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# RESEARCH PAPER

# Dietary total antioxidant capacity is positively associated with muscular strength in cirrhotic outpatients: a cross-sectional study

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# Keywords

antioxidants, cirrhosis, hand-grip strength, liver, muscular strength.

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# Abstract

**Background:** Cirrhosis is the end-stage of progressive fibrosis, in which oxidative stress and inflammation-related pathways can modulate the cellular and tissue events involved in the pathogenesis of liver fibrosis. Dietary intake of antioxidants has been suggested to protect against oxidative damage and related clinical complications. The present study aimed to investigate the potential association of the dietary total antioxidant capacity (dTAC) with anthropometric, functional and biochemical markers, as well as the severity of the disease, in cirrhotic outpatients.

Methods: Sixty-two outpatients (38 men and 24 women) with a mean (SD) age of 59.1 (9.9) years were evaluated. Dietary TAC was estimated from a food frequency questionnaire. Aetiology and severity of liver cirrhosis, life-style characteristics, occurrence of comorbidities and oedema, and anthropometric, functional and biochemical markers were all assessed.

**Results:** Cirrhotic outpatients with higher dTAC also had higher values of the hand-grip strength (P = 0.029) and arm muscle area (P = 0.027). After adjusting by sex, age, smoking and alcohol intake, the addition of 1 mmol day<sup>-1</sup> of dTAC contributed to increase 0.552 kg f<sup>-1</sup> in hand-grip strength (P < 0.05). The addition of one mmol day<sup>-1</sup> of dTAC contributed to an arm muscle area increase 0.565 cm<sup>2</sup> (P < 0.05) on average.

**Conclusions:** The dTAC was positively associated with hand-grip strength and arm muscle area in cirrhotic outpatients. The implications of the present study are important in clinical practice because a diet rich in antioxidants may be an ally in the control of excessive reactive oxygen species production in cirrhotic outpatients with repercussion on muscle mass and strength.

# Introduction

Cirrhosis is the end-stage of progressive fibrosis, in which oxidative stress and inflammation-related pathways can modulate the cellular and tissue events involved in the pathogenesis of liver fibrosis <sup>(1)</sup>. In this sense, oxidative stress causes liver damage by changes in DNA, proteins

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and lipids, as well as modulation of biological pathways associated with gene transcription, protein expression, cellular apoptosis and activation of hepatic stellate cells <sup>(2)</sup>. Moreover, inflammation is an essential component of the immune response and manifests as infiltration of inflammatory cells, mainly in the liver, in the fight against invasion of pathogens. The persistence of inflammatory

stimuli and oxidative stress can lead to cellular damage and lipid accumulation, associated with an increased risk of steatohepatitis, fibrosis and cancer  $^{(2-4)}$ .

In turn, several studies have demonstrated the role of diet in modulate inflammation <sup>(5,6)</sup> and oxidative stress <sup>(7)</sup>. Foods and bioactive compounds (such as coffee, green tea, resveratrol, curcumin, quercetin, silymarin, naringenin) have been considered beneficial to liver diseases <sup>(8–11)</sup>.

In this context, the total antioxidant capacity of foods, which describes the combined ability of dietary antioxidants to eliminate preformed free radicals, has been suggested as a tool to investigate the health effects of antioxidants in mixed diets (12-14). Our previous study involving non-alcoholic steatohepatitis (NASH) showed a negative association between dietary total antioxidant capacity (dTAC) and hepatic injury (ballooning) (15), although investigations of dTAC in cirrhotic outpatients have yet not been reported in the literature yet. Frequently patients with cirrhosis present alterations in specific aspects of nutritional status, such as micronutrient deficiencies and/or global malnutrition (e.g. as a result of poor nutritional intake). The provision of the necessary nutrients must compensate for these existing deficiencies (16-18). Thus, the present study aimed to investigate the potential association of dTAC with anthropometric, functional and biochemical markers, as well as cirrhosis severity, in outpatients.

# Materials and methods

#### Study design

This cross-sectional study was conducted in the Hepatology Service of the University Hospital at the Federal University of Juiz de Fora, Minas Gerais, Brazil. Approximately 78 outpatients with cirrhosis are attended monthly. The study was conducted from May to December 2017. The inclusion criteria were outpatients with liver cirrhosis over 18 years of age, of both sexes, who were followed up on an outpatient basis during the study period. Patients with cancer, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis), previous renal insufficiency and presence of hepatic encephalopathy or other physical or mental condition that compromised the interview process and/or anthropometric and functional evaluation were not included. Patients who underwent liver transplantation or who were awaiting transplantation were also excluded. The subjects were taken into the study after they provided their written informed consent. This study was conducted in accordance with the Declaration of Helsinki. All procedures involving human subjects/patients were approved by the Ethics Committee of the Federal University of Juiz de Fora (protocol number 1.129.516/2015) and all participants provided written informed consent.

# Data collection

Information on age, sex, alcohol, smoking and food consumption was obtained from face-to-face interviews. On the same day of the interview, the anthropometric and functional data were collected.

#### Cirrhosis severity

Aetiology and cirrhosis severity, presence of comorbidities, oedema and biochemical data were obtained from medical records. The diagnosis of cirrhosis was based on clinical, laboratory, imaging and/or histopathological evaluation, according to the routine of the Hepatology Service. Child-Turcotte-Pugh (CTP) was used to assess the cirrhosis severity (19,20), where variables such as ascites, encephalopathy, time of prothrombin, bilirubin and albumin were graduated in scores of 1 and 3 points each. The final sum made it possible to classify the patients in degrees of severity A or B. It should be emphasised that, as a result of the inclusion criteria, no patients were classified as severity grade C because the occurrence of hepatic encephalopathy, common in this class of patients, is associated with some degree of mental confusion and this factor could compromise the completion of the questionnaires.

# **Biochemical measurements**

The biochemical data originated from medical records. As a routine of the Hepatology Service, blood collection was performed after a 12-h fast. The blood was separated by centrifugation and immediately analysed in the Laboratory of Clinical Analyses of the University Hospital. Hemoglobin, leukocytes, platelets, mean corpuscular volume, mean corpuscular hemoglobin concentration, aspartate aminotransferase, alanine amino transferase, alkaline phosphatase, gammaglutamyl transferase, urea, creatinine, potassium, albumin, and total bilirubin were determined using standard laboratory methods in an autoanalyser (model CT600i; Wiener Lab, Rosario, Argentina).

# Anthropometric and functional evaluation

The arm circumference (AC) was measured at the midpoint between the acromial process and the olecranon process, using a flexible and inelastic measuring tape. Biceps skinfold (BSF) and triceps skinfold (TSF) were measured using an adipometer (Lange Skinfold Caliper; Lange, Houston, TX, USA). The arm muscle area (AMA) was calculated from the values obtained from TSF and AC.

## L. de Freitas Lima et al.

Functional assessment was performed using hand-grip strength (HSG) and adductor pollicis muscle thickness (APMT). The measurement of HSG was performed using a Jamar hydraulic hand dynamometer (Sammons Preston Rolyan, Chicago, IL, USA). Patients remained seated with their elbows supported and flexed at a 90° angle, performing the greatest possible strength with the dominant hand. Three trials were performed with a 1-min rest interval between the measurements and the largest of the three was used in the analysis. The APMT measurement was performed with the forearm and the hand resting on the knee. The adductor muscle was pinched at the apex of an imaginary triangle formed by the extension of the thumb and forefinger.

# Estimation of dietary total antioxidant capacity

The habitual diet was obtained through a food frequency questionnaire previously validated by Mannato et al. (21). Daily food consumption was estimated as frequency versus portion size for each item consumed. All food questionnaires were analysed by the same nutritionist. For the determination of dTAC, a previously published database (22) was used, combined with the supporting literature (23-30), using the ferric reducing ability of plasma (FRAP) method with a calibration curve made with ferrous sulfate, for the TAC determination of food. Intake evaluation was performed using a standard spreadsheet developed in EXCEL (Microsoft Corp., Redmond, WA, USA) by adding individual TAC values from the FRAP assay of each food and expressed as TAC in mmol day $^{-1}$ . To assign a TAC value to foods not available in the articles and in the database, botanically similar food data were used. When TAC values for cooked foods were not available, TAC levels of fresh foods were considered for estimation purposes. Total dTAC was the sum of dTAC of all consumed foods.

# Statistical analysis

The normality of the data was determined by the Shapiro–Wilk test. Comparisons of continuous variables were conducted using the parametric Student's *t*-test or nonparametric Mann–Whitney *U* test. Categorical variables were compared using the chi-squared test. To determine the influence of dTAC, outpatients were divided into two groups according to the median dTAC value (10.5 mmol day<sup>-1</sup>): lower and higher/equal dTAC. A multiple linear regression model was used to verify the association of dTAC with HSG and AMA measurements. This model was controlled by sex, age, smoking status and alcohol intake. A scatter plot was built to illustrate

the association. The contribution of each food group to the dTAC was calculated as the ratio of the antioxidant intake from that food group to the total intake from all foods. Data are presented as the mean (SD), or median and minimum and maximum. Categorical variables are expressed as relative (%) and absolute (*n*) frequencies. All statistical analyses were performed using SPSS, version 20.0 (IBM Corp., Armonk, NY, USA). P < 0.05 was considered statistically significant.

# Results

During the study period, 458 outpatients were followed up at the Hepatology Service. Of these patients, 111 were not cirrhotic. Among 347 patients with cirrhosis, 50 did not agree to participate in the study, 37 were not able to answer the questionnaires, 44 had hepatocellular carcinoma, 31 were awaiting liver transplantation and 123 were excluded for various reasons (incomplete medical records, presence of others cancers, autoimmune diseases and chronic kidney disease). Thus, 62 outpatients were included in our analyses. These outpatients had a mean (SD) age of 59.1 (9.9) years and a demonstrated a predominance of males 61.3% (n = 38).

Among the cirrhosis patients, the majority (37.1%; n = 23) were of alcoholic origin, followed by hepatitis C infection (33.9%; n = 21), NASH (20.9%; n = 13) and other causes such as autoimmune hepatitis or undefined causes (8.1%; n = 5). The most common comorbidities observed in these outpatients were hypertension (53.2%; n = 33), diabetes (45.2%; n = 28), coronary diseases (16.1%; n = 10) and hypothyroidism (12.9%; n = 8). The CTP classification revealed that 45 outpatients (72.6%) were class A and 17 (27.4%) were class B. The presence of oedema (ascites and lower limb oedema) could be considered to be a complication of cirrhosis and was present in 37.1% (n = 23) of the outpatients evaluated.

Regarding the characteristics related to the lifestyle of the outpatients, 16.1% (n = 10) were smokers. Alcohol consumption was present in 8.1% (n = 5) of outpatients, even after receiving medical advice to abolish alcohol consumption because of its deleterious role in liver function. The anthropometric/functional data, biochemical markers and cirrhosis severity (Tables 1–3) were compared from the median value of the dTAC (10.5 mmol day<sup>-1</sup>). Outpatients who had a higher dTAC also presented higher values for HSG (P = 0.029) and AMA (P = 0.027). The other anthropometric/functional, biochemical and disease severity measures did not differ between the groups.

When we performed a multiple linear regression, the adjusted model indicated that the addition of one mmol day<sup>-1</sup> of dTAC contributed to increase 0.552 kg f<sup>-1</sup> in HSG (P < 0.05). The model adjusted by dTAC, sex and

	dTAC < 10.5 mmol day <sup>-1</sup> ( <i>n</i> = 31)	dTAC $\geq$ 10.5 mmol day <sup>-1</sup> ( $n = 31$ )	P-values
AC (cm)	30.8 (4.8)	32.8 (3.3)	0.053
BSF (mm)	29.3 (12.6)	31.4 (10.2)	0.488
TSF (mm)	20.5 (11.7)	22.2 (10.4)	0.530
AMA (cm <sup>2</sup> )	36.8 (8.8)	42.3 (10.2)	0.027
HSG (kg f <sup>-1</sup> )	19.0 (5.0-42.0)	31.0 (10.0–48.0)	0.029*
APMT (mm)	10.4 (4.0–24)	11.0 (4.0–19.0)	0.657*

 Table 1
 Anthropometric and functional data according to dietary total antioxidant capacity (dTAC) in cirrhotic outpatients

 Table 2
 Biochemical markers according to dietary total antioxidant capacity (dTAC) in cirrhotic

outpatients

L. de Freitas Lima et al.

AC, arm circumference; AMA, arm muscle area; APMT, adductor pollicis muscle thickness; BSF, biceps skinfold; HSG, hand-grip strength; TSF, triceps skinfold. Continuous variables are given as the mean (SD) or median (minimum–maximum). Student's *t*-test or Mann–Whitney *U* test (\*). P < 0.05 was considered statistically signifi-

cant (bold values). r < 0.05 was considered statistically significant

(n = 31)	$dIAC \ge 10.5 \text{ mmol day}^{+}$ ( <i>n</i> = 31)	P-values
13.2 (1.9)	13.1 (1.9)	0.999
5184.3 (2124.6)	4729.4 (2152.8)	0.414
113994.8 (63287.9)	96478.7 (40964.0)	0.201
94.2 (8.7)	91.4 (7.2)	0.196
33.0 (28.0–35.0)	33.0 (28–38.0)	0.482*
36.0 (21.0–140.0)	35.0 (18.0–202.0)	0.762*
30.6 (21.2)	38.0 (35.5)	0.352
247.0 (164.5)	241.8 (196.3)	0.914
85.0 (22.0–481.0)	59.0 (17.0–711.0)	0.555*
34.0 (17.0)	39.6 (31.7)	0.482
1.0 (0.0–2.0)	1.0 (0.0–5.0)	0.407*
4.0 (4.0–6.0)	4.0 (4.0-6.0)	0.542*
4.0 (2.0–4.0)	4.0 (3.0–5.0)	0.175*
1.0 (0.0–5.0)	1.0 (0.0–5.0)	0.824*
	dIAC < 10.5 mmol day $(n = 31)$ 13.2 (1.9) 5184.3 (2124.6) 113994.8 (63287.9) 94.2 (8.7) 33.0 (28.0–35.0) 36.0 (21.0–140.0) 30.6 (21.2) 247.0 (164.5) 85.0 (22.0–481.0) 34.0 (17.0) 1.0 (0.0–2.0) 4.0 (4.0–6.0) 4.0 (2.0–4.0) 1.0 (0.0–5.0)	dIAC < 10.5 mmol daydIAC $\geq$ 10.5 mmol day $(n = 31)$ $(n = 31)$ 13.2 (1.9)13.1 (1.9)5184.3 (2124.6)4729.4 (2152.8)113994.8 (63287.9)96478.7 (40964.0)94.2 (8.7)91.4 (7.2)33.0 (28.0–35.0)33.0 (28–38.0)36.0 (21.0–140.0)35.0 (18.0–202.0)30.6 (21.2)38.0 (35.5)247.0 (164.5)241.8 (196.3)85.0 (22.0–481.0)59.0 (17.0–711.0)34.0 (17.0)39.6 (31.7)1.0 (0.0–2.0)1.0 (0.0–5.0)4.0 (4.0–6.0)4.0 (3.0–5.0)1.0 (0.0–5.0)1.0 (0.0–5.0)

ALT, alanine amino transferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Continuous variables are given as the mean (SD) or median (minimum-maximum).

Student's t-test or Mann–Whitney U test (\*). P < 0.05 was considered statistically significant.

Variable	dTAC < 10.5 mmol dia <sup>-1</sup> ( $n = 31$ )	$dTAC \ge 10.5 mmol$ $dia^{-1} (n = 31)$	P-value*
СТР А	66.7% (21)	77.4% (24)	0.393
CTP B	32.3% (10)	22.6% (7)	

CTP, Child-Turcotte-Pugh.

Nominal variables are given as the number of outpatients with the characteristic of interest.

\*Chi-squared test. P < 0.05 was considered statistically significant.

age is able to explain 52.7% of the HSG variation. There was no significant difference between smokers and nonsmokers, as well as among those who drank alcoholic or non-alcoholic beverages. With regard to AMA, the

4

addition of one mmol day<sup>-1</sup> of dTAC contributed to an increase of 0.565 cm<sup>2</sup> in this nutritional marker (P < 0.05). The model adjusted by dTAC and sex is able to explain 36.3% of AMA variation, regardless of age, smoking habit or drinking alcoholic beverage (Fig. 1).

Coffee and tea, fruits and fruit juices, vegetables, and legumes were the major food or food groups of dTAC (49.5%, 20.4%, 4.1% and 3.3%, respectively).

# Discussion

The intake of dietary antioxidants appears to protect against oxidative damage and related clinical complications <sup>(13,15,31,32)</sup>. To our knowledge, this is the first study to evaluate dTAC in cirrhotic outpatients, with the main finding being a positive association between dTAC and muscular strength.



Figure 1 Association between observed values of hand-grip strength (a) and arm muscle area (b) versus predicted values by the adjusted model (dietary total antioxidant capacity, age, sex, smoking, and alcohol intake) in cirrhotic outpatients.

Underlying the pathogenesis of chronic disease is the state of oxidative stress <sup>(33)</sup>. Oxidative stress is also present in skeletal muscle wasting <sup>(34)</sup>, being a complicating factor of liver diseases and ageing <sup>(35,36)</sup>. The main oxidant types are reactive oxygen species (ROS). Oxidative stress has been functionally linked to muscle wasting through ubiquitin–proteasome system activation, where increased ROS activates proteasome-dependent protein degradation. Another consequence of oxidative stress is oxidative damage generated in the cell, as indicated by protein and lipid oxidation <sup>(35)</sup>. Indeed, studies have confirmed increased markers of oxidative stress in sarcopaenic individuals <sup>(37,38)</sup>.

Sarcopaenia is a syndrome characterised by progressive and widespread loss of skeletal muscle mass, strength and function (36). The potential impact of sarcopaenia is great, considering that muscle tissue is the most abundant in the human body (39). In cirrhosis, the presence of sarcopaenia should be assessed because sarcopaenia is a strong predictor of mortality and morbidity (16,17). The prevalence of sarcopaenia in patients with hepatic cirrhosis ranges from 40% to 70% (40,41) and is favoured by the combination of cofactors such as advanced age associated with interference of the degree of liver disease in the nutritional status of this population (42). In addition, chronic alcohol consumption is also associated with sarcopaenia because ROS generated during ethanol metabolism can damage many tissues, including liver and skeletal muscle (33). Studies confirm that patients with liver disease as a result of chronic alcohol abuse have a marked inflammation and an oxidative imbalance with elevated malondialdehyde (oxidative stress marker) and reduced and oxidised glutathione (antioxidant function) (43,44). It should be

noted that, in the present study, the main cause of cirrhosis was alcohol consumption.

Patients with cirrhosis may develop simultaneous loss of skeletal muscle and gain of adipose tissue, culminating in a condition called 'sarcopaenic obesity' (17). Still, muscle depletion is characterised by both reduced muscle size and increased proportion of intermuscular and intramuscular fat, termed myosteatosis (45). Given the great difficulty of evaluating the nutritional status of cirrhotic patients in clinical practice, in the present study, we chose not to evaluate body mass index. More than 37% of the outpatients presented oedema, which could mask the body weight and overestimate the excess weight. However, the BSF and TSF values, which reflect subcutaneous adipose tissue, were above the expected value for the 50th percentile (46). It should be noted that these two skin folds were not influenced by water retention in our outpatients (ascites and oedema of the lower limbs).

The diagnostic criteria for sarcopaenia in cirrhosis have not been firmly established so far. Currently, an approach based on mass assessment (dual X-ray absorptiometry or computed tomography), muscular strength and/or function (gait speed or chair stand test) can be recommended. The reduction of muscular strength can be evaluated by HSG (general muscular strength indicator, with cut-off points: <20 kg f<sup>-1</sup> (women) and <30 kg f<sup>-1</sup> (men) <sup>(36)</sup>.

Our data demonstrate a relationship between dTAC versus AMA and HSG in cirrhotic outpatients, suggesting a possible role of antioxidant intake in muscle mass and strength. Indeed, studies have shown the relationship between antioxidants and muscle mass. Kim *et al.* <sup>(47)</sup>, for example, observed a beneficial effect on muscle mass and physical function measured by the ability to walk in elderly sarcopaenic women from catechin

supplementation (strong antioxidant action) associated with physical exercise. Chung et al. (48) found that consumption of at least three cups of coffee day<sup>-1</sup> was associated with a lower prevalence of sarcopaenia in elderly men. Another study demonstrated an anabolic role of resveratrol in exercise-induced adaptations in older men and women <sup>(49)</sup>. Thus, to reduce the production of free radicals and to attenuate oxidative stress with possible impact on muscle mass and strength, it is recommended to increase the consumption of foods with higher antioxidant capacity, such as coffee, tea, fruits, vegetables and legumes (13,29,50,51). In the present study, coffee/tea and fruits were the main contributors to dTAC, which is not surprising considering our previous results involving patients with NASH (15) and those of Torres and Farah (52) with the Brazilian diet. Because foods contain many different types of antioxidants (vitamins, carotenoids, polyphenols and other bioactive compounds as yet unknown), TAC has been suggested as a more appropriate tool for investigating the relationship between the antioxidant potential of the diet and the diseases/clinical complications related to oxidative stress. It is important to note that current guidelines on nutrition in liver disease reinforce the need for additional data on the efficacy of antioxidant use in patients with liver disease.

Changes in muscle function/strength may be detected earlier than changes in laboratory parameters <sup>(53)</sup>, which may partly explain the lack of a relationship of dTAC with biochemical data and severity of liver disease.

A strength of the present study was the inclusion of more homogeneous cirrhotic outpatients (all were CTP class A or B only and were also in outpatient follow-up). Limitations of the present study include a cross-sectional design that does not allow the evaluation of temporal relationships and the absence of imaging tests and tests to verify muscle function with respect to evaluating sarcopaenia.

In conclusion, the dTAC is associated with better parameters related to muscle mass and strength in cirrhotic outpatients, which may be a result of its assumed role with respect to reducing ROS or improving the quality of the diet in general. More studies are needed to address the consumption of foods with antioxidant potential over the long term to confirm our findings and to evaluate the benefit of food interventions in cirrhosis, as well as its clinical complications.

# Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

L. de Freitas Lima et al.

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LFL, APBM, FFG and LEVVCF contributed to the conception and design of the study. LFL and DGO contributed to the data collection. HHMF participated in the evaluation of the dietary total antioxidant capacity. GL and DGO carried out data analysis and interpretation. LFL and APBM performed the first draft of the article. All authors critically reviewed the manuscript and approved the final version submitted for publication.

# **Transparency declaration**

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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L. de Freitas Lima et al.

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