology (2007)[29]. For comparision with the histological parameters, all nutrients were divided into two groups: adequate, when they were within the recommended intake levels, or inadequate when they were insufficient or excessive.

Statistical analysis

Numerical variables were expressed as the mean and standard deviation. The results were compared by the chi-squared or Fisher's exact test, when appropriate. A level of significance of 0.05 (a = 5%) was adopted. All analyses were performed with the SPSS v.16 program.

RESULTS

Seventy patients with genotype 1 chronic hepatitis C, who were candidates for treatment were studied. The mean age of the patients was 49±1.22 years and there was a predominance (53%) of women. A liver biopsy was available for 69 patients. Advanced fibrosis (F3-4), more intense activity grade (A2-3) and hepatic steatosis were seen, respectively in 25%, 68% and 65% of patients.

The mean of BMI was 27±3.93 kg/m². Overweight and obesity were seen respectively in 34% and 20% of the patients. The risk for cardiovascular diseases, predicted by WC, was 79% among the patients studied. Anthropometric measures are shown in Table 1.

Qualitative analysis of food intake showed that only 41% of the patients presented a healthy intake and 59% an unhealthy intake. Patients were adequate according to intake of lipids (69%), cholesterol (61%) and carbohydrates (71%). However, several patients had an insufficient intake of calories (59%) and excessive intake of protein (36%) and saturated fat (63%). Data regarding food intake are shown in Table 2.

Comparative analysis between anthropometric parameters and histological features showed that the only histological variable associated to anthropometric parameters was hepatic steatosis, that was associated to WC (P=0.05) (Table 3). There was no association between qualitative and quantitative food intake with histological parameters (Table 4).

TABLE 1. Characteristics of patients with genotype 1 chronic hepatitis C

Characteristics	n=70
Age (years; mean)	49 ± 1
Women (%)	37 (53%)
Anthropometric parameters	
BMI (kg/m²); obesity/overweight	34%/20%
Abnormal Waist circumference	79%
Abnormal Arm circumference	20%
Abnormal Triceps skinfold	21%
Abnormal Subscapular skinfold	18%
Abnormal AMC	27%
Abnormal CAMA	30%
Histopathological features	
Fibrosis >2	24%
Inflammatory activity ≥2	68%
Steatosis	65%

BMI: body mass index; AMC: arm muscle circumference; CAMA: corrected arm muscle area.

TABLE 2. Food intake parameters of patients with genotype 1 chronic hepatitis C

Nutrients	Normal (%)	Insufficient (%)	Excess (%)
Calories (kcal mean/day)	30	59	11
Carbohydrates (%)	71	21	7
Proteins (g/kg)	33	31	36
Lipids (%)	69	4	27
Saturated fat (%)	37	-	63
Monounsaturated fat (%)	99	-	1
Cholesterol (%)	61	-	39

DISCUSSION

Assessment of the nutritional status of candidates for treatment of chronic hepatitis C is important since nutritional factors can influence disease progression, improve quality of life, and contribute to the response to treatment.

BMI is a parameter commonly used to assess the nutritional status of the population. In the present study, most patients with hepatitis C presented excess weight based on this parameter. Similar results have been reported in the study of Berzigotti et al. (2011)[3], in which 40% of the patients were overweight and 30% were obese.

Some studies suggest triceps and subscapular skinfolds to be more accurate indicators of subcutaneous fat in patients with chronic liver diseases, as well as the use of arm circumference and arm muscular circumference to evaluate lean mass[14, 17, 19, 29]. In fact, the majority of the patients of this study were normal based on those parameters. A discussion about the best method of evaluation of nutritional aspects in patients with chronic liver disease has been conducted for a long time[16, 20]. In patients with decompensated liver disease as ascites, the BMI measure would be inappropriate since it

TABLE 3. Comparison between anthropometric parameters and histopathological features

Histopathological features	Fibrosis			Activity grade			Steatosis		
	F0-2	F3-4		A0-1	A2-3		Absent	Present	
Anthropometric parameters*	n (%)	n (%)	*P*	n (%)	n (%)	*P*	n (%)	n (%)	*P*
BMI	30 (58)	7 (43)	0.3	10 (47)	25 (58)	0.4	10 (47)	25 (57%)	0.4
WC	43 (83)	11 (68)	0.2	15 (71)	37 (84)	0.2	16 (67)	38 (86)	**0.05**
AC	8 (15)	5 (31)	0.1	4 (19)	9 (20)	0.8	3 (12)	10 (23)	0.3
AMC	9 (22)	6 (37)	0.2	5 (29)	9 (26)	0.7	4 (19)	11 (32)	0.2
CAMA	11 (27)	6 (40)	0.3	6 (35)	10 (28)	0.6	6 (29)	11 (32)	0.7
TST	11 (27)	1 (7)	0.09	4 (23)	8 (23)	0.9	4 (19)	8 (23)	0.6
SST	9 (22)	1 (7)	0.1	2 (11)	8 (23)	0.3	2 (9)	8 (23)	0.1

* Anthropometric parameters described as above and below of normal range. BMI: body mass index; WC: waist circumference; AC: arm circumference; AMC: arm muscle circumference; CAMA: corrected arm muscle area; TST: triceps skinfold thickness; SST: subscapular skinfold thickness.

TABLE 4. Comparison between quality and quantitative food intake parameters and histopathological features

Histopathological features	Fibrosis			Inflammatory activity			Steatosis		
	F0-2	F3-4	*P*	A0-1	A2-3	*P*	Absent	Present	*P*
Food intake	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Calories*	35 (67)	13 (76)	0.4	13 (62)	32 (72)	0.3	18 (75)	29 (66)	0.4
Carbohydrates*	25 (48)	10 (58)	0.4	11 (52)	21 (48)	0.7	14 (58)	20 (45)	0.3
Proteins*	30 (58)	11 (64)	0.6	11 (52)	26 (59)	0.6	16 (66)	24 (54)	0.3
Lipids*	21 (40)	8 (47)	0.6	11 (52)	16 (36)	0.2	7 (29)	21 (47)	0.1
Saturated fat*	36 (69)	8 (47)	0.09	14 (66)	28 (63)	0.8	16 (66)	28 (63)	0.8
Cholesterol*	19 (36)	9 (53)	0.2	9 (43)	16 (36)	0.6	12 (50)	16 (36)	0.2
Unhealthy food intake	33 (63)	8 (50)	0.3	15 (71)	24 (55)	0.1	9 (43)	30 (68)	0.07

* Inadequate intake (excessive plus insufficient).

cannot differentiate lean mass and fat mass and therefore should not be used alone in a nutritional assessment[10, 33]. However, in the present study no patient presented ascites, which may suggest that BMI was a good measure in this population; but it should not be used alone in a nutritional assessment because it not differentiate lean mass and fat mass[16].

Another measure showing abnormality in this study was waist circumference. Most patients had central obesity and were, therefore, at high risk for cardiovascular diseases according to WC. Visceral fat is known to be associated with insulin resistance in non-diabetic patients, obesity, type 2 diabetes, and nonalcoholic hepatic steatosis[1]. In fact, hepatic steatosis was observed in the majority of the present patients (65%), and was associated to WC. The association between steatosis and HCV is well defined and it is believed that, in addition to viral factors, metabolic factors play a role in this condition[1, 6, 25, 26]. It has been demonstrated that obesity and steatosis are factors related to lower response to treatment. This is another reason to emphasize the recommendation to control nutritional disorders in hepatits C patients.

With respect to diet quality, food intake was unhealthy in most of the patients studied (59%), with the observation of excessive consumption of saturated fat. Similar findings have been reported in population studies on healthy subjects [5] and in studies of patients with hepatitis C[8].

Quantitative analysis of food intake showed inadequate consumption of calories, proteins and saturated fat. Yasutake et al.[39] observed excessive consumption of calories in 72.4% of patients with compensated cirrhosis, in contrast to the present study in which most patients presented deficient calorie intake. On the other hand, a similar intake of calories and lipids as that seen in the present study has been reported by Carreira and Pereira[8] for patients with hepatitis C not receiving antiviral treatment. These findings suggest that

eating habits are not adequately controlled in this population and that effective nutrition monitoring is necessary to prevent nutritional disorders.

In conclusion, most of the patients with hepatitis C in this study presented inadequate qualitative and quantitative food intake and excess of abdominal fat, which was associated to hepatic steatosis. Therefore, nutritional advisement should be implemented in this population in an attempt to prevent nutritional disorders and to reduce the accumulation of visceral fat, with a consequent positive influence on disease progression, quality of life and treatment response.

Authors' contributions

All the authors participated sufficiently in the intellectual content, analysis of data and in the review of the writing this article.

Santis e Silva VA, Ferraz MLG, Carvalho-Filho R, Lanzoni VP, Silva AEB, Silva ISS. Associação do estado nutricional com achados histológicos em pacientes com hepatite C genótipo 1. Arq Gastroenterol. 2015,52(4):xxx.

RESUMO - ***Contexto*** **-** Diferentes fatores são responsáveis pela progressão da fibrose na infecção crônica pelo vírus da hepatite C, mas o papel dos fatores nutricionais na progressão da doença não está definido. Este estudo teve como objetivo avaliar o estado nutricional e o perfil dietético de pacientes com hepatite C crônica candidatos a tratamento e sua associação com achados histopatológicos. ***Métodos*** **-** Foi conduzido um estudo transversal em pacientes com hepatite C crônica genótipo 1 virgens de tratamento, entre 2011 e 2013. Foram analisados, antes do tratamento, os seguintes aspectos: biópsia hepática, medidas antropométricas e análise qualitativa e quantitativa do consumo alimentar. ***Resultados*** **-** Setenta pacientes foram estudados. A maioria dos pacientes apresentava obesidade (34%) ou sobrepeso (20%) de acordo com índice de massa corporal e risco para doenças cardiovasculares de acordo com a circunferência da cintura elevada (79%). Na análise qualitativa do consumo alimentar, 59% apresentavam uma dieta inadequada. Conforme análise quantitativa, 59% tinham consumo insuficiente de calorias, 36% consumo excessivo de proteínas e 63% consumo excessivo de gorduras saturadas. Com relação à histologia, 68% apresentavam grau de atividade inflamatória ≥2, 65% mostraram esteatose hepática e 25% possuíam grau de fibrose >2. Na análise comparativa entre as medidas antropométricas e achados histológicos, somente a circunferência da cintura elevada mostrou associação com esteatose hepática (P=0,05). Não houve associação entre consumo alimentar qualitativo e quantitativo com parâmetros histológicos. ***Conclusão*** **-** A maioria dos pacientes apresentava consumo alimentar inadequado de acordo com parâmetros qualitativos e consumo excessivo de gordura saturada, além de excesso de gordura abdominal, que esteve associada à esteatose hepática. Portanto, aconselhamento nutricional deveria ser implementado em pacientes candidatos a tratamento para hepatite C crônica visando evitar distúrbios nutricionais que podem impactar negativamente no manejo dos pacientes.

DESCRITORES - Cirrose hepática. Hepatite C crônica. Fígado gorduroso. Estado nutricional. Ingestão de alimentos.

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