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SAMANTA CATHERINE FERREIRA

EFFECT OF BETA-HYDROXY-BETA-METHYLBUTYRATE (HMB) SUPPLEMENTATION WITH NUTRITIONAL COUNSELLING IN PATIENTS ON THE WAITING LIST FOR LIVER TRANSPLANTATION

Belo Horizonte

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Tese apresentada ao Programa de Pós-Graduação em Ciência de Alimentos da Faculdade de Farmácia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Doutora em Ciência de Alimentos.

Orientadora: Profª. Drª Lucilene Rezende Anastácio

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SAMANTA CATHERINE FERREIRA

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Profa. Dra. Valesca Dall'Alba - UFRGS
Profa. Dra. Lívia Garcia Ferreira - UFLA
Prof. Dr. Francisco Guilherme Cancela e Penna - HC/UFMG

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DEDICATION, *DEDICATÓRIA*

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“Certifica-te de que és um fator de soma na vida das pessoas de quem participa."

Cícero

ABSTRACT

Objective: The primary aim of this study was to evaluate the effects of HMB supplementation with nutritional counseling on anthropometric measures of muscle mass, strength, functionality, and quality of life in patients waiting for liver transplantation (LTx). The secondary aim was to evaluate food intake during 12 weeks of nutritional follow-up and assess factors independently associated with the difference between caloric and protein (end-beginning) intake in patients on the waiting list for liver transplantation LTx.

Methods: Double-blind, randomized study with supplementation of 3.0g of HMB or active control with nutritional counseling for 12 weeks in patients >18y, evaluated at five moments. Body composition and anthropometric data (resistance, reactance, phase angle, weight, body mass index (BMI), arm circumference (AC), arm muscle area, and adductor pollicis muscle thickness) were collected. Muscle strength was assessed using dynamometry, physical function was evaluated using the frailty index (FI), and quality of life was also evaluated. Dietary guidelines for patients with cirrhosis were used to prescribe the nutritional plan (35kcal/kg; 1.5g/kg dry weight for protein; other nutrients according to Dietary Recommended Allowances - DRIs; late evening snack) and to evaluate the nutritional goals (30kcal/kg; 1.2g/kg dry weight for protein). Food intake was assessed and quantified using 24-hour recall and food records in six moments: Baseline, week 0 (W0), week 2 (W2), week 4 (W4), week 8 (W8), and week 12 (W12). Data were evaluated using SPSS 22.0. The modified intention-to-treat principle was adopted. Differences between weeks and supplements were performed using the Generalized Estimating Equation (GEE) test. Dietetic consumption was evaluated through the weeks using the paired t-test or Wilcoxon test. Linear regression models were performed to identify factors independently associated with the difference between caloric (kcal/kg) and protein intake (g/kg) in W12- Baseline. The level of significance was 5%.

Results: Forty-seven patients were enrolled [HMB: 23; active control: 24]. There was a significant difference in both groups for AC (p=0.03), dynamometry (p=0.02), and FI (p=0.01). There was an increase in dynamometry between T0 and T12 in both groups [HMB (Δdynamometry: 10.1±16.4%; p<0.05); active control (Δdynamometry: 23.0±70.3%; p<0.05)]. The AC increased in both groups between T0 and T4 [HMB (ΔAC: 0.9±2.8%; p<0.05); active control (ΔAC: 1.6±3.6%; p<0.05)] and between T0 and T12 [HMB (ΔAC: 3.2±6.7%; p<0.05); active control (ΔAC: 2.1±6.6%; p<0.05)]. The FI decreased in both groups, between T0 and T4 [HMB (ΔFI: -4.2±6.9%; p<0.05); active control (ΔFI: -3.2±9.6%; p<0.05)] and between T0 and T12 [HMB (ΔFI: -4.4±11.2%; p<0.05); active control (ΔFI: -5.5±11.3%; p<0.05)]. The other variables did not change (p>0.05). About food intake, only 25.5%(n=12) of patients consumed more than 30kcal/kg, and 36.2% (n=17) more than 1.2g/kg of protein in 12 weeks of follow-up. The mean energy intake at baseline was 1782±784kcal (27.6±13.2kcal/kg), and in W12, 1695±413kcal (26.9±7.7kcal/kg; p>0.05), without difference between times. The mean of protein intake in baseline was 70.4±38.4g [1.0 (0.2 – 3.1g/kg)] and 67.5±22.7g [1.0 (0.3 – 2.5 g/kg)] in W12. The total protein intake g/kg increased between week W0 [63.4±29.8g; 0.8 (0.2 – 2.2g/kg)] and W8 [72.0±28.0g; 1.0 (0.4 – 2.6g/kg; p=0.026; p=0.032, respectively]. The consumption of cholesterol, calcium, phosphorus, magnesium, iron, and niacin increased (p<0.05) during follow-up, as well as the consumption of the leguminous; roots and tubers; dairy; and meat, poultry, and fish groups through the time

($p<0.05$). The presence of ascites, subjective global assessment classification, frailty index classification, short physical performance battery score, systemic symptoms, and emotional function were independently associated with the caloric intake difference between W12-Baseline ($p<0.05$). Diabetes mellitus, subjective global assessment, poor performance, fatigue, systemic symptoms, and emotional function were independently associated with the difference in protein intake between W12-Baseline ($p<0.05$).

Conclusion: The nutritional intervention with supplementation with HMB or active control in patients on the liver transplant waiting list improved arm circumference and dynamometry and reduced the frailty index in both groups. Concerning food intake, patients on the waiting list for LTx modestly improved food intake during nutritional follow-up, but only a few patients could reach the nutritional recommendations of current guidelines. Some clinical and nutritional variables independently influenced caloric and proteic intake between W12-Baseline weeks.

KEYWORDS: liver transplantation, skeletal muscle, muscle strength, quality of life, HMB, supplementation, malnutrition, dietary intake, nutritional intervention.

RESUMO

Objetivo: O objetivo primário deste estudo foi avaliar os efeitos da suplementação de beta-hidroxi-beta-metilbutirato (HMB) com intervenção nutricional por 12 semanas na massa muscular, força, funcionalidade e qualidade de vida em pacientes na lista de espera para o transplante hepático (TxH). O objetivo secundário foi avaliar a ingestão alimentar durante 12 semanas de intervenção nutricional e avaliar os fatores independentemente associados à diferença entre ingestão calórica e proteica (final-início) em pacientes em lista de espera para transplante hepático.

Métodos: Estudo duplo-mascarado, randomizado e prospectivo com suplementação de 3,0g de HMB ou controle (3,0g de maltodextrina) por 12 semanas em pacientes com idade superior a 18 anos em lista de espera para o TxH. Os participantes foram avaliados em cinco momentos: Avaliação inicial; Semana 0 (T0), início da intervenção; Semana 4 (T4); Semana 8 (T8) e após 12 semanas (T12). Todos os pacientes receberam intervenção nutricional de acordo com as diretrizes para doença hepática crônica avançada. Dados sociodemográficos, clínicos e de estilo de vida foram coletados. A composição corporal e os dados antropométricos [resistência, reatância, ângulo de fase, peso, índice de massa corporal (IMC), circunferência do braço (CB), área muscular do braço e espessura do músculo adutor do polegar] foram coletados. A força muscular foi avaliada por meio da dinamometria e a função muscular pelo índice de fragilidade (IF). A qualidade de vida foi avaliada. Recomendações dietéticas para pacientes com cirrose foram usadas para prescrever o plano alimentar (35kcal/kg; 1,5g/kg de peso seco de proteína; outros nutrientes de acordo com *Dietary Recommendation Allowances* - DRIs; lanche noturno) e avaliar as metas nutricionais (30kcal/ kg; 1,2g/kg de peso seco de proteína). A ingestão alimentar foi avaliada e quantificada por meio do recordatório de 24 horas e registro alimentar de 3 dias em seis momentos: Baseline, Semana 0 (S0), Semana 2 (S2), Semana 4 (S4), Semana 8 (S8) e Semana 12 (S12). Os dados foram avaliados no SPSS 22.0. As diferenças entre semanas e suplementos foram realizadas usando o teste de Equação de Estimativa Generalizada (GEE). O consumo dietético foi avaliado ao longo das semanas por meio do teste t pareado ou teste de Wilcoxon. Modelos de regressão linear foram realizados para identificar fatores independentemente associados com a diferença entre ingestão calórica (kcal/kg) e de proteína (g/kg) na S12-Baseline. O nível de significância foi de 5%.

Resultados: Quarenta e sete pacientes foram incluídos [HMB: 23; controle ativo: 24]. Houve diferença significativa em ambos os grupos para CB (p=0,03), dinamometria (p=0,02) e IF (p=0,01). Houve aumento da dinamometria entre T0 e T12 em ambos os grupos [HMB (Δdinamometria: 10,1±16,4%; p<0,05); controle ativo (Δdinamometria: 23,0±70,3%; p<0,05)]. A CB aumentou em ambos os grupos entre T0 e T4 [HMB (ΔCB: 0,9±2,8%; p<0,05); controle ativo (ΔCB: 1,6±3,6%; p<0,05)] e entre T0 e T12 [HMB (ΔCB: 3,2±6,7%; p<0,05); controle ativo (ΔCB: 2,1±6,6%; p<0,05)]. O IF diminuiu em ambos os grupos, entre T0 e T4 [HMB (ΔIF: -4,2±6,9%; p<0,05); controle ativo (ΔIF: -3,2±9,6%; p<0,05)] e entre T0 e T12 [HMB (ΔIF: -4,4±11,2%; p<0,05); controle ativo (ΔIF: -5,5±11,3%; p<0,05)]. As demais variáveis não se alteraram (p>0,05). Sobre a ingestão alimentar, apenas 25,5%(n=12) dos pacientes consumiram mais de 30kcal/kg, e 36,2% (n=17) mais de 1,2g/kg de proteína em 12 semanas de acompanhamento. A ingestão energética média no Baseline foi de 1782±784kcal (27,6±13,2kcal/kg), e na S12, 1695±413kcal (26,9±7,7kcal/kg; p>0,05), sem diferença entre os tempos. A média de ingestão de proteína no início do estudo foi de 70,4±38,4g [1,0 (0,2 – 3,1g/kg)] e 67,5±22,7g [1,0 (0,3 – 2,5 g/kg)] na S12. A ingestão total de proteína g/kg aumentou entre a semana S0 [63,4±29,8g; 0,8 (0,2 – 2,2g/kg)] e S8 [72,0±28,0g; 1,0 (0,4 – 2,6g/kg; p=0,026; p=0,032, respectivamente). O

consumo de colesterol, cálcio, fósforo, magnésio, ferro e niacina aumentou ($p<0,05$) durante o acompanhamento, assim como o consumo de leguminosas, raízes e tubérculos, laticínios e grupos das carnes, aves e peixes ao longo do tempo ($p<0,05$). A presença de ascite, a classificação da avaliação global subjetiva, a classificação do índice de fragilidade, a pontuação do teste de desempenho físico, sintomas sistêmicos e função emocional foram associados independentemente com a diferença de ingestão calórica entre S12-Baseline ($p<0,05$). Diabetes mellitus, a classificação da avaliação global subjetiva, baixo desempenho, fadiga, sintomas sistêmicos e função emocional foram associados independentemente com a diferença na ingestão de proteínas entre S12-Baseline ($p<0,05$).

Conclusão: A intervenção nutricional com suplementação com HMB ou controle ativo em pacientes em lista de espera para o transplante hepático melhorou a circunferência do braço e a dinamometria e reduziu o índice de fragilidade em ambos os grupos. Em relação à ingestão alimentar, os pacientes em lista de espera para o transplante hepático melhoraram sutilmente a ingestão alimentar durante o acompanhamento nutricional, mas apenas alguns pacientes conseguiram atingir as recomendações nutricionais das diretrizes atuais. Algumas variáveis clínicas e nutricionais influenciaram independentemente a ingestão calórica e proteica nas semanas S12-Baseline.

PALAVRAS-CHAVE: transplante hepático, massa muscular, força muscular, HMB, suplementação, intervenção dietética, desnutrição, ingestão alimentar, lanche noturno.

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24hR: 24-hour Recall

2-FRs: 2-Day Food Records

3-FRs: 3-Day Food Records

AIDS: Acquired Immunodeficiency Syndrome

AMA: Arm Muscle Area

AMC: Arm Muscle Circumference

APMT: Adductor Pollicis Muscle Thickness

ATP: Adenosine Triphosphate

BCAA: Branched Chain Amino Acids

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

CC: Calf Circumference

Cm: Centimeter

COVID-19: Coronavirus Disease of 2019

DXA: Dual-energy X-ray Absorptiometry

EI: Energy Intake

EPA: Eicosapentaenoic Acid

FFQ: Food Consumption Frequency Questionnaire

g: Grams

GEE: Generalized Estimating Equations

GH: Growth Hormone

HCC: Hepatocellular Carcinoma

HMB: Beta-Hydroxy-Beta-Methylbutyrate

HMB-Ca: Calcium Beta-Hydroxy-Beta-Methylbutyrate

HMB-FA: Free-Acid Beta-Hydroxy-Beta-Methylbutyrate

HMG-CoA: 3-Hydroxy-3-Methylglutaryl-CoA Reductase

IGF-1: Insulin-Like Growth Factor-1

INR: Prothrombin Activity Time

Kg: Kilogram

LTx: Liver Transplantation

M: Meters

M^2: Square Meter

MELD: Model for End-Stage Liver Disease

MELD-Na: Model for End-Stage Liver Disease-Sodium

mm: Millimeter

mTOR: Mammalian Target of Rapamycin

NASH: Non-Alcoholic Steatohepatitis

PCR: Polymerase Chain Reaction

PSMS: Spray Mass Spectrometry Analysis

R: Resistance

s: Seconds

SD: Standard Deviation

SGA: Subjective Global Assessment

SNT: Sistema Nacional de Transplantes National Transplant System

PA: Phase Angle

SPSS: Statistical Package for Social Sciences

SUS: Sistema Único de Saúde Health Unic System

T0: Week 0

T4: Week 4

T8: Week 8

T12: Week 12

TBCA: Tabela Brasileira de Composição de Alimentos Brazilian Food Composition Table

TCLE: Termo de Consentimento Livre e Esclarecido Term of Free and Informed Consent

TCV: Total Caloric Value

TSF: Triceps Skinfold

UFMG: Universidade Federal de Minas Gerais Federal University of Minas Gerais

USDA: United States Department of Agriculture

Vs.: Versus

W0: Week 0

W2: Week 2

W4: Week 4

W8: Week 8

W12: Week 12

Xc: Reactance

INDEX

1 INTRODUCTION

Chronic liver disease has a great impact on the patient's nutritional status at all stages of evolution, whether in the pre-, peri- and postoperative period of liver transplantation (ANASTÁCIO et al., 2011; GIUSTO et al., 2014; HAMMAD; KAIDO; UEMOTO, 2015; DEUTRICH AYDOS et al., 2016). Before transplantation, most patients on the waiting list present malnourishment (FERREIRA et al., 2009; HUISMAN et al., 2011; LIM et al., 2015). Among the causes of malnutrition are inadequate food intake, impaired digestion and absorption, and altered metabolism (MERLI et al., 2019).

As a consequence, loss of muscle mass is one of the outcomes commonly seen in patients with end-stage liver disease (PLANK; RUSSELL, 2015; VAN VUGT et al., 2016; BELARMINO et al., 2017). The presence of sarcopenia generates negative clinical outcomes, such as reduced preoperative survival rate (MONTANO-LOZA et al., 2015; VAN VUGT et al., 2018; KALAFATELI et al., 2015) and post-liver transplantation, increased occurrence of complications such as sepsis (MONTANO–LOZA et al., 2012), increased length of hospital stay, increased risk of perioperative bacterial infections (MONTANO-LOZA et al., 2014) and is associated with increased risk of mortality (MONTANO–LOZA et al., 2012; TANDON et al., 2012; DURAND et al., 2014).

The main strategies used to improve nutritional status and, consequently, muscle mass include supply of nutritional supplementation of energy and nutrients (especially proteins), increased levels of physical activity, and hormone therapy (DASARATHY, 2012, 2014, 2016; WILLIAMS; MCKENNA, 2012; SINCLAIR et al., 2016).

However, the evidence needs to be more consistent regarding the contribution of these practices to the patient's clinical improvement (ANTAR; WONG; GHALI, 2012; KORETZ; AVENELL; LIPMAN, 2012; NEY et al., 2013). A review study on therapeutic approaches in liver cirrhosis showed that nutritional supplementation was not consistently effective, as molecular and metabolic abnormalities underlying liver disease persist or were not influenced by these treatments (DASARATHY; MERLI, 2016).

In addition, nutritional goals and adherence to interventions are still great challenges to be faced. Some studies have evaluated food intake in patients on the waiting list for liver transplantation. Most of them reveal calories and nutrients intake below the recommendation (FERREIRA et al., 2013; NEY et al., 2015; MARR et al., 2017; PALMESE et al., 2019). Rates of inadequate energy intake range from 76% to 94% among these patients (FERREIRA et al., 2013; NEY et al., 2015; PALMESE et al., 2019).

More recently, beta-hydroxy-beta-methylbutyrate (HMB) supplementation has been investigated for its potential role in improving muscle quality (WU et al., 2015). HMB has been shown to have an anti-catabolic effect, increase protein synthesis, attenuate proteolysis, increase muscle mass, and decrease muscle damage in various health and disease conditions (BEAR et al., 2019; HOLLAND et al., 2022; PRADO et al., 2022). Bear et al. (BEAR et al., 2019), in a systematic review and meta-analysis, concluded that HMB increased muscle mass and strength in patients with a variety of clinical conditions (BEAR et al., 2019), but those results were not always confirmed (DEUTZ et al., 2013; FITSCHEN et al., 2017). In a study of patients with compensated cirrhosis, improvement in muscle mass (measured by ultrasound) and performance (measured by the chair test) was observed compared to the placebo group after 12 weeks of supplementation with 3.0g HMB (LATTANZI et al., 2021). However, in a more recent clinical trial with 43 patients with cirrhosis and malnourishment with prior clinical decompensation, an enriched oral nutritional supplementation with 1.5g HMB twice daily for 12 weeks showed no increase in anthropometric measurements or handgrip strength (ESPINA et al., 2022). As the efficacy of HMB supplementation has not been consistently established in all clinical settings, the positive responses to HMB supplementation still need to be investigated. Also, the effect of HMB supplementation has not been investigated in patients on the waiting list for liver transplantation.

2 OBJECTIVES

2.1 General objective

To evaluate the effect of beta-hydroxy-beta-methylbutyrate (HMB) supplementation vs. active control along with nutritional intervention for 12 weeks in patients on the waiting list for liver transplantation.

2.2 Specific objectives

2.2.1. To evaluate the effects of HMB supplementation on anthropometric muscle mass markers, strength, functionality, and quality of life (CHAPTER I).

2.2.1.1. To evaluate and compare muscle mass markers (arm circumference, arm muscle area, and adductor pollicis muscle thickness) before, during, and after nutritional intervention with HMB and active control supplementation.

2.2.1.2. To measure and compare muscle strength (dynamometry) before, during and after nutritional intervention with HMB and active control supplementation.

2.2.1.3. To evaluate and compare muscle function (Short Physical Performance Battery questionnaire and frailty index) before, during, and after nutritional intervention with HMB and active control supplementation.

2.2.1.4. To evaluate and compare the quality of life before, during, and after nutritional intervention with HMB and active control supplementation.

2.2.2. To assess food intake during 12 weeks of nutritional monitoring and to assess the factors independently associated with the difference between caloric and protein intake (end-start) in patients on the waiting list for liver transplantation (CHAPTER II).

2.2.2.1. To prescribe a nutritional guidance and eating plan based on applied surveys and current recommendations for liver cirrhosis.

2.2.2.2. To assess and calculate the calories, macronutrients, and micronutrients intake during 12 weeks of nutritional monitoring.

2.2.2.3. To assess and calculate the food group's intake during 12 weeks of nutritional monitoring.

2.2.2.4. To assess and calculate the late evening meal intake during 12 weeks of nutritional monitoring.

2.2.2.5. To assess the adequacy of nutritional intake in comparison to nutritional recommendations for patients with advanced liver cirrhosis.

2.2.2.6. To assess the adherence to nutritional interventions on food intake.

2.2.2.7. To assess factors associated with energy and protein intake at each time of evaluation as well as the independent factors related to the difference of these consumptions between the final (W12) and baseline times.

3 LITERATURE REVIEW

3.1 Liver transplantation

Liver transplantation (LTx) is considered to be the most effective treatment modality for patients with end-stage liver disease (METIN; ŞIMŞEK; GÜRAKAR, 2020), with continued improvement in post-transplant survival and quality of life (LEGAZ et al., 2016). The operation should be considered when the predicted survival exceeds the life expectancy of the individual with the disease or when there is a significant increase in quality of life after the procedure (RUSSO; FERRARESE; ZANETTO, 2016).

Currently, the median survival of patients undergoing liver transplantation in Brazil is around 70% in the first year and 60% to 45% at sixteen years (NASCIMENTO et al., 2020). This improvement is attributed to a combination of advances in surgical techniques and intensive care, patient selection, organ conservation, availability of appropriate immunosuppressive agents, and improved perioperative care (RUSSO; FERRARESE; ZANETTO, 2016).

As the operation results have improved, the number of candidates listed for the transplant has also increased over the years (TROTTER, 2017). Growing demand and the current shortage of donors increase the waiting list time for LTx. About 25% of transplant-listed patients die while waiting, and many potential candidates are not listed due to a lack of donor organs (HUSEN et al., 2019). In Brazil, family refusal is one of the main reasons for not performing the transplant (ABTO, 2021) since more than 40% of families refuse organ donation from relatives after proven brain death (MINISTÉRIO DA SAÚDE, 2021). Also, the number of transplants has reduced due to the COVID-19 pandemic in the last year. The main reason for this decline is the increase in the contraindication rate, due to the risk of transmission of COVID-19 or the difficulty in performing the polymerase chain reaction (PCR) test to detect of the virus or obtaining the result quickly (ABTO, 2021).

Due to the incompatibility between the supply and demand of organs for LTx, there is a need, including, population awareness measures and family dialogues about organ donation and for a patient selection system that is adequate, fair, and impartial. In Brazil, procurement, donation, and transplantation are coordinated by the Sistema Nacional de Transplantes (SNT) and financed by the Sistema Único de Saúde (SUS). Access is granted to Brazilian citizens and foreigners with a permanent residence visa (BITTENCOURT; FARIAS; COUTO, 2016).

Most countries use the model for end-stage liver disease (MELD) to prioritize and allocate patients for liver transplantation (TROTTER, 2017). In Brazil, the system was adopted in 2006, and the minimum MELD value accepted for enrollment in an adult list is 11 points (MINISTÉRIO DA SAÚDE, 2006). With the implementation of this model in the country, the time and mortality rate on the waiting list was reduced (SALVALAGGIO et al., 2012; PESTANA et al., 2013). The MELD score predicts three-month mortality by incorporating mathematical calculations of serum creatinine, bilirubin, and prothrombin activity time (INR) levels (WIESNER et al., 2003). In 2016, serum sodium concentration was added to biochemical parameters for MELD calculation (OPTN, 2016). The MELD-Na score is today the most used formula for liver graft allocation (RUSSO; FERRARESE; ZANETTO, 2016).

In addition to the MELD-Na, there is the Child-Turcotte-Pugh or Child-Pugh score. This model was developed in the 1960s, incorporating biochemical tests and clinical data (serum albumin, serum bilirubin, INR, ascites, encephalopathy) to predict mortality in patients with end-stage cirrhosis (CHILD; TURCOTTE, 1964). Despite being the most adopted model in clinical practice, mainly due to its practicality in the calculation, this measure has some limitations due to subjective variables such as ascites and encephalopathy (KIM; LEE, 2013). However, in a broad systematic review, both models, MELD and CHILD-PUGH, were considered good predictors of mortality for patients on the waiting list for liver transplantation (D'AMICO; GARCIA-TSAO; PAGLIARO, 2006).

Indications for LTx are diverse and can be classified into end-stage liver disease, acute liver failure, and certain benign and malignant liver tumors (FARKAS; HACKL; SCHLITT, 2014; IONESCU et al., 2022). The primary etiologies for transplantation in adults in Brazil are viral hepatitis, mainly hepatitis C, and alcoholic cirrhosis (BITTENCOURT; FARIAS; COUTO, 2016). The main indications for liver transplantation are classified according to Table 1.

Table 1. Main indications for liver transplantation.

Acute Liver Failure
Hepatitis A/B
Intoxication
Wilson's disease
Budd Chiari Syndrome
Chronic liver failure: non-cholestatic cirrhosis
Hepatitis B/C
Autoimmune hepatitis
Ethanolic cirrhosis
Chronic liver failure: cholestatic cirrhosis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Secondary biliary cirrhosis
Chronic liver failure: metabolic
Non-alcoholic hepatic steatosis (NASH)
Wilson's disease
Hemochromatosis
Alpha-1 antitrypsin deficiency
Amyloidosis
Cystic fibrosis
Tyrosinemia
Chronic liver failure: vascular
Budd Chiari Syndrome
Other indications
Primary oxalosis
Glycogen storage diseases
Hyperlipidemia
Polycystic liver disease
Malignant disease
Hepatocellular carcinoma (HCC)
Fibrolamellar carcinoma
Hepatoblastoma
Epithelioid hemangioendothelioma
Cholangiocellular adenocarcinoma
Neuroendocrine liver metástases
Benign liver tumors
Adenomatosis
Liver transplantation in pediatric patients
Biliary atresia
Byler's disease
Alagille's syndrome
Neonatal hepatitis/neonatal viral hepatitis
Autoimmune hepatites
Hepatoblastoma

Complications of chronic liver disease include portal hypertension, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy, and malnutrition (EBEL; HORSLEN, 2017; HAJ; ROCKEY, 2018).

3.2 Malnutrition and sarcopenia in chronic liver disease

Chronic liver disease has a significant impact on the nutritional status of the patient at all stages of evolution, whether in the pre, peri and postoperative periods (ANASTÁCIO et al., 2011; GIUSTO et al., 2014; HAMMAD; KAIDO; UEMOTO, 2015; DEUTRICH AYDOS et al., 2016). Before transplantation most of patients on the waiting list usually present malnourishment (FERREIRA et al., 2009; HUISMAN et al., 2011; LIM et al., 2015).

Malnutrition is usually a consequence of several risk factors, of which the severity of the disease itself is one of the most important (CORREIA; WAITZBERG, 2003; CORREIA, 2018). Although there is no consensus on the definition of malnutrition (CORREIA; PERMAN; WAITZBERG, 2017), this syndrome can be defined as a state resulting from anorexia, gastrointestinal obstruction, increased nutritional requirements, alteration in nutrient absorption, increased loss of intestinal proteins and impaired metabolism or related to inadequate food intake (CORREIA, 2018).

Malnutrition is one of the most common complications in patients with advanced liver disease (CHEUNG; LEE; RAMAN, 2012; JOHNSON et al., 2013; MOCTEZUMA-VELÁZQUEZ et al., 2013). It is estimated that the prevalence of malnutrition ranges from 50% to 80% of patients with cirrhosis (CARVALHO; PARISE, 2006; MERLI et al., 2010; FERREIRA et al., 2011; GARCÍA-RODRÍGUEZ et al., 2017) and, this rate fluctuates according to the methods used to assess nutritional status (MOCTEZUMA-VELÁZQUEZ et al., 2013).

The causes of this malnutrition in this population are well described in the literature, including decreased food intake due to anorexia, nausea, vomiting, inadequate dietary advice, malabsorption, poor digestion, altered metabolism due to impaired liver function, in addition to the hypermetabolic state (RICHARDS et al., 2005; HAMMAD; KAIDO; UEMOTO, 2015; ANASTÁCIO; CORREIA, 2016).

Loss of muscle mass is one of the aspects of malnutrition (KIM; WILSON; LEE, 2010; MOCTEZUMA-VELÁZQUEZ et al., 2013), which is commonly seen in patients with end-stage liver disease (PLANK; RUSSELL, 2015; VAN VUGT et al., 2016; BELARMINO et al., 2017). The progressive and widespread loss of skeletal muscle mass and muscle function (strength or

performance) is defined as sarcopenia (CRUZ-JENTOFT et al., 2019), combined with contractile dysfunction and metabolic and endocrine changes that affect muscle fiber quality (ANAND, 2017). There are two categories of sarcopenia, primary and secondary. Sarcopenia is considered primary when attributed to aging, while secondary sarcopenia occurs when there are causal factors of clinical contexts (CRUZ-JENTOFT et al., 2019). In the present work, sarcopenia refers to secondary sarcopenia if not otherwise specified. The prevalence of sarcopenia in patients with liver cirrhosis ranges from 40% to 76% (MONTANO–LOZA et al., 2012; GIUSTO et al., 2015).

The pathogenesis of secondary sarcopenia in patients with cirrhosis is multifactorial. Inadequate dietary intake, metabolic disorders, elevated myostatin levels, inhibition of muscle growth, increased muscle breakdown, and malabsorption may contribute to this condition (LIN et al., 2005; KIM; JANG, 2015; SINCLAIR et al., 2016). As a consequence of the presence of sarcopenia, negative clinical outcomes have been reported, such as reduced pre- (MONTANO-LOZA et al., 2015; VAN VUGT et al., 2018; KALAFATELI et al., 2015) and post-liver transplant survival rate, increased occurrence of complications such as sepsis (MONTANO–LOZA et al., 2012), increased length of hospital stay, increased risk of perioperative bacterial infections (MONTANO-LOZA et al., 2014) and is associated with increased risk of mortality (MONTANO–LOZA et al., 2012; TANDON et al., 2012; DURAND et al., 2014).

3.3 Food intake in chronic liver disease

Strategies for managing muscle wasting in patients with cirrhosis have been widely studied in recent years, resulting in several articles on the subject (DASARATHY, 2012, 2014, 2016; WILLIAMS; MCKENNA, 2012; TSIEN et al., 2015; DASARATHY; MERLI, 2016; SINCLAIR et al., 2016). The main strategies used to improve nutritional status and, consequently, muscle mass include supply of nutritional supplementation of energy and nutrients (especially proteins), increased levels of physical activity, and hormone therapy (DASARATHY, 2012, 2014, 2016; WILLIAMS; MCKENNA, 2012; SINCLAIR et al., 2016). However, the evidence needs to be more consistent regarding the contribution of these practices to the patient's clinical improvement (ANTAR; WONG; GHALI, 2012; KORETZ; AVENELL; LIPMAN, 2012; NEY et al., 2013).

A review study demonstrated that nutritional supplementation (energy and protein) and physical activity, measures generally used to combat the loss of skeletal muscle mass, were not consistently effective, as the molecular and metabolic abnormalities underlying the liver disease persist or have not been influenced by these treatments (DASARATHY; MERLI, 2016).

According to the current recommendations for patients with liver cirrhosis, nutritional therapy in the pre-LTx is centered on adequate energy (30-35kcal/kg) and protein (1.2-1.5kcal/kg), fractionated meals and a late evening snack to minimize gluconeogenesis and protein catabolism (PLANK et al., 2008; MERLI et al., 2019). However, nutritional goals and adherence to interventions are still great challenges to be faced.

There is little data on patients' dietary intake on the waiting list for liver transplantation. All studies that carried out this quantification showed that caloric and protein intake is generally below recommended recommendations (DE LUIS et al., 2006; FERREIRA et al., 2009, 2013; NEY et al., 2015; MARR et al., 2017; DAPHNEE et al., 2018; CHAPMAN et al., 2019; MIZUBUTI et al., 2021). Rates of inadequate energy intake range from 76% to 94% (FERREIRA et al., 2013; NEY et al., 2015; PALMESE et al., 2019). The energy and protein intake of patients on the liver transplant waiting list are described in Table 2.

Another strategy adopted to recover nutritional status and offer extra nutritional support to patients with liver disease is offering snacks at night ("late evening snack"). The consumption of evening meals is highly recommended for patients with liver cirrhosis (AMODIO et al., 2013; HAMMAD; KAIDO; UEMOTO, 2015), to minimize the catabolic state during the overnight fasting period (HAMMAD; KAIDO; UEMOTO, 2015). Overnight oral supplements have been used to reduce gluconeogenesis and protein catabolism in patients with liver disease (PLANK et al., 2008; CHEUNG; LEE; RAMAN, 2012). This nocturnal supply can reduce the accelerated progression of the catabolic state and, as a result, there is an improve nitrogen balance (PLANK et al., 2008).

Plank et al. (2008) conducted a randomized clinical trial in which 106 patients with cirrhosis were followed up for 12 months. The aim of the study was to compare the effects of daytime and nighttime nutritional supplementation on nutritional status. The authors observed an average of two kilograms increase of lean body mass in patients who consumed the supplement at night compared to those who consumed the supplement during the day (PLANK et al., 2008). As in the case of the oral nutritional supplement, it is also hypothesized that branched-chain amino acids, when consumed during the day, are used as an energy source, and when administered at night, are used for protein synthesis (KHANNA; GOPALAN, 2007; FUKUSHIMA et al., 2015).

Table 2. Studies evaluating the energy and protein intake of patients on the waiting list for liver transplantation.

Authors	N	Type of study	Food intake assessment method	Caloric intake Mean ± SD Median (min-max)		Protein intake Mean ± SD Median (min-max)	
				(kcal/day)	(kcal/kg)	(g/day)	(g/kg)
De Luis et al., 2006	31	Prospective study	3-FRs	2017 ± 474	28.1 ± 6.0	94.1 ± 28.8	-
Ferreira et al., 2009	159	Cross-sectional study	24hR	1490 ± 580	21.3 ± 8.8	56.0 ± 25.1	0.8 ± 0.4
Ferreira et al., 2013	73	Cross-sectional study	3-FRs	1485 (559–3432)	24.0 ± 7.3	60.5 (13.8-170.1)	1.1 ± 0.3
Ney et al., 2015	630	Retrospective study	2-FRs	-	-	68.8 ± 23.3	1.1 ± 0.4
Marr et al., 2017*	70	Prospective study	3-FRs	1466	27.9 (24.3-35.0)	-	1.0 (0.6 - 1.2)
Daphnee et al., 2018*	65	Prospective study	-	1568 ± 3216	26.6 ± 4.3	53.1 ± 13.4	-
Chapman et al., 2019*	19	Prospective study	24hR	-	17.9 ± 5.4	-	0.7 ± 0.3
Ribeiro et al., 2020	73	Prospective study	3-FRs	1578 (1162–1854)	-	-	-
Mizubuti et al., 2021*	105	Randomized clinical trial	24hR	-	20.4 (17.4-23.3)	-	0.75 (0.0 – 0.9)

Caption 1. *- not found in the article; 24hR: 24-hour Recall; 2-FRs: 2-Day Food Record; 3-FRs: 3-Day Food Record; SD: Standard Deviation; * nutritional intervention studies; values before the intervention; SD:standard deviation.*

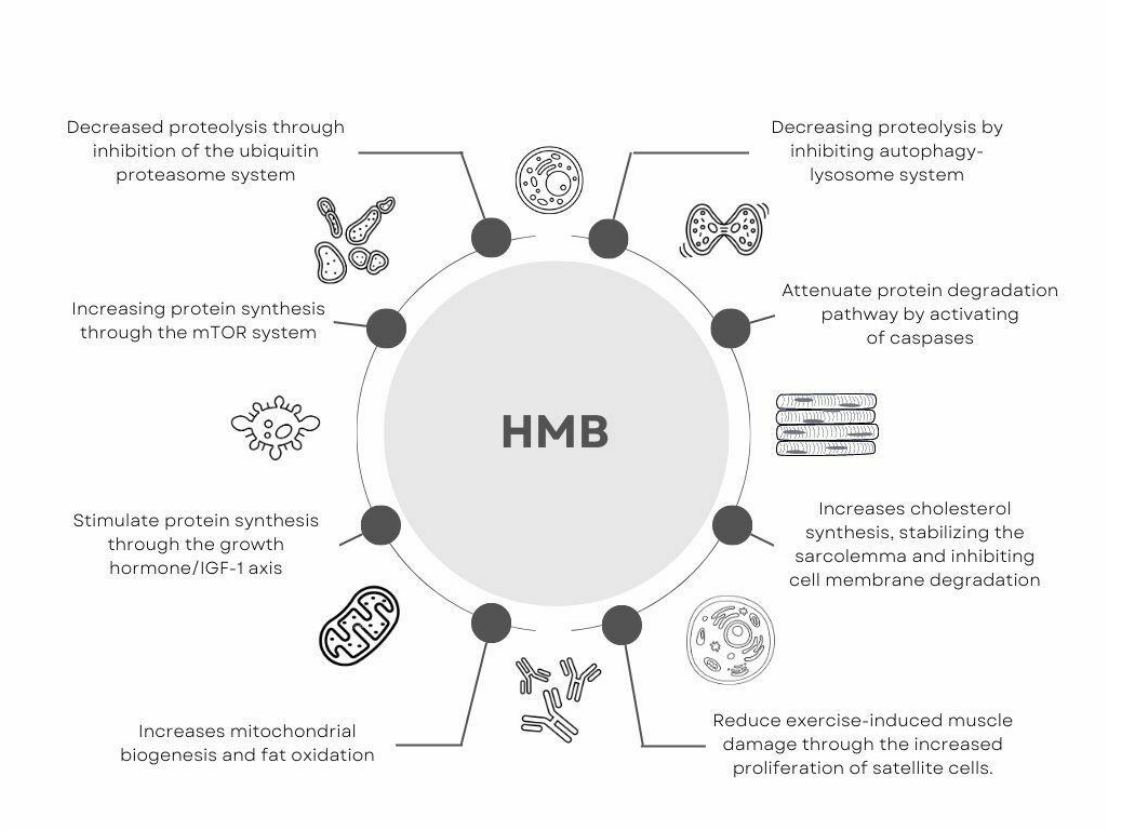
3.4 Beta-hydroxy-beta-methylbutyrate (HMB) supplementation

Nutritional supplementation is considered an efficient and safe method to improve nutritional status and, therefore, muscle quality (WU et al., 2015). Beta-hydroxy-beta-methylbutyrate (HMB) is an active metabolite of leucine, which is one of the three essential branched-chain amino acids (BCAA; leucine, valine, and isoleucine) (NISSEN; ABUMRAD, 1997). HMB has been investigated due to its potential role on muscle health, which includes both an increase in muscle protein synthesis and a decrease in muscle protein breakdown (WU et al., 2015), as this metabolite can enhance protein synthesis through the upregulation of anabolic signaling pathways and attenuate proteolysis through the downregulation of catabolic signaling pathways (SMITH; MUKERJI; TISDALE, 2005; WILKINSON et al., 2013; HASSELGREN, 2014).

Currently, the two most common forms of HMB are calcium HMB (HMB-Ca) and the free acid form of HMB (HMB-FA). Commercially, HMB-Ca is available in powder form, usually supplemented in capsules, while HMB-FA is sold in gel, capsule, and powder form (WILSON et al., 2013; ARAZI; TAATI; SUZUKI, 2018). Most studies have been conducted using HMB-Ca (JAKUBOWSKI et al., 2020). The bioavailability and clearance rate of HMB depend on dose and combination with other nutrients. Vukovich et al. (2001) indicated that the concentration of HMB-Ca in the bloodstream is dose-dependent. The ingestion of 1g of HMB-Ca resulted in a maximum peak concentration in the bloodstream after two hours. When administering 3g, the maximum concentration occurred in one hour. In the same study, the authors observed that the maximum concentrations of HMB-Ca were lower and delayed by one hour when combined with 75g of glucose. It is hypothesized that adding of glucose mitigated gastric emptying or improved HMB clearance (VUKOVICH et al., 2001). Regarding bioavailability, HMB-FA showed better results. The study by Fuller et al. (2011) demonstrated that offering HMB-FA resulted in higher and faster plasma peaks of HMB compared to HMB-Ca (FULLER et al., 2011), regardless of the form of administration of the compound, capsule, gel or powder dissolved in water (FULLER et al., 2015). The plasma half-life of HMB, when administered in the form of HMB-FA, is 3.5 hours, while in the form HMB-Ca, it is 2.5 hours. In addition, the concentration decrease in plasma levels of HMB-FA is faster, indicating more accelerated absorption and degradation of HMB with a higher clearance rate (FULLER et al., 2015). However, this compound's urinary rate does not differ significantly between forms of HMB (KACZKA et al., 2019). More recently, Wilkinson et al. (2018) concluded that the anabolic effects of HMB-Ca are equivalent to HMB-FA despite presumed differences in bioavailability. Both forms of HMB resulted in equivalent stimulation of muscle protein synthesis and suppression of muscle protein breakdown, highlighting anabolic effects independent of calcium or free acid form (WILKINSON et al., 2018).

Several studies have analyzed the molecular mechanisms of the action of HMB. The main HMB action pathways are shown in Figure 1. This compound modulates muscle protein degradation by inhibiting the proteolytic pathway of ubiquitin-proteasome (SMITH; MUKERJI; TISDALE, 2005; ELEY; RUSSELL; TISDALE, 2008), inhibits cellular apoptosis by regulating mitochondria-associated caspase signaling (HAO et al., 2011), increases myofibrillar protein synthesis through upregulation via Mammalian Target of Rapamycin (mTOR) (ELEY et al., 2007) and acts in the stabilization of cell membranes through the rate-limiting enzyme of cholesterol synthesis, HMG-coenzyme A reductase (NISSEN et al., 1996; NISSEN; ABUMRAD, 1997). Furthermore, studies suggest that specific protein kinase signaling pathways are involved in the anti-catabolic effects of HMB in skeletal muscle (KORNASIO et al., 2009; RUSSELL; TISDALE, 2009) and act on the transcription and expression of the insulin-like growth factor-1 (IGF-I) gene, which exerts anabolic and hypertrophic action on skeletal muscle fibers (TOWNSEND et al., 2015).

Figure 1. Main pathways of action of beta-hydroxy-beta-methylbutyrate (HMB).



Caption 2. *mTOR: mammalian target of rapamycin; IGF-1 Insulin-Like Growth Factor-1.*
Source: *Adapted from Landi et al. (2021).*

HMB has been shown to have an anti-catabolic effect, increase protein synthesis, attenuate proteolysis, increase muscle mass, and decrease muscle damage in meta-analyses

across multiple health and disease conditions (BEAR et al., 2019; HOLLAND et al., 2022; LIN; ZHAO; HE, 2022; PRADO et al., 2022). Bear et al. (2019), in a systematic review and meta-analysis, concluded that HMB increased muscle mass and strength in patients with various clinical conditions (BEAR et al., 2019). In a systematic review, Prado et al. (2022) investigated the effects of HMB supplementation on muscle mass, function, and other outcomes in patients with cancer. These authors found that four of four studies showed a beneficial effect of HMB supplementation on muscle mass, two of two for muscle function, three of three for hospitalization, and five of seven, for survival. However, no beneficial effects of HMB on quality of life or body weight was found in two of four and three of five studies, respectively (PRADO et al., 2022). A systematic review and meta-analysis conducted by Lin et al. (2022) showed that supplementation of HMB and preparations containing HMB ingredients increase muscle strength in an older adult population (LIN; ZHAO; HE, 2022).

However, in other studies with clinical populations and healthy individuals, the effectiveness of HMB supplementation is not always proven (MARCORA; LEMMEY; MADDISON, 2005; BERK et al., 2008; BAIER et al., 2009; DEUTZ et al., 2013; FITSCHEN et al., 2013, 2017), demonstrating that the positive responses to HMB supplementation are not yet conclusive. Fitschen et al. (FITSCHEN et al., 2017) conducted a randomized clinical study with 33 adult and in an older adult patients on hemodialysis; daily supplementation of 3g of HMB-Ca for six months was not able to significantly improve body composition, bone density, strength, function, risk of falls, quality of life or the biochemical parameters (FITSCHEN et al., 2017). Additionally, the proteolytic and anti-catabolic effects of HMB were also not found in individuals who were submitted to strength training (JAKUBOWSKI et al., 2020), men submitted to resistance training (TRITTO et al., 2019), and young athletes (MANGINE et al., 2020). Thus, the effectiveness of HMB supplementation is heterogeneous and inconclusive to determine an effect.

It is essential to highlight that HMB supplementation, as nicely as protein *per se*, may additionally not be adequate to amplify muscle mass (OKTAVIANA et al., 2020). When food intake is insufficient, in terms of energy, there is a negative energy balance and thus, the wear of skeletal muscle mass is established (HAYASHI et al., 2013). Therefore, food consumption that provides sufficient energy intake and basic nutrients is imperative.

To date, no studies provide evidence regarding the impact of HMB supplementation in active chronic liver disease patients on the LTx waiting list. Furthermore, there is a paucity of data on the effect of HMB supplementation in patients with liver disease (LATTANZI et al., 2019,

2021; ESPINA et al., 2022). The major studies performed in patients with cirrhosis/ after liver transplantation with HMB supplementation are described in Table 3.

Recently, an increase in muscle mass and strength was observed in patients undergoing liver transplantation supplemented with HMB-Ca (LATTANZI et al., 2019). Similarly, in patients with compensated cirrhosis, muscle performance was improved in the supplemented group compared to the placebo group (LATTANZI et al., 2021). Lattanzi et al. (LATTANZI et al., 2021) supplemented 24 patients with cirrhosis of both sexes for 12 weeks with 3g of HMB-Ca. The majority of patients were classified in Child–Pugh A [HMB group: 85.8% (n=12); placebo group: 90% (n=9)], and the mean of MELD was 9.0 ± 2.7 in the HMB group and 9.8 ± 3.2 in the placebo group. The authors observed that after treatment, there was a significant increase in muscle function in the HMB group (sitting and standing test: 14.2±5.0s vs. 11.7±2.6s, $p < 0.05$; walk: 361.8±68.0m vs. 409.4±58.0m, $p < 0.05$). Quadriceps muscle mass, measured by ultrasound, also increased (4.9±1.8mm vs. 5.4±1.8mm, $p < 0.05$), and the frailty index decreased (4.1±0.4mm vs. 3.7±0.4mm, $p<0.05$) (LATTANZI et al., 2021).

The same group of researchers, Lattanzi et al. (LATTANZI et al., 2019), previously performed a similar protocol in individuals 30 days after liver transplantation. Twenty-two male patients received 3g of HMB-Ca for 12 weeks. Among the observed results, there was a significant increase in the skeletal muscle mass index assessed by dual emission X-ray densitometry (DXA) in the HMB group (6.8±0.7kg/m² vs. 7.4±0.8 kg/m², $p<0.05$). Arm muscle circumference (26.1±2.3cm vs. 27.0±2.6cm, $p<0.05$) and handgrip strength (26.6±8.3kg vs. 32.7±6.4kg, $p<0.05$) also increased (LATTANZI et al., 2019). However, in a more recent clinical trial of 43 patients with cirrhosis and malnourishment prior to clinical decompensation, enriched oral nutritional supplementation with 1.5g HMB-Ca twice daily for 12 weeks showed no increase in anthropometric measurements or handgrip strength (ESPINA et al., 2022). The mean age of patients was 60.4±8.6y in the HMB group (n=22) and 61.4±9.3y in the placebo group (n=21). The median MELD score was 12 (8.5-16.5) and the majority of patients were classified in Child–Pugh B [HMB group: 52.3% (n=11); placebo group: 50% (n=11)]. There was a statistically significant increase in weight and fat mass at the end of supplementation in the HMB group but without differences in the control group. The authors used electrical bioimpedance and anthropometric data to estimate muscle mass. It was concluded that supplementation did not change muscle mass markers ($p=0.718$) or handgrip strength in either of the two treatment groups ($p=0.095$) (ESPINA et al., 2022). Collectively, these results demonstrate that it is necessary to explore the clinical benefit of HMB supplementation in this clinical population and in patients with advanced chronic liver diseases.

Table 3. Studies on the effects of HMB supplementation in patients with cirrhosis or undergoing liver transplantation.

	N	Type of study	Patients	Age (years)		MELD (score)		Child–Pugh class n (%)		Supplementation (dosage/day)		Duration of supplementation (weeks)	Food Intake (calorie kcal/kg) (protein g/kg)		Intervention with physical activity	Outcomes in the HMB group	Outcomes in the control group
				HMB	Control	HMB	Control	HMB	Control	HMB	Control		HMB	Control			
Lattanzi et al., 2019	22	Randomized controlled trial	Patients undergoing liver transplantation	60.4±5.4	59.3±7.3	15.7±7.1	16.8±8.4	-	-	3g of HMB+ 200ml of fruit juice	200ml of fruit juice	12	22.7±8.6 0.9±0.2	23.8±6.3 0.7±0.2	Yes	Increased appendix skeletal muscle mass index, arm muscle circumference, and handgrip strength	No effect
Lattanzi et al., 2021	27	Masked randomized controlled trial	Patients with cirrhosis	59.2±8.4	56.0±4.6	9.0±2.7	9.8±3.2	A=12 (85.8) B=2 (14.2) C=0	A=9 (90) B=1 (10) C=0	3g of HMB	3g of sorbitol	12	- 0.94±0.3	- 0.89±0.4	Yes	Increased muscle function and reduced frailty index	No effect
Espina et al., 2022	34	Randomized double-masked controlled trial	Patients with cirrhosis and malnourishment with previous clinical decompensation	60.4±8.6	61.4±9.3	12.7±5.3	13.0±4.7	A=9 (40.9) B=11 (50) C=2 (9.1)	A=10 (47.6) B=11 (52.3) C=0 (0)	3g of HMB+ 440ml of oral nutritional supplement	440ml of oral nutritional supplement	12	- -	- -	No	Increase in weight and fat mass	Increase in weight and fat mass

Caption 3. *- not found in the article.*

4 CHAPTER I

ARTICLE I: THE EFFECT OF BETA-HYDROXY-BETA-METHYLBUTYRATE (HMB) WITH NUTRITIONAL INTERVENTION ON ANTHROPOMETRIC MUSCLE MASS MARKERS, STRENGTH, FUNCTIONALITY, AND QUALITY OF LIFE IN PATIENTS ON THE WAITING LIST FOR LIVER TRANSPLANTATION: A DOUBLE-BLIND STUDY

THE EFFECT OF BETA-HYDROXY-BETA-METHYLBUTYRATE (HMB) WITH NUTRITIONAL COUNSELLING ON ANTHROPOMETRIC MUSCLE MASS MARKERS, STRENGTH, FUNCTIONALITY, AND QUALITY OF LIFE IN PATIENTS ON THE WAITING LIST FOR LIVER TRANSPLANTATION: A DOUBLE-BLIND STUDY

ABSTRACT

Aim: Patients on the waiting list for liver transplantation (LTx) usually lose muscle mass. Supplementation with beta-hydroxy-beta-methylbutyrate (HMB) may have a promising effect in this clinical condition. This study aimed to evaluate the effects of HMB on muscle mass, strength, functionality, and quality of life in patients on the LTx waiting list.

Methods: A double-blind, randomized study was conducted of 3g supplementation of HMB or 3g supplementation of maltodextrin (active control) with nutritional counselling for 12 wk in patients >18 y, evaluated at five points or timepoints. Body composition and anthropometric data (resistance, reactance, phase angle, weight, body mass index, arm circumference (AC), arm muscle area and adductor pollicis muscle thickness) were collected. Muscle strength was assessed using dynamometry, physical function was evaluated using the frailty index (FI), and quality of life was also evaluated.

Results: Forty-seven patients were enrolled [HMB: 23; active control: 24]. There was a significant difference in both groups for AC ($p=0.03$), dynamometry ($p=0.02$), and FI ($p=0.01$). There was an increase in dynamometry between T0 and T12 in both groups [HMB (Δdynamometry: 10.1±16.4%; $p<0.05$); active control (Δdynamometry: 23.0±70.3%; $p<0.05$)]. The AC increased in both groups between T0 and T4 [HMB (ΔAC: 0.9±2.8%; $p<0.05$); active control (ΔAC: 1.6±3.6%; $p<0.05$)] and between T0 and T12 [HMB (ΔAC: 3.2±6.7%; $p<0.05$); active control (ΔAC: 2.1±6.6%; $p<0.05$)]. The FI decreased in both groups, between T0 and T4 [HMB (ΔFI: -4.2±6.9%; $p<0.05$); active control (ΔFI: -3.2±9.6%; $p<0.05$)] and between T0 and T12 [HMB (ΔFI: -4.4±11.2%; $p<0.05$); active control (ΔFI: -5.5±11.3%; $p<0.05$)]. The other variables did not change ($p>0.05$).

Conclusion: Nutritional counselling with supplementation with HMB or active control in patients on the liver transplant waiting list improved arm circumference and dynamometry and reduced the frailty index in both groups.

KEYWORDS: liver transplantation, skeletal muscle, muscle strength, quality of life, HMB, supplementation.

1. Introduction

Decompensated advanced cirrhosis significantly impacts patient's nutritional status at all stages of evolution (ANASTÁCIO et al., 2011). Patients on the transplant waiting list generally present malnutrition (FERREIRA et al., 2009), with about 70% of individuals having evidence of malnutrition, according to the subjective global assessment (SGA) (FERREIRA et al., 2011). Malnutrition is multifactorial and is associated with factors such as ascites, inappetence, nausea, hypermetabolic state, low food intake, salt restricted food, inappropriate dietary protein restriction and disease severity (CHEUNG; LEE; RAMAN, 2012; MERLI et al., 2019).

In an attempt to mitigate this situation, nutritional supplementation, in conjunction with an adequate caloric-protein intake, is considered an efficient and safe method to improve nutritional status and, therefore, muscle quality (WU et al., 2015). Beta-hydroxy-beta-methylbutyrate (HMB) is an active metabolite of leucine, which is one of the three essential branched-chain amino acids (NISSEN; ABUMRAD, 1997). HMB has been investigated for its potential role in improving muscle quality since this metabolite can improve protein synthesis through positive stimulation of anabolic pathways and attenuate proteolysis through negative regulation of catabolic pathways (HASSELGREN, 2014). HMB has been shown to have an anti-catabolic effect, increase protein synthesis, attenuate proteolysis, increase muscle mass and decrease muscle damage in meta-analyses in various conditions of health and disease (BEAR et al., 2019; HOLLAND et al., 2022; PRADO et al., 2022). Bear *et al.* (BEAR et al., 2019), in a systematic review and meta-analysis, concluded that HMB increased muscle mass and strength in patients in various clinical conditions (BEAR et al., 2019). But, in other studies with clinical populations, the effectiveness of HMB supplementation was not consistently established (DEUTZ et al., 2013; FITSCHEN et al., 2017), demonstrating that the positive responses to HMB supplementation are not yet conclusive, especially in the context of liver disease.

Recently, a pilot study has shown an increase in muscle mass by DXA (dual-energy X-ray absorptiometry) and mid-arm circumference and strength by handgrip in patients undergoing liver transplantation (LTx) supplemented with 3.0g of HMB after 12 weeks (LATTANZI et al., 2019). In patients with compensated cirrhosis, an improvement in muscle mass (measured by ultrasound) and performance (measured by chair test) was also observed compared to the active control group after 12 weeks of supplementation with 3.0g of HMB (LATTANZI et al., 2021). However, in a more recent trial with 43 patients with cirrhosis and malnourishment with previous clinical decompensation, an oral nutritional supplement enriched with 1.5g of HMB

twice a day for 12 weeks did not show an increase in anthropometric measures or handgrip strength (ESPINA et al., 2022).

To date, no studies provide evidence in favor of HMB supplementation in active chronic liver disease patients on the LTx waiting list. Thus, the present study aimed to evaluate the effects of HMB supplementation with nutritional intervention on anthropometric measures of muscle mass, strength, functionality, and quality of life in patients waiting for liver transplantation.

2. Materials and Methods

Trial design

This is a randomized, double-blind, monocentric study. Outpatients awaiting an LTx received active control (3.0g of maltodextrin) or HMB supplementation in the form of calcium salt (HMB-Ca) (3.0g) with nutritional intervention for 12 weeks, with recruitment from August 2019 to February 2022. The study was approved by the Ethics Committee of the Federal University of Minas Gerais (3.134.996), and all participants signed the Informed Consent Form (Annex A). This study was registered on the ReBec Platform under the code RBR-9snttn.

Participants

Adult outpatients over 18 years of age, active on the waiting list for liver transplantation at the Liver Transplant Outpatient Clinic of the Alfa Institute of Gastroenterology, Hospital of Clinics from the Federal University of Minas Gerais, who agreed to participate in the study, were included in the study. Those patients who used nutritional supplements with essential and non-essential amino acids isolated and known medications that may affect skeletal muscle mass (progestational agents, steroids, and growth hormone) were excluded. Patients on dialysis, those with a body mass index (BMI) above 30kg/m², retransplantation, inflammatory bowel disease, decompensated hypothyroidism or hyperthyroidism, patients with acquired immunodeficiency syndrome (AIDS), with active cancer [except hepatocellular carcinoma: hepatocarcinoma greater than or equal to 2 cm and with no indication for resection (single nodule of up to 5 cm or, if multiple, a maximum of 3 with up to 3 cm each)], illiterate people without a literate companion present were also excluded.

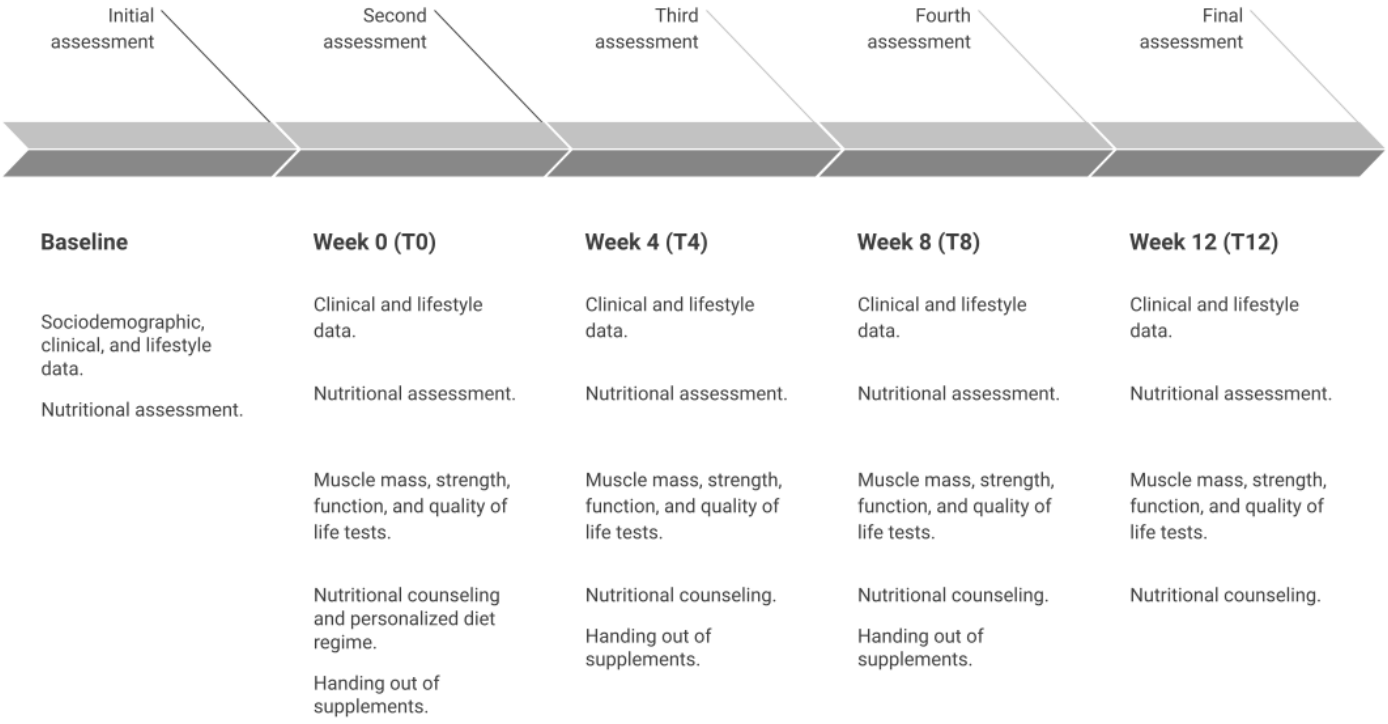
Interventions

Patients were approached and invited to participate in the study while waiting for their outpatient medical appointment. At the time, the patients received clarification on the research and the necessary conditions for participation. Participants were assessed at five moments: Initial assessment; Week 0 (T0), the start of intervention; Week 4 (T4); Week 8 (T8); and after 12 weeks (T12) (Figure 2).

In the initial assessment, before the intervention, sociodemographic, clinical, and lifestyle data were collected, and nutritional and dietary assessments were carried out to prepare the food plan. Patients were instructed to write down a 3-day food record (two weekdays and one weekend day) to be sent before the second meeting (T0).

At the second meeting (T0), enrolled patients received nutritional guidelines and a proposal for an individual and calculated eating plan following current recommendations for patients with cirrhosis – 1.5g of protein/kg; 35 kcal/kg of weight; 60% carbohydrates; 20% of lipids; 35g of fiber; vitamins and minerals according to the Dietary Reference Intakes (IOM, 1998, 2002); small meals evenly distributed throughout the day; and the last meal after 9 pm containing 50g of carbohydrates (AMODIO et al., 2013; MERLI et al., 2019; PLAUTH et al., 2019). Dietary counseling continued throughout the study. Clinical, biochemical, and lifestyle data were recorded. Anthropometric measures and dietary assessments were performed. The anthropometric assessment was performed by only one evaluator. The quantification of the 24-hour food recall and 3-day food records was performed throughout the study. Muscle mass, function, strength, and quality of life tests were also performed at week 0. After four weeks (T4), eight weeks (T8), and 12 weeks (T12), patients returned to the clinic to repeat all assessments performed in week 0 (T0).

Figure 2. Timeline of the variables evaluated during nutritional supplementation in patients on the liver transplant waiting list.



At week 0 (T0), the patients randomly received the first coded bottle with 120 capsules with 3.0g of HMB or 3.0g of maltodextrin, identical, in sufficient quantity for the next 30 days. Participants were instructed to take four capsules daily, two capsules twice a day (after lunch and dinner). Each capsule contained 0.75mg of HMB, totaling 3g per day. Adherence to supplementation was defined as patients taking 70% or more of the capsules, which is equivalent to consuming a minimum of 84 capsules over the course of one month. The assessment of supplement intake was performed fortnightly using a form and by telephone to verify treatment adherence and ask about any discomfort. The treatment adherence was evaluated by counting capsules. In addition, the patients were asked to keep the empty jars and instructed to take the packages to the next appointment for checking and counting. After four weeks (T4), the vials were collected. At that meeting, patients received the second coded bottle for the treatment for which they were randomly selected. Patients received the third and final bottle for the next 30 days in the eighth week. Patients called for transplantation before completion of treatment (12 weeks) were instructed to discontinue supplementation on the operation day.

Determination of HMB

The purity of the calcium HMB (purchased and handled by Araújo Manipulação's Laboratory, Belo Horizonte, Brazil, and produced by ViaFarma, Hong Kong, China) used in the capsules was determined in the Mass Spectrometry Lab of the Chemistry Department at the University Federal de Minas Gerais. The analyses were carried out as triplicates in negative ionization mode (-3.5 kV) with subsequent fragmentation. The spectra was obtained through the paper spray mass spectrometry analysis (PSMS) (LCQ Fleet model, Thermo Scientific, San Jose, CA, USA) of the HMB (supplementary material I). The HMB provider had no role in designing and interpreting the results and writing the manuscript. The maltodextrin was provided by Nutricium (Belo Horizonte, Brazil).

Outcomes and procedures

Differences in arm muscle area and adductor pollicis muscle thickness at 12 weeks were the primary outcome of this study. Secondary outcomes were differences in strength, function, and quality of life between baseline and week 12. Sociodemographic data such as age, sex, education, and family income were collected. The clinical data collected included the presence of clinical comorbidities (diabetes mellitus, arterial hypertension, and others), indication for liver transplantation, presence of ascites, esophageal varices, edema and encephalopathy, different stages of liver disease (CHILD-PUGH and Model for End Stage Liver Disease sodium (MELD-Na)), use and dosage of medications. Lifestyle data were also assessed, such as physical activity, hours of sleep per night, hours of daily TV, smoking, and alcohol consumption. Quality of life assessment was performed using the Chronic Liver Disease Questionnaire translated into Portuguese and validated (MUCCI, 2009).

Food consumption was assessed using a 24-hour recall (24hR) and food record of three non-consecutive days (3-FRs). Food intake at each of the four moments was calculated by summing the results of the surveys (24hR and 3-FRs), and the mean was calculated. The household measurements of the food intake were converted into grams with the help of the Table for Assessment of Food Consumption in Home Measures (PINHEIRO, 2004). Foods were quantified using the following food composition resources: the Brazilian Food Composition Table (TACO) (TACO, 2011), the Brazilian Food Composition Table (TBCA) (TBCA, 2022), and the United States Department of Agriculture (USDA) table (USDA, 2019). The average calorie intake and proteins were calculated using the Microsoft® Excel software. Energy and protein intake

were compared with nutritional requirements, calculated according to dry weight (MERLI et al., 2019).

A subjective global assessment (SGA) adapted for patients on the waiting list for liver transplantation (HASSE et al., 1993) was performed to assess nutritional status. The SGA was performed before and during the nutritional intervention, and patients were classified as nourished, with suspected malnutrition or moderately malnourished, or severely malnourished (HASSE et al., 1993).

The anthropometric data collected were weight, height, arm circumference (AC), triceps skinfold (TSF) measurement, arm muscle area (AMA), calf circumference (CC), and adductor pollicis muscle thickness (APMT). Each anthropometric measurement was taken by a single evaluator three times, and the mean of the three measurements was used. Weight was checked on a Filizola® mechanical scale (Filizola, São Paulo, Brazil). In the presence of ascites or edema, dry weight was calculated (ISHIDA et al., 2019; MERLI et al., 2019). A percentage of weight was subtracted based upon the severity of ascites - mild 5%; moderate 10%; severe 15% - with an additional 5% subtracted if bilateral pedal edema was present) (MERLI et al., 2019). The level of ascites was classified according to abdominal ultrasound. Height measurements were performed using the stadiometer of the same scale. BMI was calculated with the formula weight/height² (WHO, 1995).

The AC measurement was performed with an inelastic measuring tape on the non-dominant arm, at the midpoint between the acromion and the olecranon, with the arm flexed at an angle of 90°(LOHMAN; ROCHE; MARTORELL, 1988). TSF was measured using a LANGE® scientific adipometer (Cambridge Scientific Industries Inc., Cambridge, Maryland, USA). From these measurements, the arm muscle area (AMA) was calculated using the formulas proposed by Heymsfield *et al.* (HEYMSFIELD et al., 1982). CC was measured with the aid of an inelastic measuring tape, on the largest protrusion of the right leg, with the individual sitting on a chair, with a 90° angle of hip and knee flexion. In cases of edema, the CC measurement was discounted by 1.6cm for women and 2.0cm for men (ISHIDA et al., 2019).

The AMPT measurement was performed with the patient seated, with the arm flexed at 90°, forearm, and hand resting on the knee. Patients were instructed to keep their hands relaxed. The LANGE® adipometer was also used, and the adductor muscle was clamped in the extension of the thumb and index finger. The procedure was performed in the dominant hand three times, using the mean as the AMPT measure (BRAGAGNOLO et al., 2009).

Bioelectrical impedance was used to assess the phase angle (PA). The Quantum X (RJL Systems, Inc., Clinton Township, Michigan, USA) was the bioimpedance device used. The electrodes were placed on the right side of the body, two by two on the dorsum of the hand and foot. From the result of resistance (R) and reactance (Xc), provided by the bioimpedance device, the phase angle (R/Xc) was calculated (SELBERG; SELBERG, 2002).

Manual dynamometry was measured using a JAMAR® hydraulic dynamometer (Preston, Jackson, MI, USA) to assess muscle strength. Each participant performed a series of maximum isometric contractions, with an interval of 30 seconds. Three measurements were collected on each hand, obtaining six measures, and the highest value was used (LAURETANI et al., 2003).

The Short Physical Performance Battery questionnaire, translated into Portuguese and validated (NAKANO, 2007), was used to assess functionality. The test assesses standing static balance, gait speed, and lower limb muscle strength. The SPPB total score is obtained by adding the score of each test, ranging from zero (worst ability) to 12 (best ability) (NAKANO, 2007). The classification was performed according to the scores: 0 to 3 points – incapacity or poor ability; 4 to 6 points – low capacity; 7 to 9 points – moderate ability; and 10 to 12 points – good ability (GURALNIK et al., 1995; NAKANO, 2007).

The frailty index (FI) is a tool specifically developed in patients with cirrhosis to objectively measure physical function, a critical determinant of health outcomes. It was calculated using the handgrip strength (averaged three trials), the sit-up test, and the balance test, as described by Lai *et al*. (LAI et al., 2017). Participants were classified as robust (index < 3.2), pre-frail (index 3.2 - <4.5) and frail (index ≥4.5) (LAI et al., 2017).

Sample size

Based on sampling calculations of studies of HMB supplementation and outcome on the improvement increase in muscle mass markers (mid-arm muscle circumference) (ESPINA et al., 2022) and considering the baseline and three more observation times, an autoregressive structure of first order for the time correlation and a lag-1 correlation equal to 0.50, a minimum value for the change to be detected that is 25% greater than the standard deviation of the outcome (mid-arm muscle circumference), a patient retention rate of 0.85, a probability of 5% for the type I error and a test power of 90%, a minimum of 21 patients per group should be enrolled at baseline according to the sample size simulations run using the longpower R package (function power.mmrm).

Randomization

The randomization sequence was created by the randsample function of the Matlab Mathworks software version R2019a (The MathWorks Inc., Natick, MA, USA). The randomization scheme was only seen by the researcher who coded the study vials and was not involved in data collection. The identity of the products used in this study was not informed to the investigators, the study staff, and the participants during the entire follow-up period, which characterized this work as double-blinded.

Statistical methods

Collected data were analyzed using the modified intention-to-treat principle, which includes all subjects who completed follow-up regardless of adherence to supplementation (DEL RE et al., 2013). The last observation carried forward was used to impute missing data. Only three patients who did not come in one of the five evaluations had the missing data imputed. Data characterization analysis was performed based on absolute frequencies and percentages for categorical variables, and for the quantitative ones, the calculation of mean and standard deviation or median, minimum, and maximum was used according to data distribution (Kolmogorov–Smirnov test). Univariate analysis was performed using the Chi-square test, Fisher's exact test, Student's t-test, or Mann-Whitney test. A Cox regression analysis was used to assess the effect of supplementation on transplant or mortality up to 1 year after the initial assessment. Patients who did not transplant or who did not die within one year were censored. Differences between weeks and supplements on the dependent variables (protein intake, dry weight, body mass index, arm circumference, triceps skinfolds, arm muscle circumference, arm muscle area, calf circumference, adductor pollicis muscle thickness, phase angle, dynamometry, short physical performance battery, frailty index, quality of life) were modeled using the Generalized Estimating Equations (GEE), adjusted by age, sex, food intake (caloric intake*protein intake), MELD-Na, and adherence to supplementation. The Normal distribution was assumed for all dependent variables, and an autoregressive structure of lag 1 (AR1) was used to account for the time dependence. The Dunn-Sidak post-hoc test identified the presence of significant effects between time pairs. The intra-rater variance of measurements was calculated by coefficient of variation [(SD/mean) × 100]. The significance level adopted was 5%. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22.0.

3. Results

The result of chemical analyses confirmed the purity of the calcium HMB used in the capsules (supplementary material I). One hundred and twenty-five patients were active in the transplant waiting list, at the time of study recruitment. Twenty-nine patients did not meet the eligibility inclusion criteria, and 15 declined to participate. Seventy-one patients on the waiting list for liver transplantation were randomized, but only 47 patients completed the study, of which 24 (33.8%) patients on the active control arm and 23 (32.4%) patients on the HMB arm completed the treatment as designed per protocol. Since the analysis plan was based on modified intention-to-treat analyses, all subjects who completed follow-up regardless of adherence to supplementation were analyzed (DEL RE et al., 2013).

During follow-up, five patients died, eleven dropped out [withdrew from continuing the study], and seven were transplanted during the intervention. The other losses, refusals, and exclusions are described in Figure 3. The characteristics of the two groups, at baseline, are shown in Table 4 and 5. The participants differed regarding the supplement use [Albumin (n=1); Nutren® (n=2) and Trophic® (n=1)] and adductor pollicis muscle thickness measure ($p<0.05$).

The percentage of treatment adherence, evaluated by the number of capsules consumed, was 97.1±7.9% (T4), 98.0±5.2% (T8), and 100±0% (T12) in the HMB group and 96.8±5.5% (T4), 93.1±14.2% (T8) and 95.8±17.0% (T12) in the active control group (no statistical difference between groups and in times between groups; *Mann-Whitney and Wilcoxon tests*; $p>0.05$).

The mean age of all participants was 55.0±10.6 years. The most frequent indications for transplantation were alcoholic cirrhosis [27.7% (n=13)] and cryptogenic cirrhosis [25.5% (n=12)]. The mean MELD Na score was 14.7±4.1, and most had a CHILD-PUGH B classification [55.3% (n=26)]. Among the complications of decompensated advanced liver disease, ascites [59.6% (n=28)], 6.4% (3) of those underwent paracentesis; and edema [63.8% (n=20)] were the most frequent. As for nutritional status, 76.6% (n=36) of patients had malnutrion at the beginning of the study. Regarding the tolerability and safety of supplementation, no serious adverse events were reported during follow-up, the symptoms reported were flatulence (three participants in the HMB group and two in the active control group), bloating (three participants in the active control group and two participants in the HMB group) and nausea (two participants in the active control group). During the period of study, seven patients (10%) were transplanted, five patients

(7%) died. Of these, three (60%) were from the HMB group, and two (40%) were from the active control group. The median time on the waiting list until a transplant was 399 days (range: 211-3455 days). According to Cox regression, supplementation did not affect transplant or mortality (p=0.927).

Table 6 shows the results of the estimation of generalized equations (GEE) regression models fitted to all dependent variables considering the time and group effects. After the intervention, no differences between groups were shown. There was a significant difference in both groups a time response for arm circumference (p=0.025; Figure 4, A) and dynamometry (p=0.018; Figure 4, B). There was an increase in dynamometry between T0 and T12 in both groups [HMB group (from 27.8± 9.0kg to 29.9±7.9kg; p<0.05); active control group (from 25.8±11.4kg to 28.4±11.7kg; p<0.05). There was an increase in AC in both groups between T0 and T4 [HMB group (from 28.4±3.1cm to 28.7±3.2cm; p<0.05); active control group (from 27.7±3.4cm to 28.2±11.7cm; p<0.05)] and between T0 and T12 [HMB group (from 28.4±3.1cm to 29.4±3.6cm; p<0.05); active control group (from 27.7±11.4cm to 28.2±3.1cm; p<0.05)].

The frailty index decreased over time in both groups (p=0.003; Figure 3, C). The FI decreased over the weeks, between T0 and T4 [HMB group (from 4.2±0.4 to 4.0±0.3; p<0.05); active control group (from 4.5±0.6 to 4.3±0.6; p<0.05)] and between T0 and T12 [HMB group (from 4.2±0.4 to 4.0±0.4; p<0.05); active control group (from 4.5±0.6 to 4.2±0.6; p<0.05)]. The other anthropometric measurements did not show significant changes (p>0.05). And the analysis did not also reveal the effects of supplementation on quality of life during intervention weeks (p>0.05).

Figure 3. Flow chart of patient recruitment and distribution in the study.

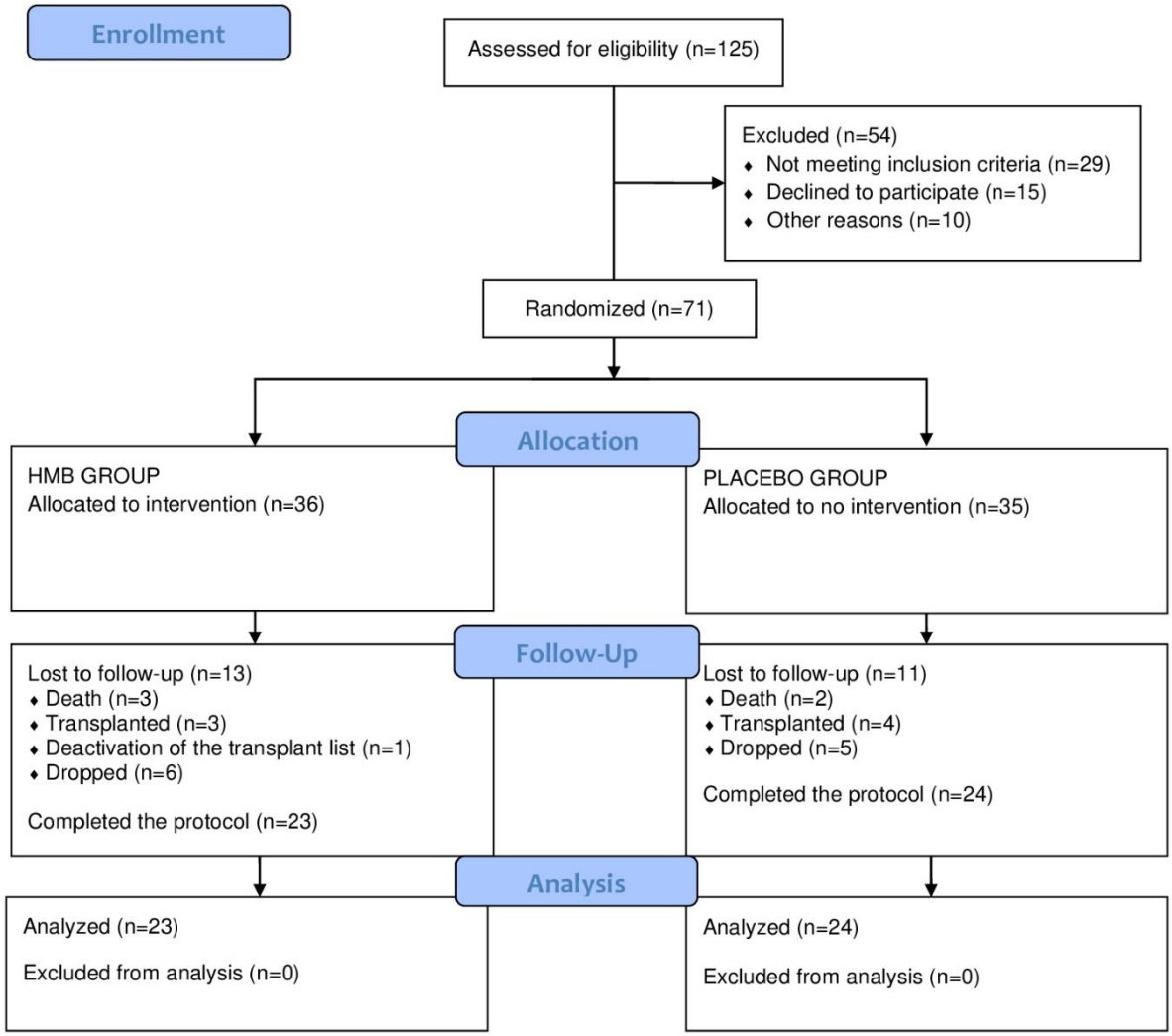


Table 4. Socio-demographic and lifestyle parameters at baseline of patients on the waiting list for liver transplantation according to the HMB supplementation or active control (n=47).

Variables	All (n=47)	HMB (n=23)	Active control (n=24)	P value
Sociodemographic				
Age (y)	55.0 ± 10.6	54.6 ± 10.6	55.4 ± 10.8	0.789
Education (y)	7.7 ± 4.6	6.9 ± 3.3	8.4 ± 5.5	0.290
Monthly family income (R$)	2237.7 ± 1625.1	1971.25 ± 1127.9	2481.85 ± 1968.6	0.292
Sex				
Male	72.3% (n=34)	78.3% (n=18)	66.7% (n=16)	0.374
Female	27.7% (n=13)	21.7% (n=5)	33.3% (n=8)	
Lifestyle				
Former smokers	42.6% (n=20)	52.2% (n=12)	33.3% (n=8)	0.173
Former drinkers	76.6% (n=36)	87.0% (n=20)	66.7% (n=16)	0.118
Physical activities	31.9% (n=15)	30.4% (n=7)	33.3% (n=8)	0.913
Physical activity per week (minutes)	0 (0.0 – 420.0)	0 (0.0 – 210.0)	0 (0.0 – 420.0)	0.485
Daily TV (h)	2.5 (0.0 – 6.0)	2.5 (0.0 – 6.0)	3.0 (1.0 – 6.0)	0.991
Sleep per night (h)	8.1 ± 2.4	8.0 ± 2.8	8.2 ± 2.1	0.848

Caption 4*. P values in bold significantly differ between the HMB and active control groups at baseline, p < 0.05; Student's t-test or Mann-Whitney test.*

Table 5. Initial characterization of patients on the waiting list for liver transplantation according to the HMB supplementation or active control (n=47).

Variables	All (n=47)	HMB (n=23)	Active control (n=24)	P value
Clinics				
Child-Pugh				
A	27.7% (n=13)	30.4% (n=7)	25.0% (n=6)	0.506
B	68.1% (n=32)	69.6% (n=16)	66.7% (n=16)	
C	4.3% (n=2)	0	8.3% (n=2)	
MELD Na	14.7 ± 4.1	13.5 ± 3.2	14.8 ± 5.2	0.300
Transplant indication				
Alcoholic Cirrhosis	27.7% (n=13)	34.8% (n=8)	20.8% (n=5)	0.285
Hepatitis B virus	8.5% (n=4)	8.7% (n=2)	8.3% (n=2)	0.965
Hepatocellular carcinoma	19.1% (n=9)	17.4% (n=4)	20.8% (n=5)	0.999
Cryptogenic Cirrhosis	25.5% (n=12)	21.7% (n=5)	29.2% (n=7)	0.559
NASH	8.5% (n=4)	4.3% (n=1)	12.5% (n=3)	0.609
Comorbidities				
Diabetes mellitus	31.9% (n=15)	21.7% (n=5)	41.7% (n=10)	0.171
Arterial hypertension	31.9% (n=15)	34.8% (n=8)	29.2% (n=7)	0.603
Indicators of liver disease severity				
Ascites	59.6% (n=28)	69.6% (n=16)	50.0% (n=12)	0.172
Paracentesis	6.4% (3)	8.7% (n=2)	4.2% (n=1)	0.600
Edema	63.8% (n=30)	65.2% (n=15)	62.5% (n=15)	0.846
Esophageal varices	44.7% (n=21)	43.5% (n=10)	45.8% (n=11)	0.871
Hepatic encephalopathy	17.0% (n=8)	13.0% (n=3)	20.8% (n=5)	0.701
Nutritional status				
Subjective Global Assessment (SGA)				
Nourished	23.4% (n=11)	26.1% (n=6)	20.8% (n=5)	0.866
Moderately malnourished	61.7% (n=29)	60.9% (n=14)	62.5% (n=15)	
Severe malnutrition	14.9% (n=7)	13.0% (n=3)	16.7% (n=4)	
Dietary Intake				
Oral nutritional supplement use	8.5% (n=4)	18.2% (n=4)	0	**0.045**

Caloric intake (kcal/kg)	25.0 ± 8.4	25.3 ± 8.5	24.7 ± 8.5	0.636
Protein intake (g/kg)	1.0 ± 0.4	1.0 ± 0.4	1.0 ± 0.4	0.996
Anthropometrics/body composition				
Dry weight (kg)	66.6 ± 10.5	66.6 ± 10.3	66.5 ± 11.0	0.971
Body Mass Index (kg/m²)	24.0 ± 3.3	24.2 ± 3.8	23.7 ± 2.8	0.637
Arm Circumference (cm)	28.1 ± 3.2	28.5 ± 3.1	27.7 ± 3.4	0.473
Calf Circumference (cm)	36.4 ± 3.8	36.8 ± 4.1	36.0 ± 3.5	0.440
Triceps Skinfold (mm)	13.7 (4.2 – 34.0)	15.3 (4.7 – 34.0)	13.7 (4.2 – 33.0)	0.749
Arm Muscle Circumference (cm)	23.0 ± 2.6	23.1 ± 2.8	22.2 ± 2.5	0.734
Arm Muscle Area (cm)	33.9 ± 8.1	34.6 ± 7.6	33.1 ± 8.8	0.532
Adductor Pollicis Muscle Thickness (mm)	17.4 ± 3.9	18.5 ± 3.4	16.3 ± 4.1	**0.045**
Resistance	486.8 ± 89.8	462.0 ± 93.7	510.6 ± 80.9	0.063
Reactance	45.0 ± 10.9	44.1 ± 10.1	45.8 ± 11.7	0.598
Phase angle	5.3 ± 0.8	5.4 ± 0.7	5.1 ± 0.9	0.154
Functionality				
Dynamometry				
Highest of the six measurements	26.8 ± 10.2	27.8 ± 9.0	25.8 ± 11.4	0.506
Short Physical Performance Battery				
Total score	8.6 ± 1.6	8.6 ± 1.4	8.6 ± 1.8	0.946
Disposity or very poor performance	0	0	0	
Low capacity	8.5% (n=4)	8.7% (n=2)	8.3% (n=2)	0.842
Moderate capacity	34.0% (n=16)	30.4% (n=7)	37.5% (n=9)	
Good capacity	14.9% (n=7)	17.4% (n=4)	12.5% (n=3)	
Frailty index				
Total score				
Robust	0	0	0	-
Pre-frail	66.0% (n=31)	78.3% (n=18)	54.2% (n=13)	0.081
Frail	34.0% (n=16)	21.7% (n=5)	45.8% (n=11)	0.081
Quality of life				
Total score	18.2 ± 6.6	18.0 ± 7.7	18.4 ± 5.8	0.470

Abdominal symptoms	3.8 ± 2.0	3.7 ± 1.8	4.0 ± 2.2	0.611
Fatigue	3.4 ± 1.7	3.5 ± 1.7	3.2 ± 1.8	0.542
Systemic symptoms	4.4 ± 1.3	4.4 ± 1.2	4.4 ± 1.4	0.914
Activity	4.4 ± 1.5	4.6 ± 1.3	4.3 ± 1.8	0.553
Emotional function	3.9 ± 1.6	4.2 ± 1.6	3.7 ± 1.5	0.304
Worry	3.5 ± 2.0	3.7 ± 2.0	3.3 ± 2.0	0.400

Caption 5. *P values in bold significantly differ between the HMB and active control groups at baseline, $p < 0.05$; Student's t-test or Mann-Whitney test.*

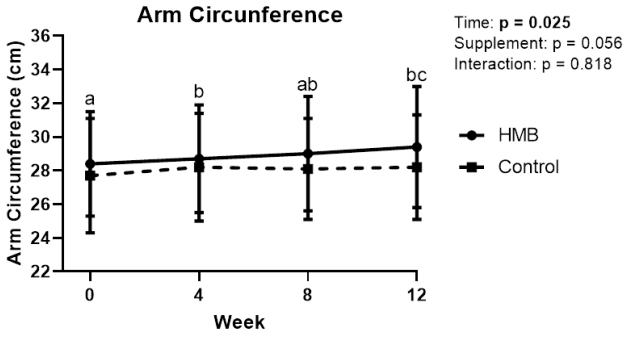
Table 6. Variables related to anthropometrics, muscle, strength, function, and quality of life in patients waiting for liver transplantation, according to time and supplement (n=47).

	Weeks				P value		
	0	4	8	12	Time	Supplement	Time x Supplement Interaction
Caloric intake (kcal/kg)							
HMB	23.3 ± 6.6	22.9 ± 5.5	24.6 ± 9.2	24.5 ± 7.2	0.596	0.714	0.059
ACTIVE CONTROL	27.2 ± 9.2	28.4 ± 8.8	27.5 ± 6.1	27.8 ± 8.0			
Protein intake (g/kg)							
HMB	0.9 ± 0.3	0.9 ± 0.2	1.1 ± 0.5	0.9 ± 0.3	0.065	0.884	0.179
ACTIVE CONTROL	1.1 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4			
Dry weight (kg)							
HMB	66.6 ± 10.3	66.3 ± 9.1	67.3 ± 9.5	66.9 ± 9.7	0.936	0.994	0.218
ACTIVE CONTROL	66.5 ± 11.0	67.2 ± 11.0	66.1 ± 9.9	66.7 ± 10.5			
Body Mass Index (kg/m²)							
HMB	24.2 ± 3.8	24.2 ± 3.7	24.6 ± 3.8	24.4 ± 3.7	0.762	0.508	0.278
ACTIVE CONTROL	23.7 ± 2.8	24.0 ± 3.0	23.6 ± 2.7	23.8 ± 3.0			
Arm Circumference (cm)							
HMB	28.4 ± 3.1[a]	28.7 ± 3.2[b]	29.0 ± 3.4[ab]	29.4 ± 3.6[bc]	**0.025**	0.056	0.818
ACTIVE CONTROL	27.7 ± 3.4[a]	28.2 ± 3.2[b]	28.1 ± 3.0[ab]	28.2 ± 3.1[bc]			
Triceps Skinfolds (mm)							
HMB	15.6 ± 8.2	15.3 ± 7.6	14.9 ± 7.3	15.4 ± 8.1	0.165	0.863	0.206
ACTIVE CONTROL	15.7 ± 7.5	16.8 ± 6.8	16.1 ± 6.2	17.2 ± 5.8			
Arm Muscle Circumference (cm)							
HMB	23.5 ± 1.9	23.8 ± 2.1	24.3 ± 2.0	24.5 ± 2.1	0.141	0.204	0.368
ACTIVE CONTROL	22.8 ± 2.5	23.0 ± 2.6	23.0 ± 2.4	22.8 ± 2.4			
Arm Muscle Area (cm)							
HMB	35.1 ± 7.2	36.5 ± 7.9	38.1 ± 7.8	39.1 ± 8.3	0.302	0.078	0.108
ACTIVE CONTROL	33.1 ± 8.8	34.0 ± 9.4	33.8 ± 8.0	33.2 ± 8.6			
Calf Circumference (cm)							
HMB	36.8 ± 4.1	36.8 ± 3.8	36.7 ± 4.0	36.8 ± 3.9	0.140	0.469	0.297
ACTIVE CONTROL	36.0 ± 3.5	36.4 ± 3.7	36.1 ± 3.8	36.6 ± 3.7			

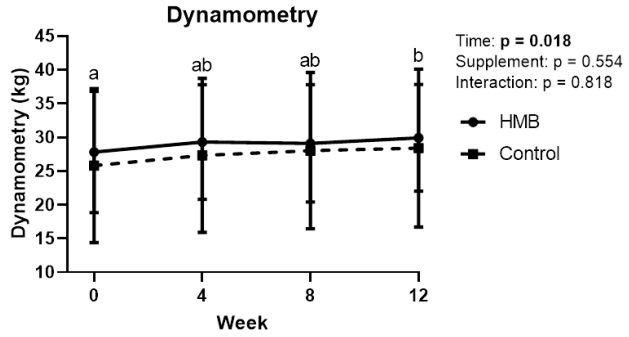
Adductor Pollicis Muscle Thickness (mm)							
HMB	18.5 ± 3.4	18.4 ± 3.5	17.3 ± 5.2	17.5 ± 3.8	0.214	0.079	0.756
ACTIVE CONTROL	16.3 ± 4.1	17.0 ± 4.3	15.8 ± 5.4	15.7 ± 5.4			
Phase angle (°)							
HMB	5.5 ± 0.7	5.4 ± 0.8	5.3 ± 1.3	5.5 ± 3.4	0.150	0.169	0.290
ACTIVE CONTROL	5.1 ± 0.9	4.9 ± 0.9	5.1 ± 0.8	5.2 ± 1.0			
Dynamometry (kg)							
HMB	27.8 ± 9.0 [a]	29.3 ± 8.5 [ab]	29.1 ± 8.7 [ab]	29.9 ± 7.9 [b]	**0.018**	0.554	0.818
ACTIVE CONTROL	25.8 ± 11.4 [a]	27.3 ± 11.4 [ab]	28.0 ± 11.6 [ab]	28.4 ± 11.7 [b]			
Short Physical Performance Battery (score)							
HMB	8.6 ± 1.7	9.4 ± 1.7	9.5 ± 1.2	9.9 ± 1.8	0.084	0.592	0.658
ACTIVE CONTROL	8.9 ±1.9	9.3 ± 1.8	9.3 ±1.6	9.3 ± 1.9			
Frailty index							
HMB	4.2 ± 0.4 [a]	4.0 ± 0.3 [b]	4.0 ± 0.3 [ab]	4.0 ± 0.4 [bc]	**0.003**	0.096	0.630
ACTIVE CONTROL	4.5 ± 0.6 [a]	4.3 ± 0.6 [b]	4.1 ± 0.6 [ab]	4.2 ± 0.6 [bc]			
Quality of life (score)							
HMB	18.0 ± 7.7	19.0 ± 7.2	17.4 ± 8.6	19.9 ± 5.3	0.089	0.792	0.403
ACTIVE CONTROL	18.4 ± 5.8	19.8 ± 6.7	19.2 ± 6.7	19.9 ± 5.6			

Caption 6. *Different letters represent a significant difference between times, $p < 0.05$; Generalized Estimating Equations (GEE) models adjusted by age, sex, food intake (caloric intake*protein intake), MELD-Na, and adherence to supplementation.*

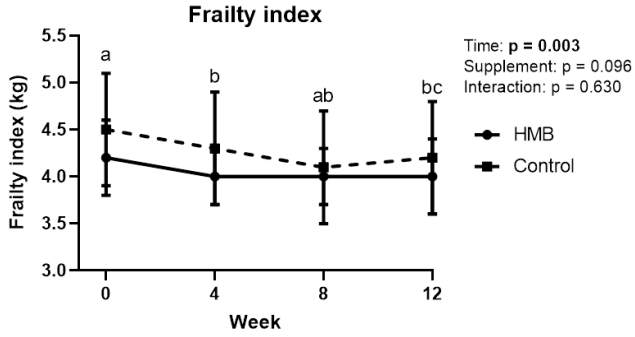
Figure 4. Absolute change (A1) and delta change (A2) in arm circumference measures. Absolute change (B1) and delta change (B2) in dynamometry measures. Absolute change (C1) and delta change (C2) in frailty index scores in the HMB and active control groups during 12 weeks of supplementation (mean ± SD), $p < 0.05$; Generalized Estimating Equation (GEE) models.



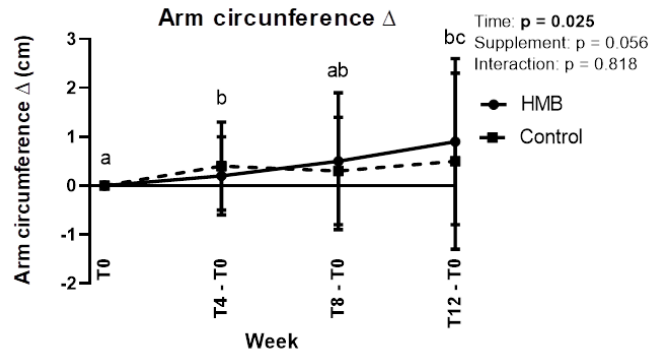
A1



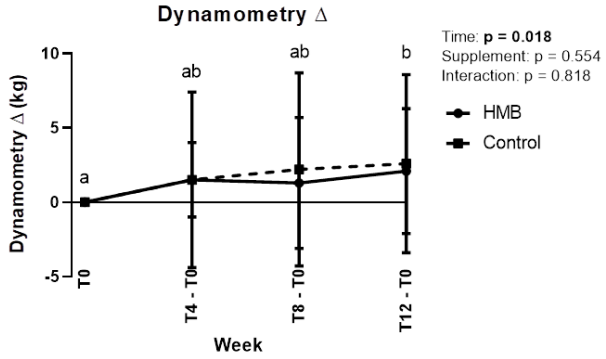
B1



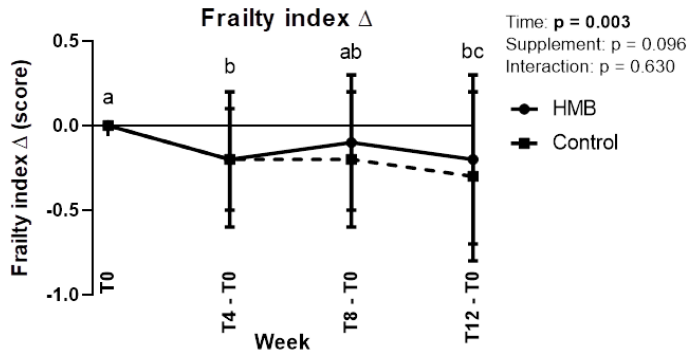
C1



A2



B2



C1

4. Discussion

Patients active on the waiting list for liver transplantation who were included in this study, supplemented with HMB or active control with nutritional intervention for 12 weeks, showed an increase in arm circumference and dynamometry in both groups. The frailty index decreased over time in both groups. Compared to the active control group, the supplementation with HMB had no effects on the anthropometric markers of muscle mass, muscle function, and quality of life in patients on the liver transplant waiting list. These results were also observed when we analyzed patients without HCC (arm circumference and frailty index) and patients with HCC (arm circumference, dynamometry and frailty index - data not shown).

The lack of data on similar populations made comparisons difficult. Our results demonstrate that the addition of HMB to nutrition support was not accompanied by a superior improvement of anthropometric parameters, strength, and functionality in this population, unlike studies recently conducted with patients with compensated cirrhosis (LATTANZI et al., 2021) or undergoing liver transplantation (LATTANZI et al., 2019) whose improvement in performance (LATTANZI et al., 2021) and increase of muscle mass and strength (LATTANZI et al., 2019) with supplementation were observed.

Lattanzi *et al*. (LATTANZI et al., 2021) supplemented 24 patients of both sexes with compensated cirrhosis for 12 weeks with 3g of HMB. The patients' mean age was 59.2 ± 8.4y in the HMB group and 56 ± 4.6y in the placebo group. The majority of patients were classified in Child–Pugh A [HMB group: 85.8% (n=12); placebo group: 90% (n=9)], and the mean of MELD was 9 ± 2.7 in the HMB group and 56 ± 4.6 in the placebo group. The authors observed that, after treatment, there was a significant increase in muscle function in the HMB group. The chair stand test improved at 12 weeks compared to enrolment only in the patients supplemented with HMB (from 14.2 ± 5s to 11.7 ± 2.6s; $p<0.05$). The six-minute walk test also improved in the HMB group at 12 weeks (from 361.8 ± 68m to 409.4 ± 58m; $p<0.05$). Quadriceps muscle mass measured by ultrasound also increased (from 4.9±1.8mm to 5.4±1.8mm; $p<0.05$) and the frailty index decreased (from 4.1±0.4mm to 3.7±0.4mm; $p<0.05$). In the placebo group, these parameters showed no significant modifications (LATTANZI et al., 2021).

The same group of researchers previously performed a similar protocol in individuals 30 days after liver transplantation (LATTANZI et al., 2019). Twenty-two male patients received 3g of HMB for 12 weeks. The patients' mean age was 59.9±6.2 years. The mean of the MELD at transplantation was 16.2±7.5. Among the results observed, there was a significant increase at 12 weeks compared to enrolment of the skeletal muscle mass index evaluated with DXA in the

HMB group (from 6.8±0.7kg/m² to 7.4±0.8 kg/m²; p<0.05); arm muscle circumference (from 26.1±2.3cm to 27.0±2.6cm; p<0.05) and handgrip strength (from 26.6±8.3kg to 32.7±6.4kg; p<0.05) also increased (LATTANZI et al., 2019).

However, in a more recent trial with 43 patients with cirrhosis and malnourishment with previous clinical decompensation, an oral nutritional supplement enriched with 1.5g of HMB twice a day for 12 weeks did not show an increase in anthropometric measures or handgrip strength (ESPINA et al., 2022). The mean age of patients was 60.4±8.6y in the HMB group (n=22) and 61.4±9.3y in the placebo group (n=21). The mean age of patients was 60.4±8.6y in the HMB group (n=22) and 61.4±9.3y in the placebo group (n=21). The median MELD score was 12 (8.5-16.5) and Child–Pugh B [HMB group: 52.3% (n=11); placebo group: 50% (n=11)]. The authors also used anthropometric data to estimate muscle mass. They concluded that supplementation did not change muscle mass (p=0.718) or handgrip strength in either of the two treatment groups (p=0.095) (ESPINA et al., 2022).

It is important to note that, in these two studies in which the authors observed improvement of muscle quality in this population (LATTANZI et al., 2019, 2021), the patients received physical activity counseling at baseline, and muscle mass assessment was assessed by direct methods, DXA, and ultrasound. Unlike the present study and Espina *et al.* (ESPINA et al., 2022), indirect methods based on anthropometric measures to estimate muscle mass were utilized. As a result, indirect methods tend to have larger predictive errors than direct methods and are affected by sample specificity and disease conditions (DUREN et al., 2008). Furthermore, most studies showed substantive effects of ingesting HMB when combined with exercise (LATTANZI et al., 2019, 2021), but these results are still controversial (HOLLAND et al., 2022). So, despite the method of assessing muscle mass and the practice of physical activity, dietary advice is recognized as effective in improving nutritional status in patients with chronic diseases and malnourishment (PLAUTH et al., 2019; RAMACHANDRAN; POTTAKKAT, 2022).

It is necessary to notice that HMB supplementation, as nicely as protein *per se*, may additionally not be adequate to amplify muscle mass (OKTAVIANA et al., 2020). When food intake is insufficient, in terms of energy, there is a negative energy balance and, thus, the wear of skeletal muscle mass is established (HAYASHI et al., 2013). Therefore, food consumption that provides sufficient energy intake and basic nutrients is imperative. In the present study, many participants did not reach the minimum calorie and protein intake recommended for patients with liver cirrhosis, indicating a low intake of staple foods during daily meals. Only 25.5% (n=12) of patients consumed more than 30kcal/kg, and 36.2% (n=17) more than 1.2g/kg of protein in

12 weeks of follow-up in both groups (data not shown). In this context, the improvement in food intake in this group of patients needs to be considered as the first and necessary criterion for the success of the nutritional intervention.

It is well established that dietary counseling and oral nutritional supplements are recommended for managing malnutrition in general clinical conditions (PLAUTH et al., 2019; RAMACHANDRAN; POTTAKKAT, 2022). But in a recent systematic review, it was shown that the results in the patient's nutritional improvement still have considerable heterogeneity, whether in the presence or absence of dietary advice, with or without oral nutritional supplements (BALDWIN et al., 2021). Some studies in which patient supplemented HMB and made only the dietary protocol, without physical activity counseling, had mixed results. Fitschen *et al*. (FITSCHEN et al., 2017) offered 3g of HMB to 33 hemodialysis patients for six months, the patients also received dietary advice, and the authors also found no results in muscle mass improvement (FITSCHEN et al., 2017). Unlike Stout *et al.* (STOUT et al., 2013) who also offered 3g of HMB over ten days to 24 hospitalized elderly patients and observed positive effects on measures (STOUT et al., 2013). But, in Espina *et al.* (ESPINA et al., 2022), the oral nutritional supplement enriched with 1.5g of calcium HMB per bottle offered twice a day for 12 weeks did not change fat-free mass in the patients with decompensated liver cirrhosis. Even offering a supplement with high energy content, providing approximately 550–660 additional kcal per day. Taken together, these mixed results could be explained for many reasons, different studies presented a different methodological combination of dietary counseling, such as the number of times the counseling sessions were provided, how long each session was held and the person who conducted the counseling session (LOW et al., 2021), therefore the outcome may also vary. Hence, it is necessary to explore further the clinical benefit of HMB supplementation in this clinical population and in patients with advanced chronic liver diseases.

Among the measures evaluated in the present study, a significant increase in arm circumference and dynamometry was verified in both groups. Showing that these parameters increased with time but not with treatment. We concluded that modifications were induced by the nutritional intervention with prescription and dietary monitoring. All patients received an individualized meal plan calculated according to guidelines (AMODIO et al., 2013; MERLI et al., 2019; PLAUTH et al., 2019), preferences, and financial conditions. And between each evaluation, patients were contacted to apply the food records and asked about the consumption of capsules and the presence of any side effects of supplementation, if any. These factors enabled better monitoring and greater proximity. Although previous systematic reviews on nutritional therapy in chronic liver disease reached conflicting results (DUPONT et al., 2012; KORETZ; AVENELL;

LIPMAN, 2012; NEY et al., 2013), existing shreds of evidence support that nutritional interventions through dietary counseling have good results in improving the clinical prognosis of cirrhosis (IWASA et al., 2013; FIALLA et al., 2015; YAO et al., 2018).

Patients with liver disease who do not receive dietary advice during follow-up tend to have lower food intake and a greater number of clinical complications than those who do [46,48]. Similar effects can be observed in both groups, intervention and placebo, upon dietary advice (CABRÉ et al., 2000). Therefore, these results reinforce that, regardless of treatment, all patients may benefit from supervised nutritional monitoring.

Another parameter that presented alteration in our assessment was the frailty index, and this marker was reduced in both groups. Otherwise, in Lattanzi *et al.* (LATTANZI et al., 2021) study, an improvement in frailty index was observed in the HMB group (from 4.1±0.4 at enrolment to 3.7±0.4 at the end of protocol; p=0.04), without significant changes in the placebo group (LATTANZI et al., 2021). This reduction in our study may correlate with the clinical condition these patients were in. All participants in this study were active on the transplant waiting list, where the need for a new organ was essential, and the severity of liver disease could impact this index (LAUBE et al., 2018). Up to 43% of patients with advanced liver disease have reduced physical function as consequence of this liver disease (LAUBE et al., 2018). In our study, 31.9% of patients were classified as fragile. The frailty index measured physical function and was calculated using the handgrip strength, the sit-up test, and the balance test (LAI et al., 2017). Our data showed an improvement only in dynamometry during follow-up, but no statistical difference in the other two components, which could have impacted the values of this score.

Chronic liver disease negatively impacts patients' quality of life on the waiting list for liver transplantation (STINE et al., 2020; LANKARANI et al., 2022). Previous studies that have examined the effects of HMB on quality of life in clinical populations have mainly shown no effect (BERK et al., 2008; FITSCHEN et al., 2017) but not all (OLVEIRA et al., 2016). Likewise, using a quality of life questionnaire previously validated in patients with chronic liver disease (MUCCI, 2009), we did not observe significant improvement in any domain of the quality of life questionnaire.

The phase angle is a predictive indicator of disease-related malnutrition (NORMAN et al., 2012). The reduction in PA was independently associated with mortality (SAUERESSIG et al., 2020; RUIZ-MARGÁIN et al., 2021), worse metabolic, nutritional and disease progression profiles in patients with cirrhosis (BELARMINO et al., 2017). Phase angle is related to cell membrane capacitance (YAMADA et al., 2010). The phase angle may reflect twitch contractile properties

and neuromuscular activity which are affected at least in part by cellular membrane function (HIRATA et al., 2022). In the present study, this measurement did not show statistical difference over time and per supplement (Table 6), remained stable throughout follow-up. A similar observation was reported in a study by Lattanzi et al. (LATTANZI et al., 2021). The phase angle remained substantially unchanged during the study in both groups (LATTANZI et al., 2021). It is speculated that these results may be related to maintenance of nutritional status, since these individuals also received nutritional intervention. It is important to emphasize that serial phase angle measurements provide data independent from training effects, while serial measurements of handgrip strength are subject to patients' voluntary muscle contraction.

Among the main strengths of this study, the nutritional counseling provided to all patients needs to be pointed out. However, the present study has limitations that need to be discussed. It was not possible to implement an isonitrogenous intervention as the placebo supplement. It is important to highlight that less than 7% of our patients underwent paracentesis during nutritional monitoring. These patients could show some compromise of the circulating protein/amino acid pool, electrolyte and protein losses can occur during paracentesis (SAUNDERS et al., 2010), so these results should be interpreted with caution. The assessment of muscle mass was not performed as a direct measure of muscle mass but by anthropometric parameters such as arm muscle area and adductor pollicis muscle thickness. Therefore, in an attempt to circumvent the limitations inherent to the anthropometric assessment, these were performed by only one evaluator (coefficient of variation is 3%). Such simple and practical methods of assessing muscle mass have already been highly correlated with robust and comparable methods (KAWAKAMI et al., 2015; NISHIKAWA et al., 2020). If differences exist between the two groups in protein intake but were not detected due to sample sizes, these differences would be very small, judging by the distribution of values for this variable in both groups and at all times. Our patients did not receive physical activity counseling. Nutritional intervention with a multidisciplinary team, with physical therapist and physical educator, during the treatment of cirrhosis can potentially improve long-term nutritional and clinical outcomes.

5. Conclusion

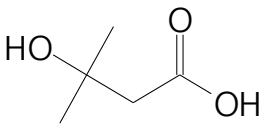
In conclusion, this study demonstrated that the intervention performed with supplementation with beta-hydroxy-beta-methylbutyrate, or active control with nutritional intervention for 12 weeks, improved arm circumference and dynamometry in patients on the liver transplant waiting list. Regarding the frailty index, the analysis showed a reduction over the weeks in both groups. Compared to the active control group, the supplementation with HMB had no effects on anthropometric muscle mass markers, muscle function, and quality of life in patients on the liver transplant waiting list. More studies, conducted with a more specific population when nutritional needs are met, are needed to confirm or refute these results.

5 SUPPLEMENTARY MATERIAL I

β-hydroxy-β-methylbutyrate

Comparison of the three HMB samples

1, 2.3



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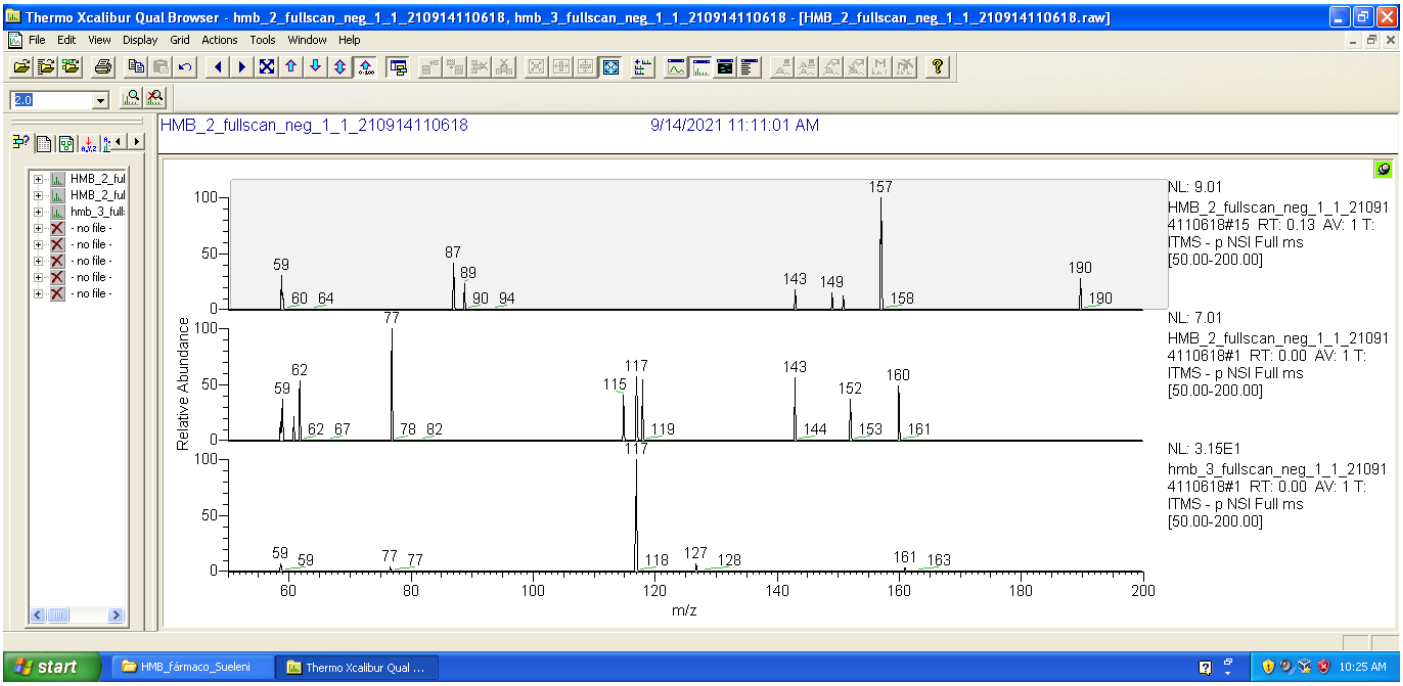

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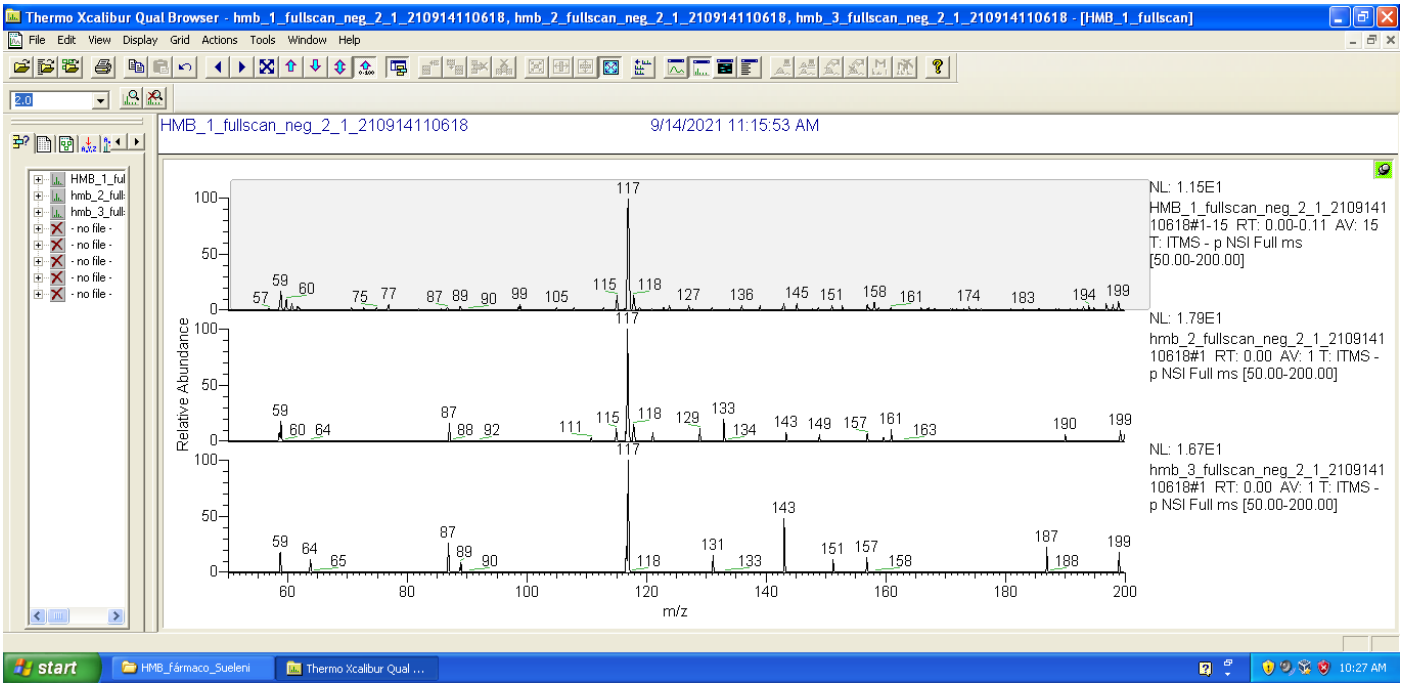

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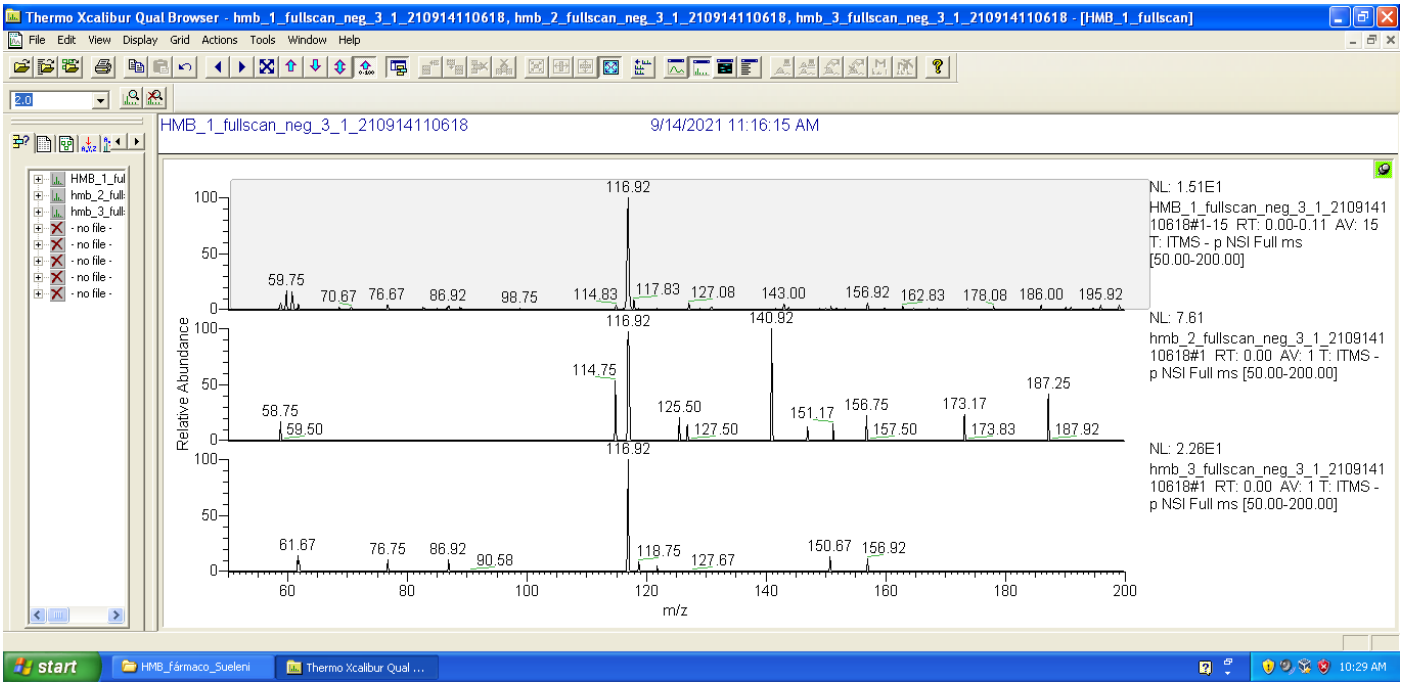

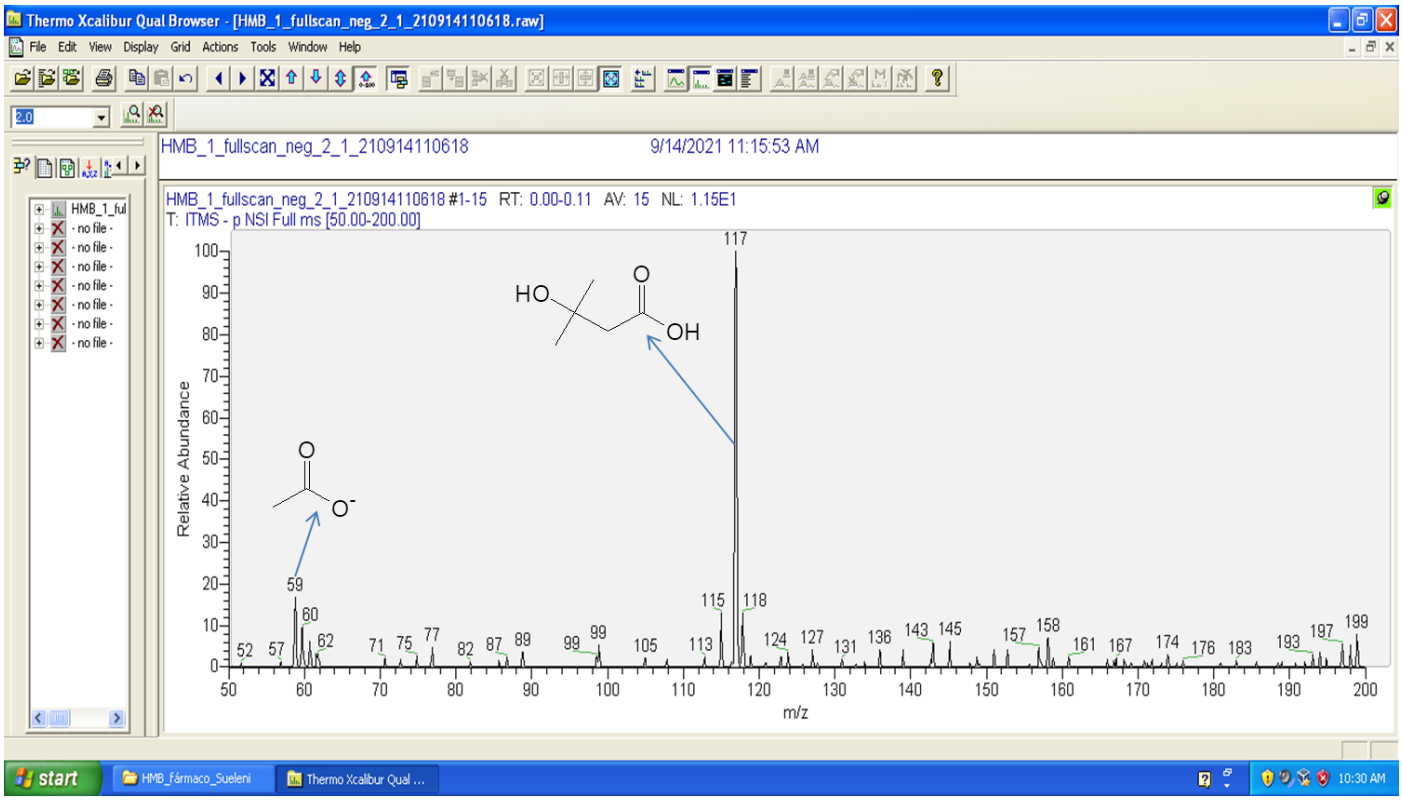
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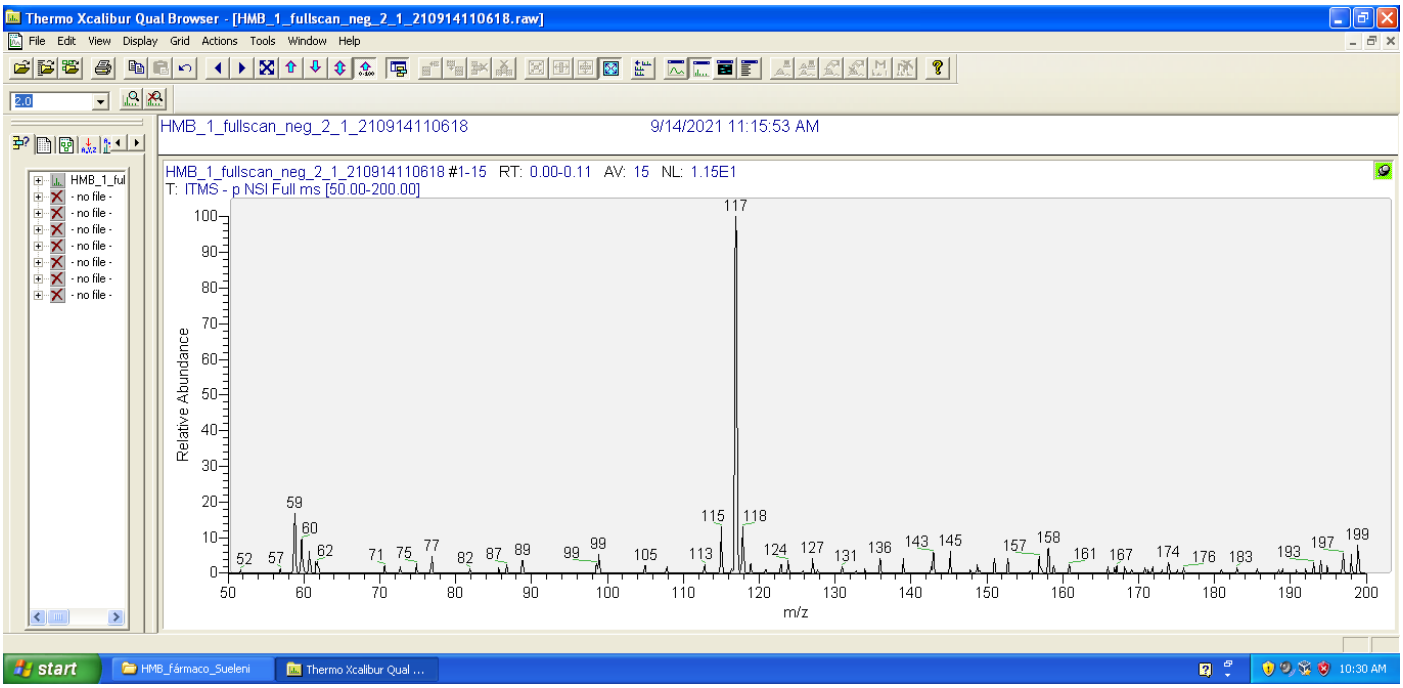
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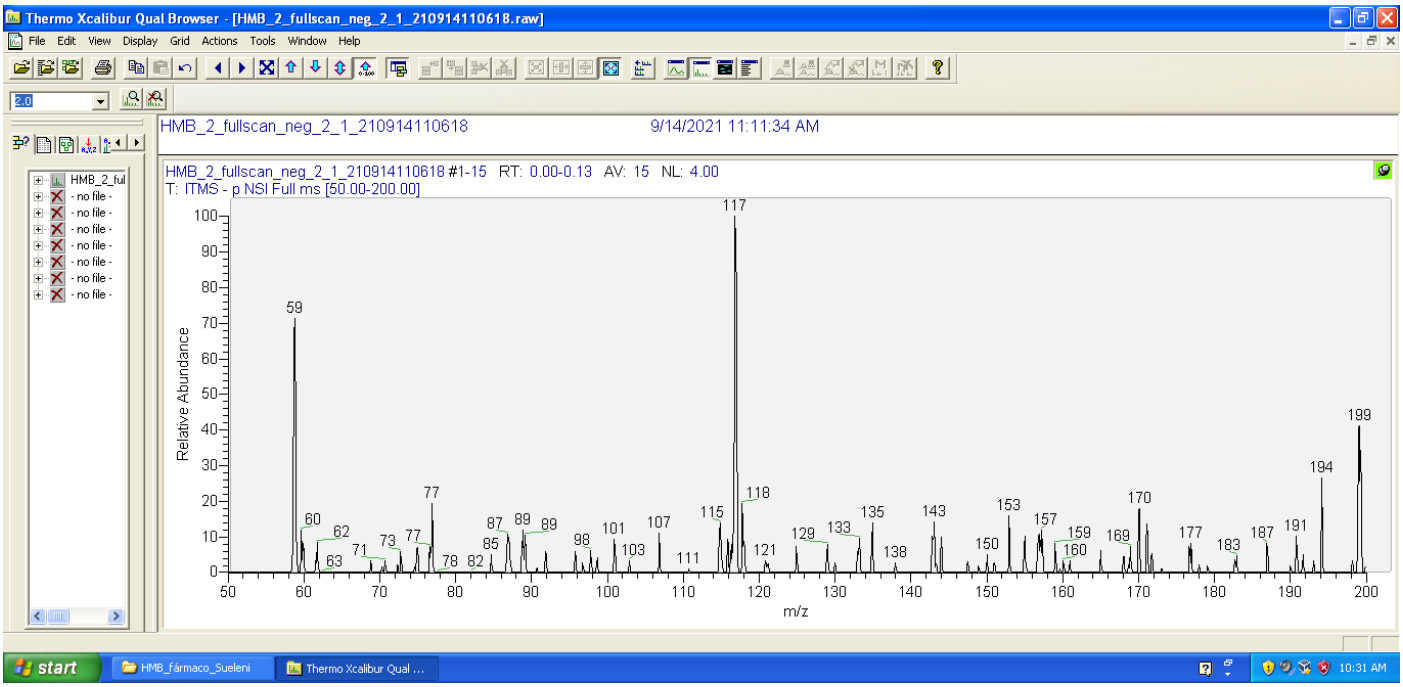
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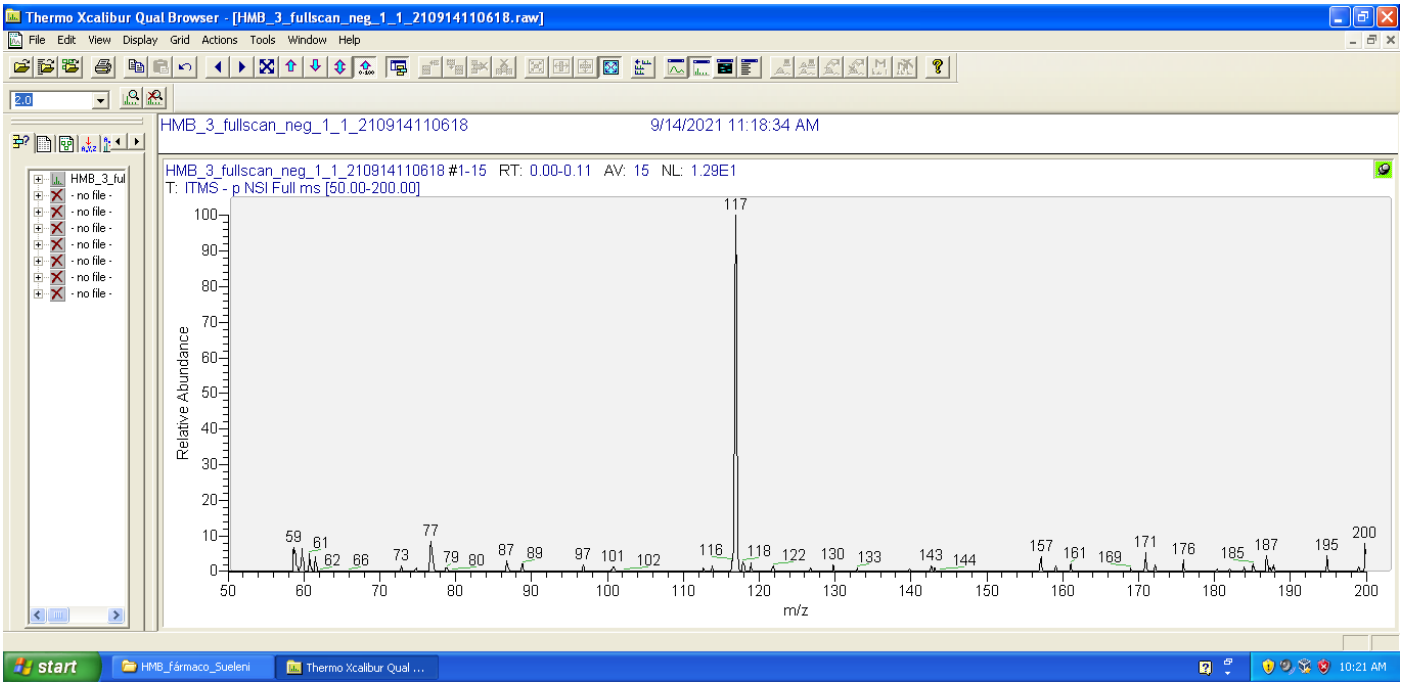
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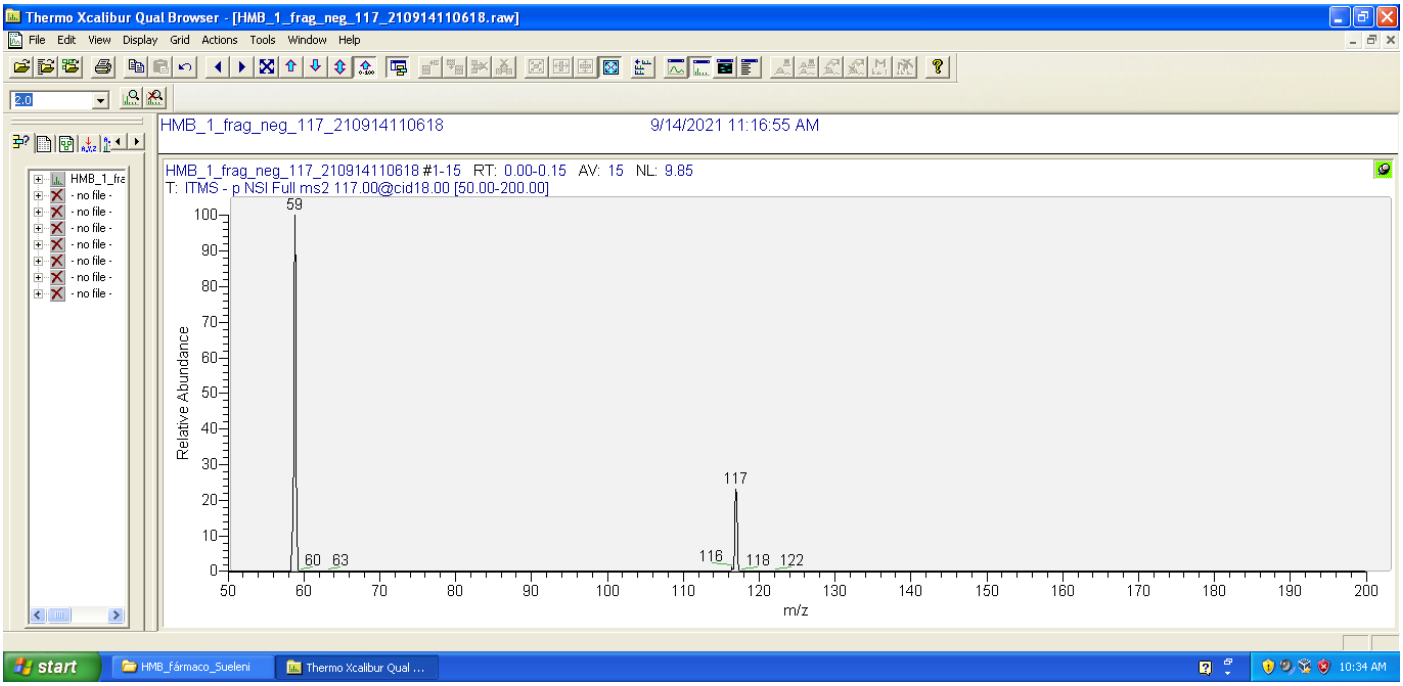
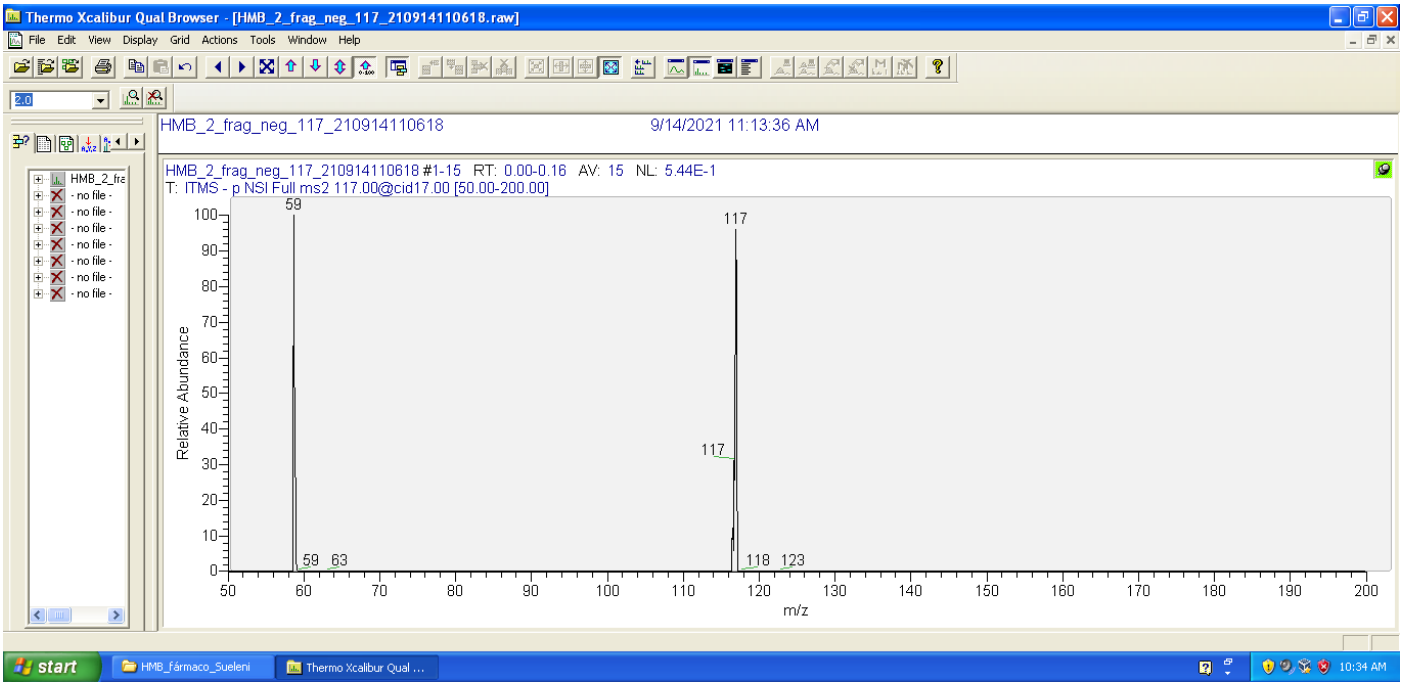
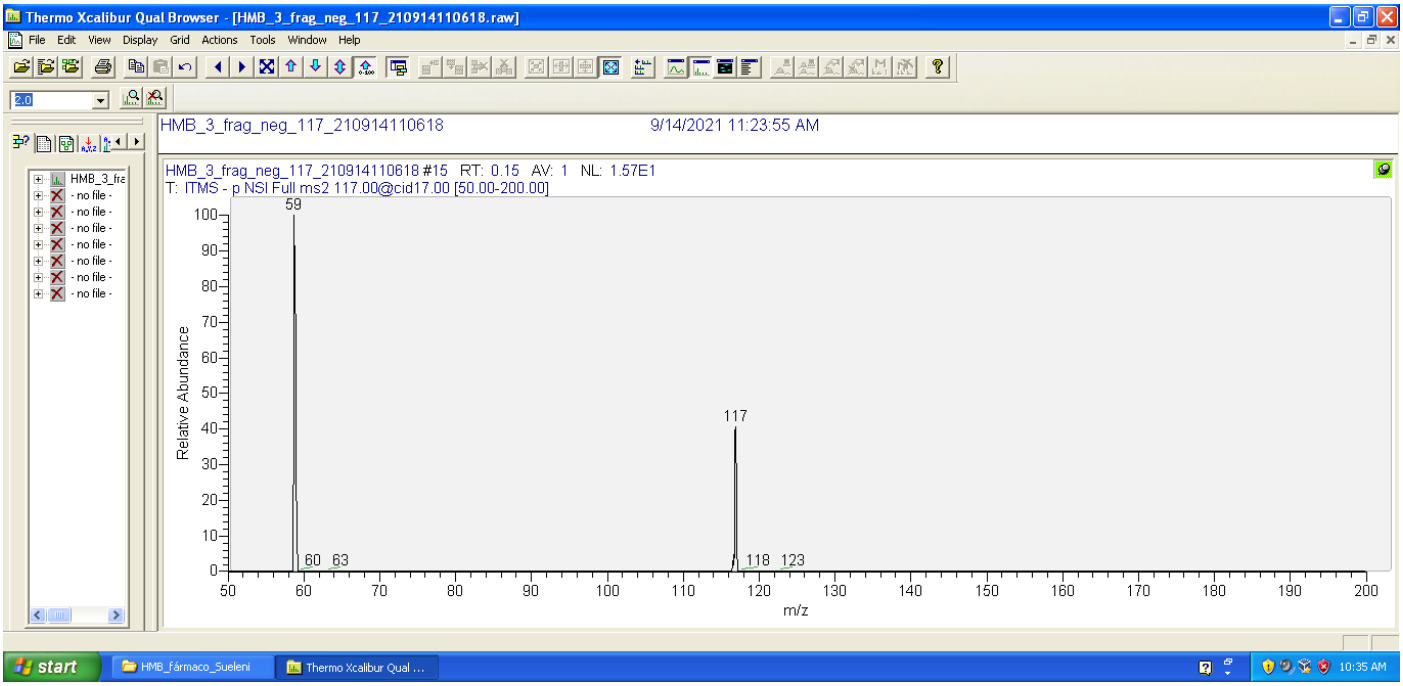
FRAGMENTATION 117



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6 CHAPTER II

ARTICLE II: EFFECT OF A 12-WEEK NUTRITIONAL INTERVENTION IN THE FOOD INTAKE OF PATIENTS ON THE WAITING LIST FOR LIVER TRANSPLANTATION: A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

EFFECT OF A 12-WEEK NUTRITIONAL INTERVENTION IN THE FOOD INTAKE OF PATIENTS ON THE WAITING LIST FOR LIVER TRANSPLANTATION: A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Background: Inadequate food intake is one of the causes of malnutrition in patients with decompensated cirrhosis. Nutritional interventions, through dietary counseling, generally have good results in quality diet improvement. However, nutritional goals are still a challenge for these patients. **Objective:** To evaluate food intake during 12 weeks of nutritional follow-up and assess factors independently associated with the difference between caloric and protein (end-beginning) intake in patients on the waiting list for liver transplantation (LTx). **Methods:** A secondary analysis of a randomized controlled trial with supplementation of 3.0g HMB or active control (3.0g of maltodextrin) and nutritional counseling, prescription, and dietary monitoring in patients on the waiting list for LTx (>18y) for 12 weeks. Sociodemographic, clinical, lifestyle, nutritional/anthropometric/body composition, physical function, and quality of life data were collected. Dietary guidelines for patients with cirrhosis were used to prescribe the nutritional plan (35kcal/kg; 1.5g/kg dry weight for protein; other nutrients according to Dietary Recommended Allowances - DRIs; late evening snack) and to evaluate the nutritional goals (30kcal/kg; 1.2g/kg dry weight for protein). Food intake was assessed and quantified using 24-hour recall and/or 3-day food record in six moments: baseline, week 0 (W0), week 2 (W2), week 4 (W4), week 8 (W8), and week 12 (W12). Dietary consumption was evaluated through the weeks using the paired t-test or Wilcoxon test. Linear regression models were performed to identify factors independently associated with the difference between caloric (kcal/kg) and protein intake (g/kg) in W12- Baseline. **Results:** Forty-seven patients (55.0±10.6y, 72.3% male) were evaluated. Only 25.5% (n=12) of patients achieve nutritional goals at the end of the study. The mean energy intake in baseline was 1782±784kcal (27.6±13.2kcal/kg) without difference between times. The total protein intake g/kg increased between week W0 [63.4±29.8g; 0.8 (0.2-2.2g/kg)] and W8 [72.0±28.0g; 1.0 (0.4 – 2.6g/kg; p=0.026; p=0.032, respectively]. The consumption of cholesterol, calcium, phosphorus, magnesium, iron, and niacin increased ($p<0.05$) during follow-up, as well as the consumption of the leguminous; roots and tubers; dairy; and meat, poultry, and fish groups through the time ($p<0.05$). The presence of ascites, subjective global assessment classification, frailty index classification, short physical performance battery score, systemic symptoms, and emotional function were independently associated with the caloric intake difference between W12-Baseline ($p<0.05$). Diabetes mellitus, subjective global assessment classification, poor performance, fatigue, systemic symptoms, and emotional function were independently associated with the difference in protein intake between W12-Baseline ($p<0.05$). **Conclusion:** Patients on the waiting list for LTx marginally improved food intake during nutritional follow-up, but only a few patients could reach the nutritional recommendations of current guidelines. Some clinical and nutritional variables independently influenced energy and protein intake between W12-Baseline weeks.

KEYWORDS: liver cirrhosis, liver transplant, malnutrition, dietary intake, nutritional intervention.

1. Introduction

Malnutrition is one of the most common complications in patients with decompensated advanced liver disease (CHEUNG; LEE; RAMAN, 2012; JOHNSON et al., 2013; MOCTEZUMA-VELÁZQUEZ et al., 2013). This situation has a negative impact on the clinical evolution of these patients, as it is related to sarcopenia, compromised quality of life and is an independent predictor of morbidity and mortality before and after liver transplantation (LTx) (DUONG; SADOWSKI; RANGNEKAR, 2021).

The causes of malnutrition are inadequate food intake, impaired digestion and absorption, and altered metabolism (MERLI et al., 2019). In an attempt to minimize this outcome, nutritional interventions through dietary counseling generally have good results in improving the clinical prognosis of cirrhosis (YAO et al., 2018). Nutritional status significantly improves liver function and regeneration, surgical outcomes, transplantation, survival, and complication rates (IWASA et al., 2013; FIALLA et al., 2015; CORNIDE-PETRONIO et al., 2020).

According to current recommendations for patients with cirrhosis, nutritional therapy in the pre-LTx is centered on adequate caloric (30-35kcal/kg) and protein (1.2-1.5kcal/kg) supply, fractionated meals and an appropriate night snack to minimize gluconeogenesis and protein catabolism (PLAUTH et al., 2019). However, nutritional goals and adherence to interventions are still great challenges to be faced. Some studies have evaluated food intake in patients on the LTx waiting list. Among these, most reveal food consumption below the recommendation (FERREIRA et al., 2013; NEY et al., 2015; MARR et al., 2017; PALMESE et al., 2019). Insufficient energy intake among cirrhotic patients range from 76% to 94% (FERREIRA et al., 2013; NEY et al., 2015; PALMESE et al., 2019).

Clinical trials with prescription and dietary monitoring in patients with decompensated advanced liver disease on the waiting list for liver transplantation are still limited. Few authors have presented data on macronutrients and micronutrients intake, and total food intake has rarely been studied (LUNATI et al., 2013; RUSU et al., 2013). Investigations assessing dietary intake in this population are helpful to verify the adherence and effect of nutritional interventions on consumption intake, and, consequently, prevent malnutrition as well as its harmful consequences. Therefore, this study aimed to evaluate adherence and food intake during 12 weeks of nutritional counseling, prescription, and dietary monitoring in patients awaiting LTx. We also aimed to assess independent factors related to the difference between

caloric and protein intakes in the final assessment (W12) in comparison to the baseline (Baseline) in patients on the waiting list for LTx.

2. Materials and Methods

Trial design

This work is a secondary analysis of a double−masked randomized clinical trial with a nutritional intervention and supplementation of 3.0g HMB or active control (3.0g of maltodextrin) without effects of supplementation on the outcomes studied (FERREIRA et al., 2023) (ReBec Platform code RBR-9snttn). In the present article, we explored the prospective nature of the nutritional intervention (nutritional counseling, prescription, and dietary follow-up) for 12 weeks in patients on the waiting list for LTx, being followed up at the Hospital das Clínicas of the Federal University of Minas Gerais, from August 2019 to February 2022. The study was approved by the Ethics Committee of the Federal University of Minas Gerais (3.134.996), and all participants signed the Informed Consent Form (Annex A).

Participants

Adult outpatients over 18 years of age, active on the liver transplant waiting list, of both genders, who agreed to participate in the study and finalized the randomized controlled trial were included in this evaluation. Patients using protein and free amino acid nutritional supplements and known medications that may affect skeletal muscle mass (progestational agents, steroids, and growth hormone) were excluded. Patients on dialysis, those with a body mass index (BMI) above 30kg/m², retransplantation, inflammatory bowel disease, decompensated hypothyroidism and hyperthyroidism, patients with acquired immunodeficiency syndrome (AIDS), with active cancer [except hepatocellular carcinoma: hepatocarcinoma greater than or equal to 2 cm and with no indication for resection (single nodule of up to 5 cm or, if multiple, a maximum of 3 with up to 3 cm each)], illiterate people without a literate companion present were also excluded.

Interventions

Patients were invited to participate in the study while waiting for the outpatient medical appointment. At this moment, they received clarifications about the research and the conditions to participate. Participants were assessed in person five times: Initial assessment (Baseline); Week 0 (W0), the start of intervention; Week 4 (W4); Week 8 (W8) and after 12 weeks (W12) (Figure 1). During face-to-face consultations, 24-hour recalls (24hR) were applied. The three

non-consecutive-day food records (3-FRs), including two weekdays and one of the weekends, were requested every two weeks after the face-to-face consultations. Participants food intake was assessed in six moments: Initial assessment (Baseline) (24hR + 3-FRs) (2 weeks before intervention day); Week 0 (W0) (24hR), the start of intervention; Week 2 (W2) (3-FRs) (2 weeks after intervention day); Week 4 (W4) (24hR + 3-FRs); Week 8 (W8) (24hR + 3-FRs) and after 12 weeks (W12) (24hR + 3-FRs) (Figure 5). Photographs of household measurements were available for the participants in order to improve the accuracy of food quantification in dietary recall.

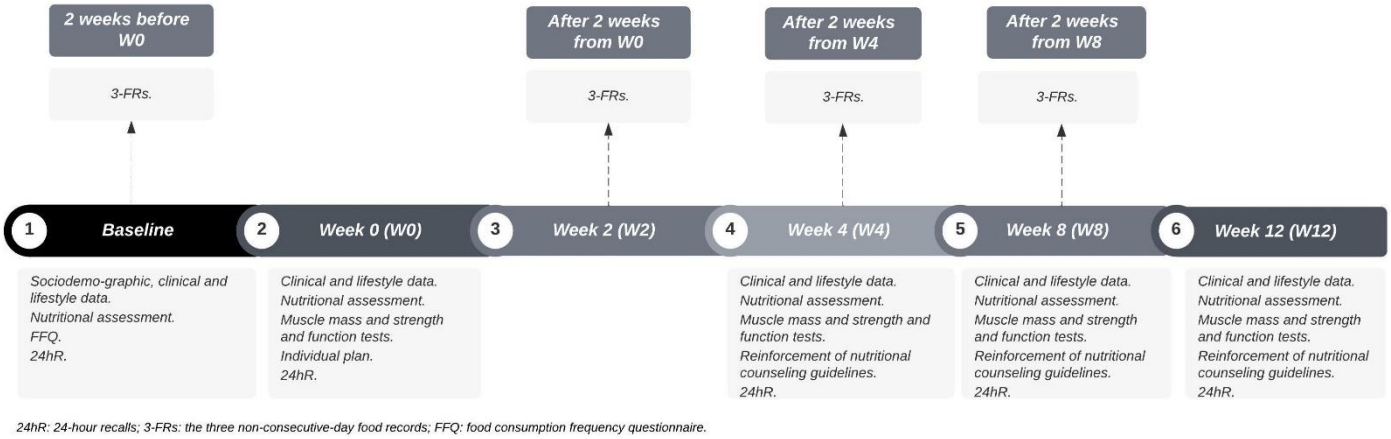
In the initial assessment (Baseline), before the intervention, sociodemographic, clinical, and lifestyle data were collected, and nutritional assessments were carried out. Ascites was classified as mild, moderate, and severe, according to the criteria of the International Club of Ascites (MOORE et al., 2003). To quantify food and nutrients intakes, the 24hR and the food frequency questionnaire (FFQ) were applied in the Baseline (MINISTÉRIO DA SAÚDE, 2015). At the end of this appointment, instructions regarding the 3-FR register and nutritional counseling were performed. Patients were instructed to write down (or their literate companion) the 3-day food records (3-FRs) at home to be delivered on the second meeting (W0), that is, 2 weeks before starting supplementation. The other 3FRs were performed in the same way: 2 weeks before the next face-to-face appointment (on W4, W8, ad W12). Nutritional counseling was carried out from information obtained regarding food consumption, with emphasis on food fractioning, avoiding periods of fasting longer than 3 hours, as well as late evening snack consumption (after 9 p.m.).

At the second meeting (W0), enrolled patients received nutritional guidance and a proposal for an individual eating plan, calculated based on applied surveys and current recommendations for liver cirrhosis: 1.5g/kg of protein; 35 kcal/kg; 60% carbohydrates; 20% lipids; micronutrients according DRI´s, small meals evenly distributed throughout the day; and a late evening snack after 9 p.m. containing 50g of carbohydrates (AMODIO et al., 2013; MERLI et al., 2019). Energy and protein intake were compared with nutritional requirements, calculated according to dry weight (a percentage of weight was subtracted based upon the severity of ascites - mild 5%; moderate 10%; severe 15% - with an additional 5% subtracted if bilateral pedal edema was present) (MERLI et al., 2019). Clinical, biochemical, and lifestyle data were recorded. Anthropometric, dietary (24hR), and body composition evaluations were performed. At the end of the appointment, patients received a 3-day food record form to record the foods and beverages consumed. Therefore, this 3-FRs refers to 2 weeks (W2) after the day patients received the dietary plan (W0). Fortnightly calls were made to remind them of the notes or for

application over the phone. Tests for muscle mass, function, strength, and quality of life were performed as described in our first study (Ferreira et al. 2023).

All assessments carried out in W0 were performed in W4, W8, and W12 as well. During these meetings, patients were asked about adherence to previously provided nutritional counseling and changes in eating habits. In view of the difficulties reported by the patients, changes in the dietary plan were presented, orally and/or in writing, using educational materials and according to the specific guidelines for liver diseases. Patients were encouraged to eat fruits and vegetables every day, to take frequent and small meals, to minimize fasting (late evening snack), and to control sodium intake. Counseling and dietary monitoring were provided throughout the study period as well as the emphasis on compliance with the dietary plan, including the use of supplements.

Figure 5. *Timeline of the variables evaluated during the nutritional intervention in patients on the liver transplant waiting list.*



Dietary and nutritional assessment

Food consumption was assessed using a 24hR and 3-FRs. Food intake at each of the six times (Baseline, W0, W2, W4, W8, W12) was calculated by summing the nutrient and food groups intake values in the surveys (24hR and 3-FRs), and the average was calculated. In total, 799 dietary surveys were requested (235 24hR and 564 3-FRs). Foods and beverages were categorized into 13 food groups (Bakery products; Cereals; Leguminous; Roots and tubers; Vegetables; Fruit; Beverages; Dairy; Meat, poultry, and fish; Egg; Fats and oils; Oleaginous; and

Sugars and sweets) (MINISTÉRIO DA SAÚDE, 2015). The homemade measures of food were converted into grams according to the Table for Assessment of Food Consumption in Home Measures (PINHEIRO, 2004). Foods were quantified using the following food composition resources: the Brazilian Food Composition Table (TACO) (TACO, 2011), the Brazilian Food Composition Table (TBCA) (TBCA, 2022), and the United States Department of Agriculture (USDA) table (USDA, 2019). In the case of using oral nutritional supplements, all nutrients were quantified according to the nutritional label. The average calculation of calories, macronutrients, micronutrients, and food groups intake was performed using Microsoft® Excel software. Energy and protein intake were compared with nutritional established for liver diseases, considering the dry weight (a percentage of weight was subtracted based upon the severity of ascites - mild 5%; moderate 10%; severe 15% - with an additional 5% subtracted if bilateral pedal edema was present) (MERLI et al., 2019).

The cutoff point for adequate consumption of calories and protein was equal to or greater than 30 kcal/kg and 1.2 g/kg, respectively (PLAUTH et al., 2019). The delta between calorie (kcal/kg) and protein (g/kg) in each moment considering Baseline and the initial moment (W0) values were performed. The difference between calorie (kcal/kg) and protein (g/kg) at the end of the study (W12) and the Baseline was used as the dependent variable in the univariate and multivariate analyses.

Macronutrients were analyzed according to the amount in grams and the percentage related to the energy intake (EI) of the diet. Fiber and micronutrient intake were compared with values recommended by the Dietary Reference Intakes (DRI) and the percentage of patients above these ranges. The Estimated Average Requirement (EAR) was used, and, for nutrients without EAR, the Adequate Intake (AI), according to the gender and age group of the patients (IOM, 1998, 2002). The late evening snack was considered if the last meal was eaten after 9 p.m. (AMODIO et al., 2013; MERLI et al., 2019; PLAUTH et al., 2019). Factors that could interfere with non-adherence to dietary prescription were qualitatively recorded when informed by the patient and perceived by researchers.

Investigation of independent factors associated with food intake

Sociodemographic data such as age, sex, education, and family income were collected. The clinical data collected were: the presence of clinical comorbidities (diabetes mellitus, arterial hypertension, and others), indication for liver transplantation, presence of ascites, edema, esophageal varices, encephalopathy, different stages of liver disease (CHILD-PUGH and Model for End Stage Liver Disease sodium (MELD-Na)), use and dosage of medications. Lifestyle data

were also assessed, such as physical activity practice, hours of sleep per night, hours of daily TV, smoking, alcohol consumption, and current use of oral nutritional supplements.

The anthropometric data collected were weight, height, body mass index (BMI), arm circumference (AC), triceps skinfold (TSF), arm muscle circumference (AMC), calf circumference (CC), and adductor pollicis muscle thickness (APMT). The nutritional status assessment was carried out using the subjective global assessment (SGA), and patients were classified as nourished, moderately malnourished, and severely malnourished (HASSE et al., 1993). Bioelectrical impedance analysis (BIA) was performed to obtain phase angle (PA). Muscle mass was assessed by indirect markers: arm muscle area (AMA), arm muscle circumference (AMC), and adductor pollicis muscle thickness (APMT). Muscle strength was assessed through dynamometry and functionality by the Short Physical Performance Battery (SPPB) test (NAKANO, 2007) and by the frailty index (FI) (LAI et al., 2017). The quality of life assessment was performed using the Chronic Liver Disease Questionnaire (MUCCI, 2009). How these variables were measured, as well as the cutoff points, are described in the previous article (FERREIRA et al., 2023).

Statistical methods

The last observation carried forward (LOCF) method was used to impute missing data from patients who did not attend the five assessments (n=3). These individuals had the missing data imputed using the method of last observation carried forward (LOCF). The categorical variables were analyzed by absolute frequencies and percentages. For the quantitative ones, the calculation of mean and standard deviation (for normally distributed data according to Shapiro Wilk test) or median, minimum, and maximum (for non-normally distributed data) was used. The amount of calories, macronutrients, micronutrients, late evening snacks, and food groups intake over time (Baseline; W0; W2; W4; W8 and W12) were evaluated through the paired t-test or Wilcoxon test, and McNemar test. The differences among delta of caloric (kcal/kg) and proteins (g/kg) each time and baseline or the last time were checked by paired t-test or Wilcoxon test.

Factors associated and correlated with the difference between W12 and Baseline in caloric (kcal/kg) and protein intake (g/kg) were investigated using the Kruskal-Wallis test, Student's t-test, or the Mann–Whitney U-test (according to the distribution of the data) and the chi-squared test (or Fisher's exact test when appropriate) or using Spearman test or Pearson test (according to the distribution of the data), respectively The variables with $p<0.2$ in the univariate analysis were included in the multiple linear regression model. The difference between W12 and

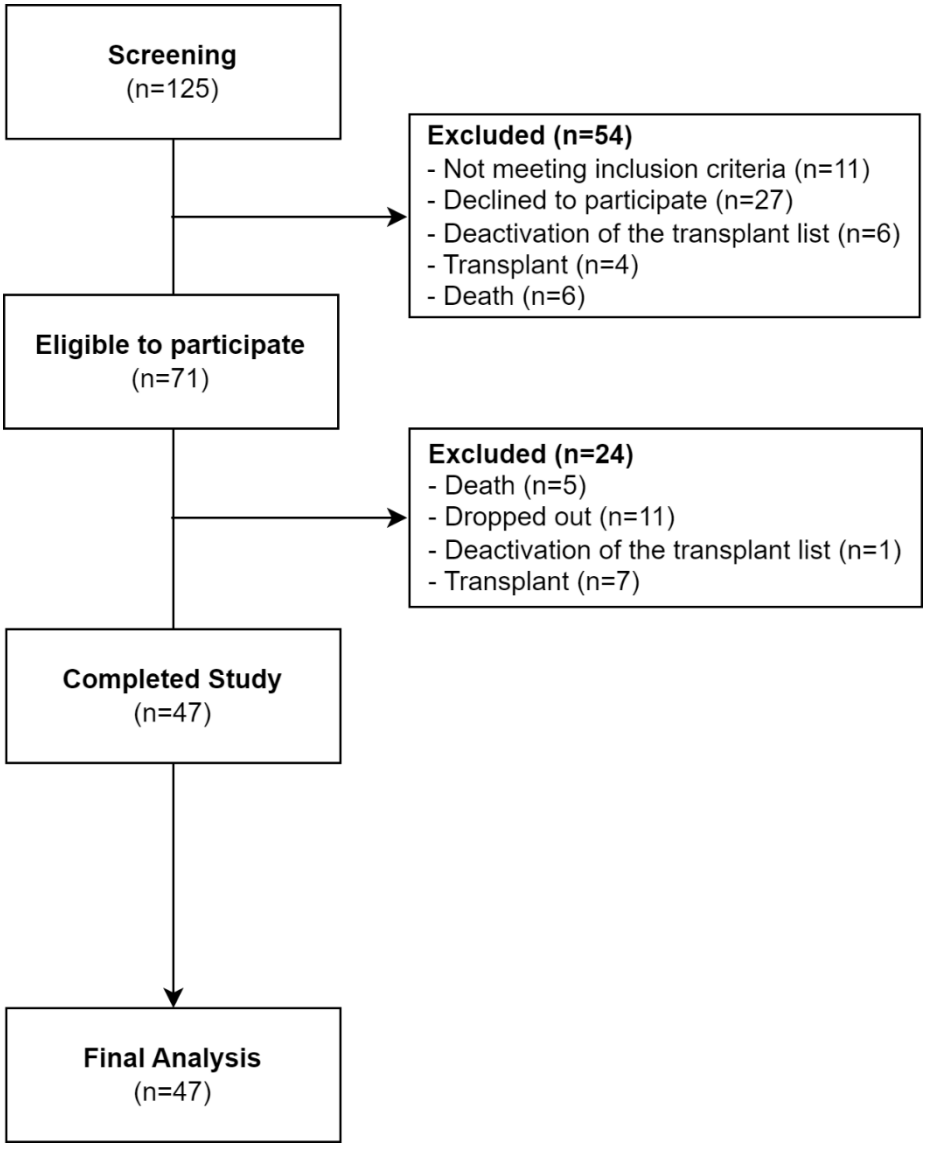
Baseline in caloric (kcal/kg) and protein intake (g/kg) was used as dependent variables in the multiple linear regression model. Multicollinearity was tested using Variance Inflation Factor (VIF) > 10 inside the linear regression function of SPSS. The significance level adopted was 5% for statistical analyses. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc, Chicago, IL, USA).

3. Results

General categorization of patients enrolled in the nutritional intervention

Forty-seven patients were evaluated, with a mean age of 55.0 ± 10.6y, 72.3% (n=34) male. During follow-up, five patients died, eleven dropped out, and seven underwent transplantation during the intervention. The other losses, refusals, and exclusions are described in Figure 6.

Figure 6. *Flow chart of subject's recruitment.*



The main indications for liver transplantation were ethanolic cirrhosis (27.7%), cryptogenic cirrhosis (25.5%), and hepatocellular carcinoma (19.1%). Among the most frequent

clinical complications of liver failure at the Baseline were edema (63.8%), ascites (59.6%), and esophageal varices (44.7%). Only 8.5% (n=4) used dietary supplements, and most did not practice any physical activity (68.1%).

At the Baseline, most of the patients, 76.6% (n=36), had malnutrition, according to the SGA. The means of usual weight before liver disease and of current dry weight were 71.4±15.6kg and 66.6±10.5kg, respectively. Characterization data of patients are shown in Table 7.

Table 7. Baseline characteristics of patients on the waiting list for liver transplantation enrolled in the nutritional intervention (n=47).

Variables	Baseline
Sociodemographic	
Age (y)	55.0 ± 10.6
Education (y)	7.7 ± 4.6
Monthly family income (R$)	2237.7 ± 1625.1
Sex	
Male	72.3% (n=34)
Female	27.7% (n=13)
Clinics	
Child-Pugh	
A	27.7% (n=13)
B	68.1% (n=32)
C	4.3% (n=2)
MELD-Na	14.7 ± 4.1
Transplant indication	
Alcoholic Cirrhosis	27.7% (n=13)
Hepatitis B virus	8.5% (n=4)
Hepatocellular carcinoma	19.1% (n=9)
Cryptogenic Cirrhosis	25.5% (n=12)
NASH	8.5% (n=4)
Others	23.4% (n=11)
Comorbidities	
Diabetes mellitus	31.9% (n=15)
Arterial hypertension	31.9% (n=15)
Indicators of disease severity	
Ascites	59.6% (n=28)
Mild	71.5% (n=20)
Moderate	17.8% (n=5)
Severe	10.7% (n=3)
Edema	63.8% (n=30)
Esophageal varices	44.7% (n=21)
Hepatic encephalopathy	17.0% (n=8)
Lifestyle	
Former smokers	42.6% (n=20)
Former drinkers	76.6% (n=36)
Physical activity practice	31.9% (n=15)
Physical activity per week (minutes)	39.7 ± 80.7

Daily TV (h)	2.5 (0.0 – 6.0)
Sleep per night (h)	8.1 ± 2.4
Nutritional status	
Subjective Global Assessment (SGA)	
Nourished	23.4% (n=11)
Moderately malnutrition	61.7% (n=29)
Severe malnutrition	14.9% (n=7)
Dietary Intake	
Oral nutritional suplement use	8.5% (n=4)
Albumin	25% (n=1)
Nutren/Trophic ®	75% (n=3)
Anthropometrics/body composition	
Dry weight (kg)	66.6 ± 10.5
Body Mass Index (kg/m²)	24.0 ± 3.3
Arm Circumference (cm)	28.1 ± 3.2
Calf Circumference (cm)	36.4 ± 3.8
Triceps Skinfold (mm)	13.7 (4.2 – 34.0)
Arm Muscle Circumference (cm)	23.0 ± 2.6
Arm Muscle Area (cm²)	33.9 ± 8.1
Adductor Pollicis Muscle Thickness (mm)	17.4 ± 3.9
Resistance (ohm)	486.8 ± 89.8
Reactance (ohm)	45.0 ± 10.9
Phase angle (º)	5.3 ± 0.8
Functionality	
Dynamometry	
Highest of the six measurements (kgf)	26.8 ± 10.2
Short Physical Performance Battery	
Disability or very poor performance	-
Low capacity	12.8% (n=6)
Moderate capacity	46.8% (n=22)
Good capacity	40.4% (n=19)
Total score	8.6 ± 1.6
Frailty index	
Robust	-
Pre-frail	66.0% (n=31)
Frail	34.0% (n=16)
Total score	4.3 ± 0.5
Quality of life	
Total score	18.2 ± 6.6
Abdominal symptoms	3.8 ± 2.0
Fatigue	3.4 ± 1.7
Systemic symptoms	4.4 ± 1.3
Activity	4.4 ± 1.5
Emotional function	3.9 ± 1.6
Worry	3.5 ± 2.0

Food intake of patients before and during the nutritional intervention

The qualitative factors perceived as interfering with adherence to dietary prescriptions reported by patients and observed by researchers were worse financial conditions, low level of education, difficulty in communicating over the telephone, and lack of support from family members.

The calorie, macronutrient, and micronutrient intakes of patients on the LTx waiting list during the 12-week follow-up are described in Table 8 and Table 9. In total, 228 24hR were applied, and 564 3-FRs were requested but 451 were delivered, totalizing 679 dietary surveys. Neither the total energy intake nor the energy intake per kg of dry weight significantly changed over the weeks ($p>0.05$). Only 25.5% (n=12) of patients consumed more than 30kcal/kg, and 36.2% (n=17), 1.2g/kg of protein in 12 weeks of follow-up.

A significant difference was observed in protein consumption over the 12 weeks ($p<0.05$). The total protein intake increased between W0 (63.4±29.8g) and W8 (72.0±28.0g; $p=0.026$) as well as the amount per kg/dry weight between W0 [0.8 g/kg (0.2 – 2.2g/kg)] and W8 [1.1 g/kg (0.4 – 2.6g/kg); $p=0.032$]. On the other hand, the percentage of total protein intake to EI reduced between week W8 [16.3% (11.2 – 29.3%)] and W12 [15.2% (9.3 – 27.0%); $p=0.022$] (Table 8).

At baseline, less than 30% of patients achieved the minimum recommendation for calcium, niacin, magnesium, and vitamin A. The cholesterol, calcium, phosphorus, magnesium, iron, and niacin consumption increased ($p<0.05$) during follow-up. At the end of follow-up (W12), more than 60% of the sample reached the minimum DRI recommendations, according to sex and age, for phosphorus, iron, niacin, riboflavin, thiamine, and vitamin C. The other macronutrients and micronutrients showed no statistical difference considering the intake over time ($p>0.05$) (Table 9).

The late evening snack was consumed by 40.4% (n=19) participants before the nutritional intervention (Baseline). This percentage increased to 76.6% (n=36) at W8; $p<0.001$. There was an increase in the percentage of fat content in this meal between baseline (17.5±16.3%) and W12 (28.1±16.5%; $p=0.041$). Differences in the amount of carbohydrate ingested were also observed over time (Table 10).

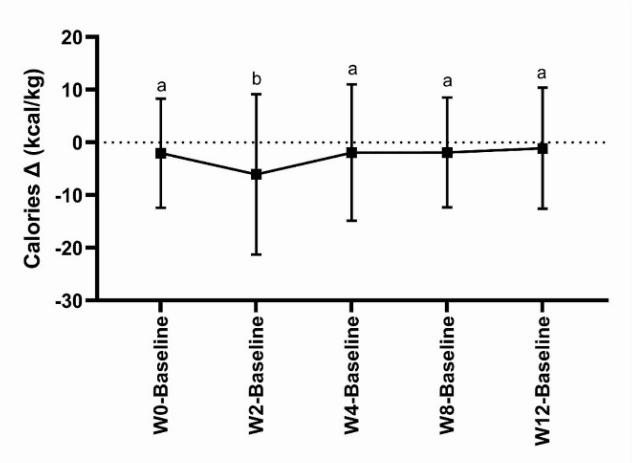
Analysis of food group intake indicated that the amount of food from the cereals group reduced between baseline [310.0g (0.0 – 850.0g)] and W12 [250.0g (0.0 - 519.1g); $p<0.05$]. There was an increase in the leguminous consumption; roots and tubers; dairy; meat, poultry, and fish groups over the time ($p<0.05$). However, meat, poultry, and fish groups reduced at W12 [78.3g (0.0 – 245.0g)] when compared to W2 [104.0g (0.0 – 380.0g); $p<0.05$] (Table 11).

Associated factors with the difference in caloric and protein intake between W12 and baseline of patients during the nutritional intervention

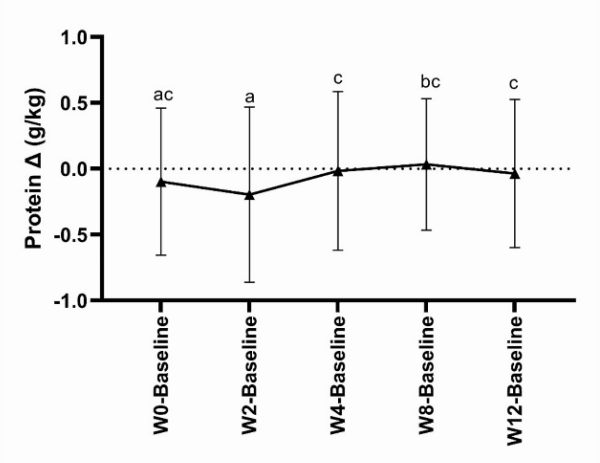
The difference in caloric intake (kcal/g) and protein intake (g/kg) between each moment and Baseline are shown in Figures 7 – A. The difference in caloric intake of W0-Baseline (Δ-2.0±10.4 kcal/kg) differentiated of W2-Baseline delta (Δ-6.0±15.2 kcal/kg; p=0.040). The difference in caloric intake of W2-Baseline (Δ-6.0±15.2 kcal/kg) was significantly different from W4-Baseline (Δ-1.9±12.9 kcal/kg; p=0.030); from W8-Baseline (Δ-1.9±10.4 kcal/kg; p=0.013) and W12-Baseline (Δ-1.9±11.5 kcal/kg; p=0.005). There was a difference between the protein deltas between W0-Baseline (Δ-0.9±0.5 g/kg) and W8-Baseline (Δ0.3±0.5 g/kg; p=0.045). The difference in protein intake of W2-Baseline (Δ-0.2±0.7 g/kg) differentiated of W4-Baseline delta (Δ-0.0±0.6 g/kg; p=0.038); from W8-Baseline (Δ-0.0±0.5 g/kg; p=0.003); and W12-Baseline (Δ-0.0±0.6 g/kg; p=0.044).

In Figure 7 – B, the difference in caloric intake (kcal/g) and protein intake (g/kg) considering each moment and the last moment are shown. The difference in caloric intake of W0-Baseline [Δ-2.2 (-32.9 – 22.2 kcal/kg)] differentiated of W4-W2 delta [Δ-1.7 (-17.3 – 42.2kcal/kg; p=0.023). And between W2-W0 [Δ-1.5 (-36.5 – 20.0kcal/kg) and W8-W4 [Δ-0.0 (-23.8 – 23.5kcal/kg; p=0.05). There was a difference between the protein deltas between W0-Baseline [Δ-0.1 (-1.5 – 2.3g/kg) and W4-W2 [Δ0.0 (-1.1 – 1.9g/kg; p=0.035). And between W4-W2 [Δ0.0 (-1.1 – 1.9g/kg) and W12-W8 [Δ-0.1 (-1.3 – 1.0g/kg; p=0.024). More than 23% and 30% of patients had a greater than 30% increase in caloric and protein intake, respectively, at week 12 when compared to Baseline (Figures 8).

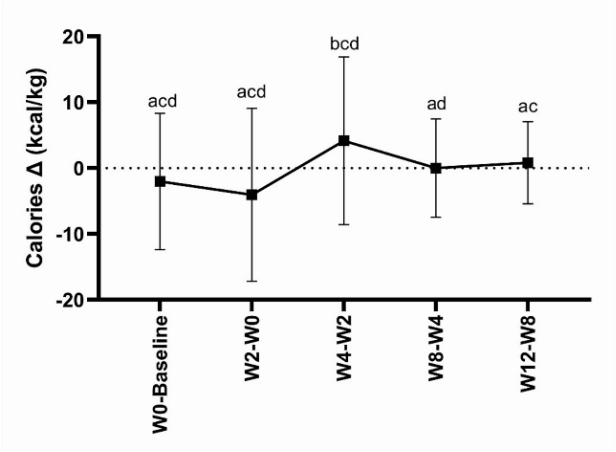
Figure 7. *Difference in caloric intake (kcal/g) and protein intake (g/kg) between W12 and Baseline (A) and difference in caloric intake (kcal/g) and protein intake (g/kg) considering each moment and the last moment (B).*



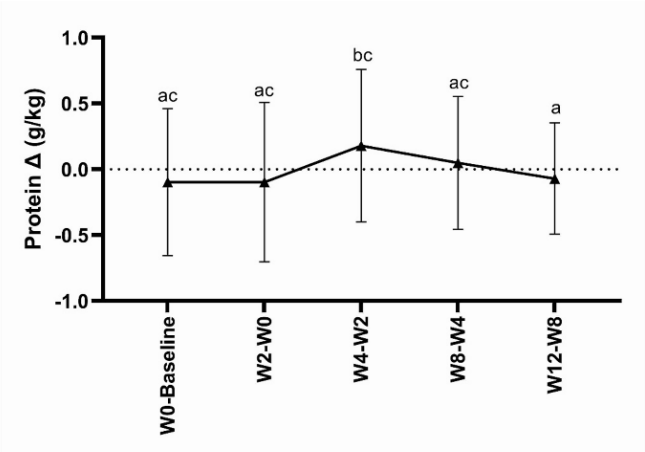
A



A

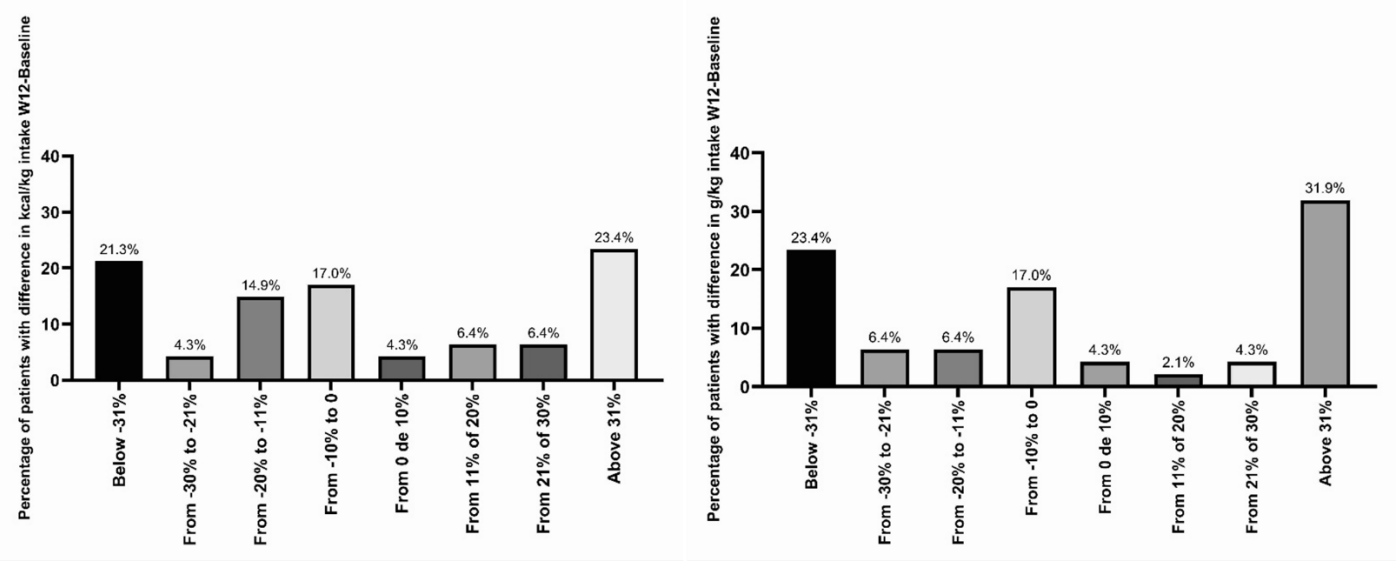


B



B

***Figure 8**. Percentage of patients with difference in caloric intake (kcal/g) and protein intake (g/kg) between W12 and Baseline.*



Patients with indication for LTx for hepatitis B virus showed greater caloric intake difference between W12 and Baseline than those with other indications (Δ 14.2 ± 18.5kcal/kg vs. Δ 0.5 ± 9.9kcal/kg). Numerical variables that were correlated with the difference in protein intake were as follows: fatigue ($r=0.336$; $p<0.05$), systemic symptoms ($r=0.420$; $p<0.05$), activity ($r=0.342$; $p<0.05$), emotional function ($r=0.376$; $p<0.05$) and quality of life score ($r=0.388$; $p<0.05$). MELD-Na score ($r=-0.355$; $p<0.05$) and adductor pollicis muscle thickness ($r=0.336$; $p<0.05$) were correlated with the difference in caloric intake (Table S2; supplementary material II).

Independently associated factors to delta changes in caloric and protein intake are described in Table 12. The presence of ascites, the subjective global assessment, frailty index score, short physical performance battery score, quality of life score, systemic symptoms, and emotional function was associated to the difference of caloric intake between W12 and Baseline ($p<0.05$). The presence of diabetes mellitus, the subjective global assessment classification, SPPB, fatigue, systemic symptoms, and emotional function scores were independently associated with protein intake difference between W12 and Baseline ($p<0.05$).

The presence of ascites (W12), patients nourished (W4), according to SGA, worse categories of the frailty index (W0), and greater scores in SPPB (W4) were a predictor of the lower difference in caloric intake between W12 and Baseline. As well as greater systemic symptoms (W4) and emotional function (W4) were also predictors of greater difference in caloric intake between W12 and Baseline. Patients with diabetes, poor performance, according

to SPPB, greater systemic symptoms (W4), and emotional function scores were a predictor of greater difference in protein intake between W12 and Baseline. Those diagnosed with moderately malnourishment (W4), according to SGA, greater fatigue score (W0), were independently associated with a lower difference in protein intake between W12 and Baseline ($p<0.05$). The other variables did not remain in the final linear regression model ($p>0.05$).

Table 8. Calories and macronutrient intakes of the patients on the waiting list for liver transplantation during nutritional intervention through the 12 weeks (n=47).

	Baseline (2 weeks before intervention)	Start of intervention (W0)	2 weeks after the intervention (W2)	4 weeks after the intervention (W4)	8 weeks after intervention (W8)	12 weeks after intervention (W12)
Calories (kcal)	1782 ± 784	1627 ± 620	1642 ± 486	1656 ± 458	1643 ± 483	1694 ± 413
Calories (kcal/kg)	27.6 ± 13.2	25.0 ± 10.2	25.2 ± 8.6	25.1 ± 7.3	25.1 ± 8.4	26.9 ± 7.7
% ≥30kcal/kg	34.0 (n=16)	29.8 (n=14)	19.1 (n=9)	27.7 (n=13)	27.7 (n=13)	25.5 (n=12)
Carbohydrate (g)	229.0 (59.9 – 624.5)[a]	232.4 (65.1 – 453.3) [ab]	216.3 (89.8 – 368.7) [ab]	230.1 (65.5 – 390.0) [ab]	208.2 (106.0 – 435.3)[b]	226.0 (116.3 – 423.1) [ab]
Carbohydrate (%)	57.7 (28.4 – 74.8)[a]	57.0 (37.7 – 74.8) [ab]	53.3 (39.4 – 65.3) [ab]	55.5 (32.5 – 70.3) [ab]	52.7 (41.1 – 88.1)[b]	54.1 (41.7 – 106.0) [ab]
% ≥ 50%	78.7 (=37)[a]	72.3 (=34) [ab]	55.3 (n=26)[b]	80.9 (n=38)[a]	74.5 (=35)[a]	66.0 (n=31) [ab]
Protein (g)	70.4 ±38.4 [ab]	63.4 ± 29.8[a]	68.7 ± 22.0 [ab]	68.6 ± 21.3 [ab]	72.0 ± 28.0 [b]	67.5 ± 22.7 [ab]
Protein (g/kg)	1.0 (0.2 – 3.1) [ab]	0.8 (0.2 – 2.2)[a]	1.0 (0.6 – 2.5) [ab]	1.0 (0.4 – 2.5) [ab]	1.0 (0.4 – 2.6)[a]	1.0 (0.3 – 2.5) [ab]
% ≥1.2g/kg	34.0 (n=16)[ab]	29.8 (n=14)[ab]	19.1 (n=9)[a]	34.0 (n=16)[b]	38.3 (n=18)[b]	36.2 (n=17)[b]
Protein (%)	14.3 (7.8 – 29.4)[a]	14.9 (9.1 – 28.0)[a]	16.6 (11.5 – 27.3) [ab]	16.2 (10.1 – 31.8) [ab]	16.3 (11.2 – 29.3)[b]	15.2 (9.3 – 27.0)[a]
Fat (g)	46.9 (18.8 – 182.9) [ab]	48.4 (14.2 – 109.0)[a]	51.4 (21.3 – 116.6) [ab]	52.0 (9.2 – 139.4) [ab]	51.4 (16.5 – 87.4) [ab]	57.1 (10.7 – 101.4)[a]
Fat (%)	26.5 (15.8 – 51.1)[a]	27.0 (10.9 – 46.8) [ab]	29.2 (20.1 – 39.1) [ab]	28.5 (8.5 – 54.1) [ab]	29.7 (16.1 – 43.1) [ab]	29.9 (14.6 – 43.3)[b]
% ≥ 20%	85.1 (n=40)	83.0 (n=39)	83.0 (n=39)	91.5 (n=43)	89.4 (n=42)	91.5 (n=43)
Polyunsaturated fat (g)	13.1 (0.6 – 59.0)	13.1 (3.1 – 25.8)	14.1 (4.1 – 27.9)	14.1 (1.2 – 30.9)	13.5 (3.3 – 24.7)	13.8 (0.6 – 28.4)
Polyunsaturated fat (%)	7.9 ± 2.4	7.6 ± 3.7	7.7 ± 1.8	7.8 ± 2.7	7.7 ± 2.6	7.4 ± 2.7
% ≥ 10%	19.1 (n=9)	19.1 (n=9)	6.4 (n=3)	12.8 (n=6)	17.0 (n=8)	12.8 (n=6)
Monounsaturated fat (g)	15.5 (2.2 – 62.8)	12.9 (3.6 – 37.6)	14.1 (4.7 – 39.9)	15.1 (3.0 – 43.3)	14.2 (4.7 – 39.9)	15.8 (1.4 – 30.9)
Monounsaturated fat (%)	8.3 ± 3.2	8.2 ± 3.2	8.3 ± 2.4	8.2 ± 2.9	8.3 ± 1.9	8.5 ± 2.3
% ≥ 10%	23.4 (n=11)	27.7 (n=13)	14.9 (n=7)	19.1 (n=9)	12.8 (n=6)	23.4 (n=-11)
Saturated fat (g)	14.0 (2.2 – 45.1)	13.8 (2.9 – 39.6)	14.2 (5.5 – 37.1)	15.6 (3.6 – 42.3)	15.2 (5.2 – 29.1)	15.7 (2.4 – 55.7)
Saturated fat (%)	8.3 ± 3.3	8.7 ± 3.3	8.7 ± 2.4	8.6 ± 2.9	8.7 ± 1.9	9.3 ± 3.3
% ≤ 10%	25.5 (n=12) [ab]	40.4 (n=19) [ab]	23.4 (n=11)[a]	29.8 (n=14) [ab]	27.7 (n=13) [ab]	44.7 (n=21)[b]
Cholesterol (mg)	233.2 (3.5 – 1176.5) [ab]	183.1 (26.3 – 1467.5) [ab]	161.6 (52.2 – 531.7) [ab]	190.8 (36.2 – 852.4) [a]	240.6 (60.5 – 790.4) [b]	236.3 (10.7 – 757.8)[b]
% ≥ 300mg	34.0 (n=16)	27.7 (n=13)	17.0 (n=8)	19.1 (n=9)	25.5 (n=12)	34.0 (n=16)
Fibre (g)	22.4 (2.8 – 55.7)	20.4 (3.4 – 50.2)	26.6 (8.9 – 44.3)	24.5 (6.7 – 47.9)	22.2 (8.6 – 44.8)	23.4 (6.8 – 54.3)
% ≥ 25g	40.4 (n=19)	44.7 (n=21)	44.7 (n=21)	46.8 (n=22)	44.7 (n=21)	42.6 (n=20)

Caption 7. *Different letters represent significant difference p<0.05. (Paired t-test or Wilcoxon test, McNemar test).*
Cutoff points according to Estimated Average Requirement or Adequate Intake (Dietary Reference Intakes), classified by gender and age.

Table 9. Adherence intake of the patients in the waiting list for liver transplantation during nutritional intervention through the 12 weeks (n=47).

Micronutrient	Baseline (2 weeks before intervention)	Start of intervention (W0)	2 weeks after the intervention (W2)	4 weeks after the intervention (W4)	8 weeks after intervention (W8)	12 weeks after intervention (W12)
Calcium (mg)	375.5 (23.0 – 1254.6)[ac]	418.4 (34.6 – 1394.8)[abc]	431.2 (153.6 – 1515.4) [abc]	444.5 (171.3 – 1218.2)[ac]	456.8 (117.1 – 1145.6) [abc]	524.9 (160.2 – 1658.3)[b]
%AI compliance	2.1 (n=1)	4.3 (n=2)	8.5 (n=4)	4.3 (n=2)	8.5 (n=4)	8.5 (n=4)
Phosphorus (mg)	750.2 (82.5 – 1908.4)[a]	831.4 (136.3 – 2089.6)[a]	851.0 (136.3 – 2089.6)[ab]	873.8 (389.7 – 1749.6)[ab]	870.1 (391.3 – 1712.1) [ab]	861.3 (168.9 – 1807.1)[b]
% EAR compliance	74.5 (n=35)[a]	72.3 (n=34) [a]	72.3 (n=34) [ab]	89.4 (n=42) [ab]	85.1 (n=40) [ab]	91.5 (n=43)[b]
Magnesium (mg)	191.3 (22.8 – 672.3)	183.0 (25.6 – 759.9)	192.3 (95.0 – 453.3)	212.8 (44.9 – 523.8)	187.6 (64.5 – 598.8)	205.5 (70.0 –460.2)
% EAR compliance	23.4 (n=11)	31.9 (n=15)	21.3 (n=10)	31.9 (n=15)	27.7 (n=13)	31.9 (n=15)
Potassium (mg)	2058.1 (228.1 – 4322.3)	1933.0 (241.0 – 4679.1)	2172.9 (1097.5 – 3668.0)	2146.8 (781.4 – 3784.1)	2071.7 (479.6 – 4315.6)	2291.2 (633.1 – 4133.7)
% AI compliance	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)
Iron (mg)	8.6 (0.6 – 594.6)[ac]	7.4 (1.4 – 102.7)[a]	13.2 (3.4 – 211.7)[b]	9.8 (3.3 – 199.6)[bc]	9.8 (2.6 – 141.5)[bc]	12.0 (2.6 – 392.2)[bc]
% EAR compliance	51.1 (n=24)	46.8 (n=22)	55.3 (n=26)	59.6 (n=28)	57.4 (n=27)	63.8 (n=30)
Niacin (mg)	11.5 (0.2 – 47.6)[ab]	8.9 (0.0 – 75.7)[a]	12.6 (5.3 – 40.2)[b]	13.6 (1.6 – 40.5)[b]	14.2 (0.8 – 45.1)[b]	12.3 (3.0 – 34.1)[b]
% EAR compliance	51.1 (n=24)[ae]	40.4 (n=19) [ab]	66.0 (n=31)[cd]	57.4 (n=27) [abe]	70.2 (n=33) [cde]	53.2 (n=25) [ab]
Riboflavin (mg)	0.7 (0.0 – 5.1)	0.8 (0.2 – 4.6)	1.0 (0.3 – 3.2)	0.9 (0.2 – 4.8)	0.9 (0.1 – 3.9)	1.0 (0.2 – 3.4)
% EAR compliance	36.2 (n=17)	42.6 (n=20)	44.7 (n=21)	48.9 (n=23)	57.4 (n=27)	55.3 (n=26)
Thiamin (mg)	0.8 (0.1– 7.4)	0.8 (0.1 – 5.4)	1.1 (0.4 – 4.4)	1.0 (0.2 – 3.0)	0.9 (0.3 – 2.8)	1.0 (0.3 – 4.0)
% EAR compliance	48.9 (n=23)	44.7 (n=21)	48.9 (n=23)	57.4 (n=27)	53.2 (n=25)	61.7 (n=29)
Vitamin C (mg)	115.0 (0.3 – 811.1)	99.1 (0.0 – 844.2)	136.7 (8.7 – 1073.6)	113.0 (8.9 – 527.2)	113.7 (1.2 – 661.2)	125.0 (6.3 – 1343.9)
% EAR compliance	68.1 (n=32)	61.7 (n=29)	59.6 (n=28)	70.2 (n=33)	70.2 (n=33)	72.3 (n=34)
Vitamin A (mcg)	89.5 (0.0 – 20602.6)	105.7 (0.0 – 15524.7)	127.3 (30.9 – 882.5)	160.3 (19.5 – 3018.2)	155.1 (42.0 – 13261.5)	198.9 (0.0 – 3083.9)
% EAR compliance	12.8 (n=6)	10.6 (n=5)	6.4 (n=3)	12.8 (n=6)	10.6 (n=5)	8.5 (n=4)

***Caption 8**. Different letters represent significant differences p<0.05. (Paired t-test or Wilcoxon test, McNemar test).*
Cutoff points according to Estimated Average Requirement or Adequate Intake (Dietary Reference Intakes), classified by gender and age.

Table 10. Late evening snack intake of the patients on the waiting list for liver transplantation during nutritional intervention through the 12 weeks (n=47).

Late evening snack patterns	Baseline (2 weeks before intervention)	Start of intervention (W0)	2 weeks after the intervention (W2)	4 weeks after the intervention (W4)	8 weeks after intervention (W8)	12 weeks after intervention (W12)
Late evening snack intake	40.4% (n=19)[a]	53.2% (n=25) [ab]	61.7% (n=29) [b]	76.6% (n=36)[c]	76.6% (n=36) [cd]	59.6% (n=28) [abde]
Calories (kcal)	136 (7 – 1966)	191 (15 – 1550)	150 (23 – 897)	182 (1 – 977)	191 (2 – 731)	182 (0 –882)
Carbohydrate (g)	20.1 (1.6 – 235.5) [a]	28.4 (1.6 – 216.7)[ab]	28.9 (3.8 – 140.6)[b]	29.3 (0.2 – 179.5) [ab]	32.9 (0.0 – 136.3) [ab]	26.9 (0.0 – 151.1) [ab]
Carbohydrate (%)	74.4 ± 26.3[a]	53.6 ± 25.4[b]	87.9 ± 51.8[ab]	60.4 ± 23.9 [ab]	64.0 ± 30.0 [ab]	63.6 ± 30.0 [ab]
Protein (g)	4.7 (0.0 – 49.3)	6.6 (0.4 – 64.3)	3.8 (0.0 – 57.2)	5.0 (0.0 – 78.5)	6.9 (0.0 – 38.9)	4.8 (0.0 – 38.1)
Protein (%)	11.8 ± 10.1	15.7 ± 10.4	11.5 ± 7.0	12.9 ± 9.4	11.7 ± 7.0	12.6 ± 7.4
Fat (g)	4.0 (0.0 – 96.7)	8.3 (0.0 – 52.1)	4.0 (0.0 – 31.9)	4.5 (0.2 – 57.2)	8.3 (0.0 – 25.5)	6.4 (0.0 –30.4)
Fat (%)	17.5 ± 16.3[a]	31.1 ± 21.4[bcd]	20.3 ± 15.8[abcd]	28.3 ± 18.1 [bcd]	27.4 ± 18.0 [abcd]	28.1 ± 16.5 [bcd]

Caption 9. *Different letters represent significant difference; $p < 0.05$. (Paired t-test or Wilcoxon test, McNemar test).*

Table 11. Consumed amount (g) of food groups by patients on the waiting list for liver transplantation during nutritional intervention through the 12 weeks (n=47).

Food group	Baseline (2 weeks before intervention) (g/day)	Start of intervention (W0) (g/day)	2 weeks after the intervention (W2) (g/day)	4 weeks after the intervention (W4) (g/day)	8 weeks after intervention (W8) (g/day)	12 weeks after intervention (W12) (g/day)
Bakery products (g)	80.0 (0.0 – 410.0)[a]	78.0 0.0 – 300.0)[ab]	78.0 (0.0 – 200.0) [ab]	88.5 (0.0 – 175.0) [ab]	85.0 (0.0 – 255.5) [b]	83.9 (0.0 – 200.0) [ab]
Cereals (g)	310.0 (0.0 – 850.0)[a]	170.0 (0.0 – 751.0)[b]	200.0 (0.0 – 850.0) [b]	183.7 (0.0 – 685.8) [b]	197.5 (10.0 – 554.3) [b]	250.0 (0.0 – 519.1) [b]
Leguminous (g)	0.0 (0.0 – 364.0) [a]	86.0 (0.0 – 420.0) [b]	51.0 (0.0 – 280.0) [a]	106.0 (0.0 – 332.5) [bc]	101.2 (0.0 – 328.0) [c]	108.7 (0.0 – 322.5) [bc]
Roots and tubers (g)	0.0 (0.0 – 332.0)[ad]	0.0 (0.0 – 430.0) [abcd]	35.0 (0.0 – 330.0) [bc]	40.0 (0.0 – 477.0) [c]	22.5 (0.0 – 238.5) [abcd]	18.7 (0.0 – 150.0) [ad]
Vegetables (g)	93.0 (0.0 – 440.0)	50.0 (0.0 – 600.0)	116.3 (0.0 – 355.0)	92.5 (0.0 – 327.5)	81.6 (0.0 – 608.0)	96.2 (0.0 – 450.0)
Fruits (g)	215.0 (0.0 – 1390.0)	170.0 (0.0 – 1200.0)	185.0 (0.0 – 908.3)	179.6 (0.0 – 860.8)	200.0 (0.0 – 745.0)	167.5 (0.0 – 753.8)
Beverages (mL)*	150.0 (0.0 – 1750.0)	112.5 (0.0 – 850.0)	197.5 (0.0 – 800.0)	209.4 (0.0 – 655.0)	187.5 (0.0 – 807.5)	224.4 (0.0 – 700.0)
Dairy (g)	50.0 (0.0 – 600.0) [a]	110.0 (0.0 – 700.0) [abc]	122.5 (0.0 – 660.0) [abc]	118.7 (0.0 – 620.6) [abc]	137.2 (0.0 – 815.0) [bc]	156.2 (0.0 – 790.0) [bc]
Meat, poultry, and fish (g)	120.0 (0.0 – 650.0) [abc]	80.0 (0.0 – 300.0) [ac]	104.0 (0.0 – 380.0) [ab]	105.0 (0.0 – 241.3) [abc]	91.2 (0.0 – 293.5) [b]	78.3 (0.0 – 245.0) [c]
Eggs (g)	0.0 (0.0 – 200.0)	0.0 (0.0 – 200.0)	0.0 (0.0 – 135.0)	0.0 (0.0 – 230.0)	11.2 (0.0 – 103.8)	11.2 (0.0 – 125.0)
Fats and oils (ml)	16.0 (0.0 – 68.0)	16.0 (0.0 – 60.0)	13.3 (0.0 – 100.0)	14.0 (0.0 – 37.0)	15.0 (6.0 – 39.5)	15.0 (0.0 – 52.5)
Oleaginous (g)	0.0 (0.0 – 60.0)	0.0 (0.0 – 60.0)	0.0 (0.0 – 60.0)	0.0 (0.0 – 30.0)	0.0 (0.0 – 16.0)	0.0 (0.0 – 30.0)
Sugars and sweets (g)	5.0 (0.0 – 158.0)	5.0 (0.0 – 199.0)	8.3 (0.0 – 200.0)	12.0 (0.0 – 128.8)	9.5 (0.0 – 139.8)	13.5 (0.0 – 118.0)

Caption 10. *Different letters represent significant difference; p<0.05. (Wilcoxon test). *Beverages: fruit juice, coffee and tea.*

Table 12. Independently associated factors of the difference of caloric (kcal/kg) and protein (g/kg) intake between W12 and Baseline in patients on the waiting list for liver transplantation (n=47).

Independently associated factors to the difference of caloric intake (kcal/kg) between W12 and Baseline			
	B	IC (95%)	P value
Presence of ascites (W12)	- 0.31	- 11.27 – (-) 2.39	0.004
Nourished (Subjective Global Assessment) (W4)	-0.24	- 11.06 – (-) 0.92	0.022
Frail (Frailty index) (W0)	- 0.48	-19.17 – (-) 3.22	0.007
Short Physical Performance Battery score (W4)	- 0.59	- 5.03 – (-) 2.49	< 0.001
Quality of Life Test score (W4)	- 0.87	- 2.18 – (-) 0.61	< 0.001
Systemic symptoms score (Quality of Life Test) (W4)	1.11	5.21 – 10.82	< 0.001
Emotional function score (Quality of Life Test) (W4)	0.45	0.91 – 5.98	0.009
Independently associated factors to the difference in protein intake (g/kg) between W12 and Baseline			
	B	IC (95%)	P value
Presence of diabetes mellitus	0.46	0.23 – 0.85	< 0.001
Moderately malnourished (Subjective Global Assessment) (W4)	- 0.40	- 0.76 – (-) 0.17	0.003
Poor performance (Short Physical Performance Battery) (W12)	0.27	0.03 – 1.15	0.038
Fatigue (Quality of Life Test) (W4)	- 0.56	- 0.30 – (-) 0.45	0.009
Systemic symptoms (Quality of Life Test) (W4)	0.43	0.03 – 0.27	0.014
Emotional function (Quality of Life Test) (W0)	0.36	0.01 – 0.24	0.036
Emotional function (Quality of Life Test) (W12)	0.38	0.02 – 0.27	0.026

Caption 11. *CI: Confidence interval; Difference between W12 and Baseline of caloric intake analyses, adjusted by age and sex (R^2: 0.50. R^2 adjusted: 0.25%). Difference between W12 and Baseline of protein intake analyses (R^2: 0.71. R^2 adjusted: 0.51%). (Multiple linear regression model).*

4. Discussion

The present study aimed to evaluate the food intake of patients on the waiting list for LTx enrolled in a nutritional intervention, including dietary prescription, monitoring, and counseling for 12 weeks. Independent factors associated with the difference in caloric (kcal/kg) and protein intake (kcal/kg) of patients on the waiting list for liver transplantation were also researched. In our study, most patients presented calorie and protein intake below the guidelines recommendations. Energy inadequacy was observed in 74.5% of patients, and protein inadequacy in nearly half of them throughout the study. Although protein intake improved at W8 compared to W0, the nutritional intervention could not promote sustained changes in dietary intake considering this nutrient. These findings are slightly better than the results of a cross-sectional and descriptive study carried out by our research group 10 years ago at the same outpatient center. Ferreira et al. (2013) evaluated the total caloric intake of 73 patients on the waiting list for liver transplantation and observed insufficient consumption of energy and protein intake in 91.8% and 72.6% of patients , respectively (FERREIRA et al., 2013). Similar results were posteriorly described by some other studies (MARR et al., 2017; CRISAN et al., 2020; MIZUBUTI et al., 2021). In the study conducted by Crisan et al. (2020) with advanced cirrhosis patients, 56.4% and 33% of them presented energy and protein intake, respectively, below ideal (CRISAN et al., 2020). Marr et al. (2017) also evaluated food intake in 70 patients on the waiting list for liver transplantation. The authors showed that patients diagnosed with malnutrition, according to the SGA, consumed less than the other patients (SGA A or B). Those patients consume only 79.2% of recommended calories and 62.5% of protein requirements (MARR et al., 2017). These data demonstrate that intake targets for patients with liver cirrhosis are challenging to achieve in clinical practice, even though these patients are followed longitudinally as in the present study. These findings are of concern, as poor intake of nutrients, especially protein, has already been considered an independent predictor of mortality in patients with liver cirrhosis (NEY et al., 2015).

Contrary to insufficient oral intake in patients under outpatient follow-up, different results occur when patients on the waiting list are hospitalized and under nutritional therapy. Daphnee et al. (2018) evaluated 65 patients on the liver transplant waiting list. They received nutritional intervention, including a personalized nutritional care plan and dietary advice based on the severity of malnutrition. The nutritional therapy plan (oral nutrition / enteral nutrition / parenteral nutrition) was customized according to spontaneous oral intake. During this period, there was a significant improvement in the nutritional status of patients, and 69% achieved more than 75% of nutritional goals, both in calories and protein (DAPHNEE et al., 2018). However, it

is possible to verify that even hospitalized patients with decompensated cirrhosis have inadequate food intake. A cross-sectional study was performed with 94 patients hospitalized with decompensated cirrhosis by Saueressig et al. (2021) with objective to compare the prescribed nutrition with dietary intake. The participants were hospitalized and received a calculated oral nutritional prescription. The mean energy prescribed, and the actual mean dietary intake were 2191.3 ± 295.8 kcal/d (31.3 ± 7.7 kcal/kg/d) and 1289.4 ± 509.7 kcal/d (18.6 ± 7.9 kcal/kg/d), respectively. The actual mean dietary intake was 902.7 ± 475.1 kcal/d less than the prescribed energy ($p<0.001$) (SAUERESSIG et al., 2023). The patients in the present study were not hospitalized or undergoing enteral nutritional therapy during the study but under outpatient follow-up, and despite frequent monitoring, substantial changes in food intake were not observed.

Although the dietary caloric and protein intake were quantitatively below the recommended level, some micronutrients were adequate according to the DRI recommendations. Iron, niacin, and phosphorus are found in animal products, such as meat, poultry, and fish, whose food group showed a significant increase at W8 compared to W0 (Table 11). So, the rise of these micronutrients can be explained by the consumption of these food groups. The lower percentual of adequacy of dietary fiber, magnesium, potassium, and vitamin A (carotenoids) was observed and could be attributed to patients' low consumption of fruits and vegetables. World Health Organization recommends consuming a minimum of 400 grams of fruits and vegetables per day (WHO, 2003). And in our sample, when both groups (fruits and vegetables) are added together [at Baseline 315.0g (0.0 – 1566.0g); at W0 290.0g (0.0 – 1419.0g); at W2 322.0g (0.0 – 908.3g); at W4 290.3g (0.0 – 1102.5g); at W8 350.0g (0.0 – 952.5g); and at W12 273g (0.0 – 963.3g)], these values are still insufficient. In addition, low potassium intake may be related to specific guidelines for this patients in order to avoid hyperkalemia. Hyperkalemia is associated with severe liver cirrhosis. It is directly related to serum creatinine levels, an indicator of renal function, and inversely related to serum albumin levels, an indicator of hepatic synthesis function (GURNANI et al., 2021). Dietary calcium intake increased during follow-up, likely due to improve in the consumption of dairy products, although most remained below the recommendations.

In the cross-sectional study conducted by Ferreira et al. (2013) with a sample of patients awaiting for LTx, there were also observed a portion of patients with adequate intake for iron, thiamin, and riboflavin but inadequacies of ingestion of fiber, calcium, and potassium (FERREIRA et al., 2013). Similar results could also be observed in the study of Andrade et al. (2018). The authors prospectively evaluated changes in dietary patterns in 23 patients before and after liver

transplantation. It was observed that the most of patients, before the transplant, had an intake of fiber, vitamins A, D, E, and K lower than recommended, remaining inadequate after the operation (ANDRADE et al., 2018). The inadequacy of other micronutrients can also be observed in other studies with this population (NUNES et al., 2016; VIANA et al., 2019). Therefore, individual nutritional counseling is essential for these patients to identify deficiencies and excesses and suggest appropriate measures.

As one of the interventions for patients with liver cirrhosis, the late evening snack is strongly advised (PLANK et al., 2008; MERLI et al., 2019; PLAUTH et al., 2019). As the rate of gluconeogenesis increases during fasting, there is an increase in the consumption of amino acids as an energy source. This accelerates skeletal muscle protein loss and reduces muscle protein synthesis (TSIEN; MCCULLOUGH; DASARATHY, 2012). In a meta-analysis of eight studies evaluating the effects of late evening snacks on the liver function of patients with cirrhosis, the benefit of this meal on liver function was shown, favoring the nutritional intervention in this public (CHEN et al., 2019). Therefore, providing this meal, by shortening the fasting period, was able to reverse anabolic resistance, sarcopenia and negative clinical outcomes (CHEN et al., 2019). At baseline, only 40.4% (n=19) of patients ate a late evening snack. Our results showed a statistical difference in the frequency of late evening snack considering W2 [61.7% (n=29)] and W8 [76.6% (n=36)] compared to baseline [40.4% (n=19)] ($p<0.05$), showing that the supervised nutritional monitoring favored the increase of the frequency of the late evening snack.

Based on the difference in caloric intake (kcal/g) and protein intake (g/kg) between each moment and baseline; and considering each moment and the last moment, it is possible to verify that the caloric and protein intake increased slightly up to two months but decreased to the baseline values at the end of the intervention. Adherence across these recommendations, including attainment of such recommendations in the context of multi-behavior intervention trials, needs to be better reported to date.

The pathophysiological mechanisms and clinical conditions that lead patients with chronic liver disease to decrease energy and protein intake are multiple and intertwined. Ascites, esophageal varices, inappetence, gastroparesis, encephalopathy, and unpalatable diets are the main factors that impact food consumption (MAZURAK; TANDON; MONTANO-LOZA, 2017; CHAPMAN et al., 2020), which further contribute to the worsening of the nutritional status (JUAKIEM; TORRES; HARRISON, 2014). Among the most common indicators of disease severity verified in our patients, 63.8% had edema, 59.6% had ascites, and 44.7%, had esophageal varices. The presence of ascites was a predictor for the lower difference in caloric intake

between W12 and Baseline in the present study; these patients presented smaller and negative changes in caloric intake compared to those without ascites (Δ -0.5 ± 8.6 kcal/kg vs. Δ 3.5 ± 13.2 kcal/kg; <0.001).

Our results showed an independent association between protein intake and muscle function, as in each decrease of SPPB score (that is related to poor performance), there was a decrease of 0.59 in the difference of caloric intake (kcal/kg) between W12 and Baseline. Functional changes could be a result of malnutrition and worsening of liver disease (DEUTZ et al., 2019). This result reinforces our findings that food intake is related to muscle quality/functionality. In a cohort study, Oey et al. (2020) evaluated 102 patients pre-liver transplantation. The authors found that impaired muscle function, but not muscle mass depletion, was a significant predictor of decompensation and mortality, independent of liver disease severity (OEY et al., 2020). In addition to being a consequence of malnutrition, the reduction in muscle function occurs with progression of liver disease (DASARATHY, 2016; DE BANDT; JEGATHEESAN; TENNOUNE-EL-HAFAIA, 2018) resulting in a decrease in quality of life, greater susceptibility to infection, and an increased risk of mortality (DASARATHY, 2016; ALLEN et al., 2021; KUMAR et al., 2022). In this sense, the slightest difference between caloric intake between W12 and Baseline was an independent factor associated with worse quality of life in the present study. Some studies have demonstrated a reduction in clinical events and improved quality of life with longer-term use of BCAAs (MARCHESINI et al., 2003; MUTO et al., 2005). Therefore, in addition to the focus of nutritional interventions on improving food intake or oral nutritional supplements, it is important to identify and treat malnutrition to maintain or minimize its impacts on muscle function and quality of life.

At the same time that malnutrition can occur due to starvation, subsequent to the clinical manifestations of cirrhosis, the socioeconomic aspects are also a determining factor in non-intake (ALKERWI et al., 2015). Although our results did not find a significant correlation between food intake and family income (p>0.05), it is known that low income, low education, multi-morbidity, and place of residence are associated with the dietary patterns of Brazilians (MONTEIRO DOS SANTOS et al., 2021). Therefore, food intake cannot and should not be assessed in isolation. In addition to clinical conditions, depression (SHAAT et al., 2020), few hours of sleep (BAKSHI; SINGH, 2021), and social myths (SHARMA et al., 2021) were previously associated with low food intake in patients with liver disease. As a result of this deficit, malnutrition sets in, which is a prognostic factor independent of complications in the pre- (MAHARSHI; SHARMA; SRIVASTAVA, 2015) as well as in the post-operative (KALAFATELI et al., 2017) of liver transplantation. The lack of financial resources that can guarantee basic food and

transportation to outpatient care, the low level of education for the complete understanding of the interventions, the difficulty of communication by telephone due to the absence of a mobile/residential device, the lack of support as well as denial from family members, among other insufficiencies, were reported during follow-up. In addition, due to the COVID-19 pandemic, data collection was affected mainly owing to confinement at home, economic changes and food insecurity (NEIRA et al., 2021). Thus, it is clear that promoting the consumption of 30kcal/kg and 1.2g/kg of protein in the face of social determinants that reach and exceed their maximum levels of paucity is also an obstacle that should not be ignored.

In this context, measures with educational guidelines as well as multidisciplinary intervention are essential to ensure the effectiveness of outpatient treatment in this public, especially when considering the early initiation of nutritional therapy in anticipation of an impending malnutrition scenario. According to the SGA, 76.6% had malnutrition at the end of nutritional monitoring period. Despite the minority of patients present nutritional intake below 50% (less than 15% of patients during the entire intervention, data not shown), nutritional therapy proves necessary (CEDERHOLM et al., 2019). The offer of an oral nutritional supplement must be implemented and if the intake is still insufficient, enteral nutritional therapy offers the possibility of increasing or guaranteeing the adequate intake of nutrients in patients with liver disease (PLAUTH et al., 2006; MERLI et al., 2019). However, none of the patients evaluated were on enteral nutritional therapy and only 8.5% were consuming oral nutritional supplements (because they/their families could afford them). In this context, offering oral nutritional supplements can increase or ensure nutrient intake in case of insufficient oral food intake (BISCHOFF et al., 2020).

In addition to the role of social determinants in non-adherence to dietary prescription, other factors also influence the support of long-term nutritional counseling. Among these factors, behavioral factors such as ingrained eating habits (FUSTER, 2017), lack of motivation and time, and lack of family support (ESTRELA et al., 2017; MOSTAFAVI-DARANI et al., 2020), as well as psychological factors, such as self-efficacy and previous experiences of failure (HALL; KAHAN, 2018). It is believed that new nutritional intervention strategies should be developed to promote awareness of self-care. Thus, patients can identify their own difficulties and develop techniques to overcome them (DINEEN-GRIFFIN et al., 2019). The individual will be able to make better choices in the face of daily challenges, acquire skills to overcome barriers, and develop nutritional empowerment and, therefore, obtain better results in the maintenance of behavior change (KWASNICKA et al., 2016; DINEEN-GRIFFIN et al., 2019).

This study has some limitations. To assess food intake, the three-day food record were applied. Not all patients turned in all food records at long follow-up [at W0, 78.7% (n=37) had turned in all 3-FRs; at W4, 80.9% (n=38); at W8, 85.1% (n=40) and at W12, 68.1% (n=32)]. Furthermore, food intake evaluation is biased, due to the difficulty in the quantification estimated by the patient, resulting in under- or over-estimation (ORTEGA; PÉREZ-RODRIGO; LÓPEZ-SOBALER, 2015). To reduce this adversity, photographs of household measures were made available, and then, patients could more reliably quantify meals. Forgetting to write down meals and foods could also occur. Fortnightly calls were made to remind patients of the notes and in case they forgot to write the record, the application of the 3-FRs record was carried out by telephone with some patients. It is also important to mention that patients could be familiarized with the dietary assessments over the intervention weeks. The first ones could be less reliable than the others. Finally, this work is a secondary analysis of a double−masked randomized clinical trial, therefore, the statistical power was not calculated based on this sample size.

Among the strengths of this study, it is a prospective study with nutritional counseling, prescription, and dietary follow-up for 12 weeks with patients on the waiting list for LTx. All these patients received an individualized meal plan calculated according to guidelines, their needs, preferences, and financial conditions. Our study evaluated food consumption by quantifying nutrient intake and by food groups based on 679 food surveys (24hR and 3-FRs) applied throughout follow-up. In addition, it was evaluated several factors associated with calorie and protein intake in this public.

5. Conclusion

Patients with liver cirrhosis awaiting liver transplantation modestly improved food intake, reducing intake of food groups rich in carbohydrates, increasing total protein and micronutrients intake, and increasing the intake of some food groups through the time of follow-up, mainly in 8 weeks. On the other hand, most of them did not reach the minimum nutritional recommendations of current international guidelines for energy intake per kg/weight (30kcal/kg) and protein intake per kg/weight (1.2g/kg) at the end of nutritional monitoring.

At the baseline, less than two-fifths of the patients consumed the late evening snack. However, this percentage increased significantly over time. More than 75% of patients started eating this meal at 4 weeks of follow-up. There was an increase in the consumption of cholesterol, calcium, phosphorus, magnesium, iron, niacin, leguminous, roots and tubers, dairy, and meat, poultry, and fish groups during follow-up.

The presence of ascites, the subjective global assessment, frailty index, short physical performance battery score, quality of life score, systemic symptoms, and emotional function were associated with the difference between W12 and Baseline of caloric intake. The presence of diabetes mellitus, poor performance, systemic symptoms, and emotional function also was independently associated with greater difference between W12 and Baseline protein intake. The subjective global assessment and presence of fatigue were independent predictors of lower difference in protein intake between W12-Baseline.

Barriers to food intake are common in cirrhosis and should be screened and treated in all patients. Our data demonstrate that reaching the caloric and protein target is still a challenge, however, it is possible to improve food patterns in clinical practice. In this context, measures with educational guidelines as well as multidisciplinary intervention are essential to ensure the effectiveness of outpatient treatment in this public. It is noteworthy that food intake cannot and should not be assessed in isolation, and the need for an early start of nutritional therapy in the context of imminent malnutrition. Future research should explore techniques to overcome modifiable barriers and improve enablers.

7 SUPPLEMENTARY MATERIAL II

Table S1. Difference between caloric (kcal/kg) and protein (g/kg) intake between T12 and T0 in each time of evaluation according to each of the variables collected (n=47).

Variables	Baseline		0		4		8		12	
	T12-T0		T12-T0		T12-T0		T12-T0		T12-T0	
	(kcal/kg)	ptn (g/kg)	(kcal/kg)	ptn (g/kg)	(kcal/kg)	ptn (g/kg)	(kcal/kg)	ptn (g/kg)	(kcal/kg)	ptn (g/kg)
Sex										
Male	2.8 ± 10.9	0.1 ± 0.6								
Female	-1.1 ± 12.3	-0.1 ± 0.5								
Clinics										
Child-Pugh										
A	1.3 ± 14.5	-0.1 ± 0.6	6.0 ± 14.6	0.2 ± 0.7	2.1 ± 15.2	-0.0 ± 0.7	5.0 ± 15.5	0.1 ± 0.7	4.0 ± 14.3	0.1 ± 0.7
B	2.5 ± 10.4	0.1 ± 0.5	1.3 ± 9.3	0.0 ± 0.3	3.1 ± 9.5	0.1 ± 0.3	2.1 ± 9.6	0.1 ± 0.4	2.0 ± 9.3	0.1 ± 0.3
C	3.5 ± 6.6	0.4 ± 1.0	-5.2 ± 11.5	0.4 ± 2.0	-2.9 ± 6.7	0.1 ± 1.0	-3.1 ± 6.4	0.1 ± 1.0	-4.4 ± 8.3	0.2 ± 1.5
Transplant indication										
Ethanol Cirrhosis										
Yes	0.4 ± 11.7	0.0 ± 0.5								
No	2.1 ± 11.3	0.1 ± 0.6								
Hepatitis B virus										
Yes	14.2 ± 18.5*	0.4 ± 0.6								
No	0.5 ± 9.9*	0.0 ± 0.6								
Hepatocellular carcinoma										
Yes	-0.1 ± 8.0	0.0 ± 0.6								
No	2.1 ± 12.0	0.1 ± 0.6								
Cryptogenic Cirrhosis										
Yes	3.2 ± 10.7	-0.3 ± 0.7								
No	1.2 ± 11.6	-0.0 ± 0.5								
NASH										
Yes	2.1 ± 6.4	0.1 ± 0.5								
No	1.7 ± 11.8	0.1 ± 0.6								

Comorbidities										
Diabetes mellitus										
Yes	1.9 ± 7.4	0.2 ± 0.7								
No	1.6 ± 12.8	-0.1 ± 0.5								
Arterial hypertension										
Yes	2.5 ± 6.2	0.1 ± 0.4								
No	1.3 ± 13.0	0.0 ± 0.6								
Supplement use										
Yes	-0.6 ± 15.7	-0.1 ± 0.4								
No	1.9 ± 11.0	0.8 ± 0.6								
Ascites										
Yes	2.8 ± 13.2	0.1 ± 0.5	2.7 ± 13.2	0.1 ±0.5	1.7 ± 12.6	0.0 ± 0.5	-0.3 ± 12.3	-0.0 ± 0.5	-0.2 ± 8.7	0.0 ± 0.4
No	0.2 ± 8.1	0.1 ± 0.6	0.2 ± 7.7	0.1 ± 0.6	1.6 ± 8.8	0.1 ± 0.6	4.2 ± 9.6	0.2 ± 0.7	3.5 ± 13.2	0.1 ± 0.7
Edema										
Yes	2.5 ± 8.7	0.1 ± 0.5	3.6 ± 12.3	0.1 ± 0.6	2.4 ± 10.0	0.1 ± 0.6	1.1 ± 9.5	0.1 ± 0.6	0.4 ± 9.8	0.0 ± 0.6
No	0.8 ± 13.7	0.0 ± 0.7	-1.4 ± 9.0	-0.0 ± 0.5	0.3 ± 14.0	-0.1 ± 0.5	2.7 ± 14.3	0.1 ±0.6	3.8 ± 13.5	0.1 ± 0.6
Esophageal varices										
Yes	2.8 ± 9.0	0.1 ± 0.4								
No	0.8 ± 13.0	0.1 ± 0.7								
Hepatic encephalopathy										
Yes	3.4 ± 8.3	0.0 ± 0.5	1.9 ± 6.3	0.1 ± 0.4	3.2 ± 5.6	0.2 ± 0.7	3.2 ± 6.8	0.1 ± 0.4	-1.7 ± 4.1	-0.1 ± 0.2
No	0.8 ± 12.6	0.1 ± 0.6	1.7 ± 12.2	0.1 ± 0.6	1.2 ± 12.6	0.0 ± 0.5	1.4 ± 12.1	0.1 ± 0,6	2.2 ± 12.0	0.1 ± 0.6
Lifestyle										
Smoking										
Non smokers	-0.4 ± 9.3	-0.1 ± 0.5								
Smokers	4.0 ± 10.7	0.1 ± 0.5								
Former smokers	3.2 ± 13.4	0.2 ± 0.6								
Alcohol consumption										
Non drinkers	1.5 ± 9.0	-0.1 ± 0.5								
Drinkers	2.2 ± 0.5	0.1 ± 0.1								
Former drinkers	1.7 ± 12.2	0.1 ± 0.6								
Physical activity practice										
Yes	3.3 ± 11.9	0.1 ± 0.7								
No	0.9 ± 11.1	0.0 ± 0.5								

Nutritional status										
Subjective Global Assessment (SGA)										
Nourished	0.5 ± 7.1	0.0 ± 0.3	2.3 ± 12.1	0.1 ± 0.5	-0.5 ± 8.7	-0.1 ± 0.4	3.0 ± 8.6	0.2 ± 0.4	-0.4 ± 11.9	-0.0 ± 0.5
Moderately malnourished	3.6 ± 11.8	0.1 ± 0.5	3.0 ± 11.1	0.0 ± 0.5	4.1 ± 11.7	0.1 ± 0.5	0.9 ±11.0	-0.1 ± 0.5	1.1 ± 9.5	-0.0 ± 0.5
Severe malnutrition	-9.9 ± 10.5	0.2 ± 1.1	-4.4 ± 10.1	0.1 ± 0.8	-6.9 ± 11.3	0.2 ± 1.0	3.4 ± 17.6	0.4 ± 1.0	9.8 ± 17.9	0.7 ± 0.8
Functionality										
Short Physical Performance Battery										
Disability or very poor performance										
Low capacity			2.0 ± 5.2	0.0 ± 0.3	11.9 ± 23.1	0.3 ± 0.9			8.4 ± 4.3	0.5 ± 0.1
Moderate capacity			1.8 ± 13.4	0.1 ± 0.7	4.5 ± 9.5	0.2 ± 0.5	2.1 ± 11.0	0.1 ± 0.5	3.1 ± 12.5	0.0 ± 0.5
Good capacity			1.4 ± 10.6	0.1 ± 0.5	-2.0 ± 10.0	-0.1 ± 0.6	1.3 ± 12.0	0.0 ± 0.6	0.1 ± 11.0	0.0 ± 0.6
Frailty index										
Robust									-4.5 ± 8.1	-0.1 ± 0.3
Pre-frail			4.2 ± 11.2	0.2 ± 0.6	2.7 ± 11.9	0.1 ± 0.6	2.7 ± 11.6	0.1 ± 0.6	2.5 ± 12.2	0.1 ± 0.6
Frail			-2.8 ± 10.3	-0.1 ± 0.4	-0.1 ± 8.8	-0.0 ± 0.5	-0.2 ± 10.0	-0.1 ± 0.4	1.0 ± 8.9	-0.1 ± 0.4

Caption 12. *Values with asterisk are significantly different within the group, $p < 0.05$. (Student's t-test or Mann-Whitney test; Kruskal-Wallis test).*

Table S2. R values for correlation test of different factors in relation to the difference between T12 and T0 of caloric intake and the difference between T12 and T0 of protein intake in patients on the waiting list for liver transplantation (n=47).

Variables	Correlation									
	Baseline		0		4		8		12	
	T12-T0		T12-T0		T12-T0		T12-T0		T12-T0	
	(kcal/kg)	(g/kg)	(kcal/kg)	(g/kg)	(kcal/kg)	(g/kg)	(kcal/kg)	(g/kg)	(kcal/kg)	(g/kg)
Sociodemographic										
Age (y)	-0.176	0.013								
Education (y)	0.225	0.107								
Monthly income ($)	0.047	0.077								
Clinics										
MELD Na	-0.167	-0.112	-0.244	-0.118	-0.355*	-0.259	-0.168	-0.082	-0.284	-.0113
Lifestyle										
Physical activity per week (minutes)	0.037	0.013								
Daily TV (h)	-0.136	-0.049								
Sleep per night (h)	-0.093	-0.147								
Anthropometrics/body composition										
Dry weight (kg)	-0.053	-0.018	0.036	0.036	0.037	0.026	0.109	0.147	0.026	0.033
Body Mass Index (kg/m²)	-0.041	-0.081	0.045	-0.022	0.048	0.005	0.059	0.056	-0.026	-0.062
Arm Circumference (cm)			-0.054	-0.176	-0.025	-0.068	-0.002	-.0.031	-0.061	-0.052
Calf Circumference (cm)			-0.048	-0.107	0.001	-0.083	-0.073	-0.132	-0.035	-0.050
Triceps Skinfold (mm)			-0.077	-0.238	-0.098	-.0186	-0.165	-.0263	-0.148	-0.236
Arm Muscle Circumference (cm)			0.008	0.007	0.083	0.120	0.154	0.205	0.051	0.143
Arm Muscle Area (cm)			-0.037	-0.028	0.058	0.100	0.116	0.173	0.004	0.103
Adductor Pollicis Muscle Thickness (mm)			0.281	0.127	0.336*	0.255	0.304*	0.184	0.064	-0.021
Resistance			-0.135	-0.070	-0.021	-0.003	0.101	0.014		
Reactance			-0.127	-0.071	-.0112	-0.130	0.021	0.018	0.029	-0.037
Phase angle			-0.004	-0.047	-0.025	-.0102	-0.056	0.015	-0.011	0.019
Functionality										
Dynamometry										
Highest of six measurements			0.270	0.197	0.156	0.109	0.150	0.174	0.166	0.167
Frailty index										
Total score			-0.176	-0.148	0.060	0.051	0.000	0.020	0.066	0.069

Quality of life								
Abdominal symptoms	0.018	0.138	-0.065	0.250	0.229	0.268	0.052	0.249
Fatigue	0.147	0.310*	0.133	0.336*	0.107	0.296*	0.121	0.349*
Systemic symptoms	0.055	0.232	0.266	0.420*	0.215	0.289	0.120	0.157
Activity	-0.013	0.053	0.108	0.342*	-0.035	0.090	-0.040	0.169
Emotional function	0.138	0.299*	0.193	0.285	0.201	0.298*	0.229	0.376*
Worry	-0.133	0.114	0.008	0.245	-0.122	0.133	-0.029	0.269
Total score	0.055	0.264	0.177	0.388*	0.141	0.321*	0.105	0.356*

Caption 13. *Values with asterisk are significantly different, $p < 0.05$. (Pearson or Spearman test).*

8 FINAL CONSIDERATIONS

In conclusion, this study demonstrated that compared to the active control group, the supplementation with HMB had no effects on muscle mass markers, muscle, function, and quality of life in patients on the liver transplant waiting list compared to the active control group. However, these results should be interpreted with caution, as many participants did not reach the minimum calorie and protein intake recommended for patients with liver cirrhosis. Therefore, these factors may have interfered with the ability of the HMB to act positively on the studied variables. More studies, conducted with a more specific population when nutritional needs are met, are needed to confirm or refute these results.

Concerning food intake, patients on the waiting list for liver transplant waiting list marginally improved food intake during nutritional follow-up but reaching the caloric and protein target is still a challenge, however, it is possible to improve food patterns in clinical practice. The need for early initiation and continuing of nutritional therapy in the context of imminent malnutrition is highlighted, whether offering oral nutritional supplements or enteral nutritional therapy, which can increase or guarantee nutrient intake in case of insufficient oral food intake.

Suggestions for future studies include using a direct measure of muscle mass, establishing a protocol to meet the nutritional requirements of patients, and exploring techniques to promote awareness of self-care, overcome modifiable barriers and improve patient adherence, and consider that several factors can influence food intake, and provide subsidies that can improve dietary counseling practices and the need for adjustments during nutritional interventions.

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10 APPENDIX A – TERMO DE CONSETIMENTO LIVRE E ESCLARECIDO

Termo de Consentimento Livre e Esclarecido

O Sr. (a) está sendo convidado (a) como voluntário (a) a participar da pesquisa **"Efeito da suplementação de beta-hidroxi-beta-metilbutirato sobre o estado nutricional, massa magra muscular e funcionalidade de pacientes em lista de espera para transplante hepático"** pela pesquisadora Samanta Catherine Ferreira, nutricionista, para obtenção do título de Doutora pelo Programa de Pós-Graduação em Ciências dos Alimentos da Faculdade de Farmácia, Universidade Federal de Minas Gerais.

O estudo em questão visa avaliar o efeito da suplementação de leucina e beta-hidroxi-beta-metilbutirato (HMB) sobre a massa magra, funcionalidade e qualidade de vida em pacientes em lista de espera para transplante hepático. Tendo em vista as propriedades anti-proteolíticas e anabólicas da leucina e do HMB, esses suplementos poderiam ser efetivos no tratamento de distúrbios nutricionais, como desnutrição/sarcopenia que acometem doentes hepáticos terminais.

Para participar desta o Sr (a) deverá estar em jejum de 10-12 horas para realização do exame bioquímico e responderá algumas perguntas sobre dados pessoais e clínicos, como idade, residência, ocupação, sexo, escolaridade, renda, estado civil, número de filhos, hábito de fumar, hábito de consumo de bebidas alcoólicas, atividade física, ingestão de medicamentos, os dados clínicos serão coletados em prontuários médicos após autorização. Ademais, serão coletadas informações sobre ingestão dietética, além de se submeter a medidas antropométricas (peso, altura, medida da circunferência do braço, circunferência da panturrilha, prega cutânea tricipital e espessura do músculo adutor do polegar). O Sr (a) também será submetido ao teste de bioimpedância elétrica, para determinação da composição corporal, dessa forma, esse teste será realizado em sala com temperatura ambiente controlada, baixa luminosidade e sem ruídos, após repouso de 20 minutos. Para avaliação, quatro eletrodos (tipo esparadrapo) serão colados na mão (dois) e no pé (dois) por onde passa uma corrente elétrica que não se percebe e não causa dor ou qualquer outra sensação e tem como objetivo avaliar a quantidade de gordura, água e músculo do corpo. Para a realização desse teste, o Sr (a) deverá estar em jejum de 12 horas, não ter praticado exercícios físicos e ingerido bebidas alcóolicas no dia anterior, trajar roupas leves. Também será realizada avaliação da funcionalidade, através da medida da avaliação da força do aperto de mão e dos testes de equilíbrio estático, velocidade de marcha em passo habitual e de força muscular estimada de membros inferiores. Em seguida, o Sr (a) receberá um plano alimentar, conforme as minhas necessidades nutricionais e os suplementos (leucina, HMB ou controle ativo) que deverão ser consumidos durante 12 semanas junto a última refeição do dia (ceia).

Riscos e desconfortos: Os métodos utilizados não causam nenhuma lesão e a dosagem dos suplementos se encontra dentro dos limites de segurança. No entanto, o Sr (a) poderá achar o gosto do suplemento ruim e sentir algum desconforto gástrico após a utilização do suplemento, tais como náuseas e vômitos. Quando acontecerem comunique a um dos pesquisadores, existem tratamentos específicos que serão aplicados imediatamente após a detecção do problema.

Sigilo: Os dados serão sigilosos e o Sr (a) poderá ter acesso às informações em qualquer momento sobre os riscos e benefícios relacionados ao estudo, inclusive poderá esclarecer as suas dúvidas em qualquer momento. Ainda será garantida confidencialidade, sigilo e privacidade dos dados.

Benefícios: Ao participar do estudo você poderá contribuir para que novos métodos sejam empregados na melhora do estado nutricional de pacientes pré-transplante hepático. Isto pode contribuir na evolução do tratamento, com importante melhora dos resultados. Ainda, em caso de sucesso dos tratamentos avaliados, essa suplementação também será disponibilizada para os participantes do grupo controle (controle ativo) após o fim do estudo.

O (A) Sr. (a) não terá nenhum custo, nem receberá qualquer vantagem financeira. O Sr. (a) terá o esclarecimento sobre o estudo em qualquer aspecto que desejar e estará livre para participar ou recusar-se a participar e a qualquer tempo e sem quaisquer prejuízos, pode retirar o consentimento dos dados coletados, valendo a desistência a partir da data de formalização desta. A sua participação é voluntária, e a recusa em participar não acarretará qualquer penalidade ou modificação na forma em que o Sr. (a) é atendido (a) pelo pesquisador, que tratará a sua identidade com padrões profissionais de sigilo. Os resultados obtidos pela pesquisa, estarão à sua disposição quando finalizada. Seu nome ou o material que indique sua participação não será liberado sem a sua permissão. O (A) Sr. (a) não será identificado (a) em nenhuma publicação que possa resultar. Em caso de dúvidas, poderá entrar em contato com as pesquisadoras nos telefones abaixo e poderá procurar os Comitês de Ética em Pesquisas (COEP).

Este termo de consentimento encontra-se impresso em duas vias originais, sendo que uma será arquivada pelo pesquisador responsável, na Faculdade de Farmácia da UFMG, e a outra será fornecida ao Sr. (a). Os dados, materiais e instrumentos utilizados na pesquisa ficarão arquivados com o pesquisador responsável por um período de 5 (cinco) anos na sala 2074 da Faculdade de Farmácia da UFMG e após esse tempo serão destruídos. Os pesquisadores tratarão a sua identidade com padrões profissionais de sigilo, atendendo a legislação brasileira (Resoluções Nº 466/12; 441/11 e a Portaria 2.201 do Conselho Nacional de Saúde e suas complementares), utilizando as informações somente para fins acadêmicos e científicos.

Eu, _____, portador do documento de identidade _____ fui informado (a) dos objetivos, métodos, riscos e benefícios da pesquisa "**Efeito da suplementação de beta-hidroxi-beta-metilbutirato sobre o estado nutricional, massa magra muscular e funcionalidade de pacientes em lista de espera para transplante hepático**", de maneira clara e detalhada e esclareci minhas dúvidas. Sei que a qualquer momento poderei solicitar novas informações e modificar minha decisão de participar se assim que desejar.

( ) Concordo que os meus dados coletados sejam utilizados somente para esta pesquisa.

Declaro que concordo em participar desta pesquisa. Recebi uma via original deste termo de consentimento livre e esclarecido assinado por mim e pelo pesquisador, que me deu a oportunidade de ler e esclarecer todas as minhas dúvidas.

_____

(Participante)

_____

(Assinatura)

_____

(Pesquisador)

_____

(Assinatura)

_____

(Testemunha)

_____

(Assinatura)

Belo Horizonte, ____ de _____ de 20__.

Endereço do Comitê de Ética em Pesquisa da UFMG: Av. Antônio Carlos, 6627, Unidade Administrativa II - 2º andar, Campus Pampulha, Belo Horizonte, MG, CEP: 31270-901. Telefone: (31) 3409-4592.

Doutoranda Samanta Catherine Ferreira (31) 993114382
e-mail: samanta_catherine@hotmail.com
Orientador: Prof. Dra. Lucilene Rezende Anastácio

11 ANNEX A

Qualitative study on factors that affect adherence to nutritional intervention in a clinical study with patients on the waiting list for liver transplantation

Trabalho de Conclusão de Curso da aluna Nathália Pereira de Souza, bolsista de extensão participante do projeto, sob orientação de Samanta Catherine Ferreira e coorientação de Lucilene Rezende Anastácio

Abstract

Background: Patients with end-stage liver disease are at increased risk of malnutrition. Nutritional interventions are essential to minimize this situation. However, adherence to nutritional prescriptions is still a challenge to be faced.

Aim: Identify and understand the factors and perceptions that interfere with adherence to nutritional intervention in patients on the waiting list for liver transplantation.

Methods: Qualitative study with patients on the waiting list for liver transplantation. The interview was scripted according to the aspects of a semi-structured questionnaire. The guiding questions were divided into two topics: personal aspects and aspects that cover the patient's relationship with food. The dialogues were recorded and transcribed in full manually. Thematic analysis was performed to identify themes and sub-themes that interfere with adherence to nutritional intervention. Data saturation was used to determine the size of the sample.

Results: Fourteen interviews were conducted and five themes were identified and stratified into subthemes: 1. Family relationships: "autonomy to make food choices", "family concern/charge"; 2. Perception of the disease: "knowledge about the aspects of the disease"; 3. Physiological factors: "complications", "anorexia", "change in food patterns", "hospitalization"; 4. Understanding about diet: "putting the diet into practice", "benefits of nutritional treatment", "conflicting nutritional guidelines", "long-term nutritional guidelines", "influence on the disease", "knowledge about food"; and 5. Social aspects: "increase in food pricing", "removal from work due to illness". In these themes, positive and negative factors that can interfere with adherence were analyzed.

Conclusions: The results show that the factors that affect adherence to nutritional intervention include family relationships, perception of the disease, physiological factors, understanding of diet, and social aspects. The findings demonstrated that patients' perceptions about nutritional treatment can influence the success of the nutritional intervention.

Keywords: Liver Transplantation. Patient Adherence. Nutritional Intervention.

1. INTRODUCTION

The liver is responsible for several functions of the human body, such as metabolizing nutrients, hormones and potentially harmful substances to the body (BEIER et al., 2014). Compromised liver function can be caused by several etiological factors, such as viral infections, use of drugs and hepatotoxic substances, excessive alcohol consumption, iron accumulation, fat accumulation in the organ, and autoimmune processes. These aspects can lead to chronic liver diseases (CLD) (HEIDELBAUCH; BRUDERLY, 2006; WIEGAND; BERG, 2013).

Cirrhosis is characterized by chronic damage to the liver, which replaces normal liver tissue with non-functional scar tissue. Cirrhosis is considered the final stage of CLD (WIEGAND; BERG, 2013). The prognosis of patients with liver disease is determined according to the degree and extent of this injury, and based on this, if indicated, liver transplantation (LTx) may be recommended as the only intervention capable of improving the clinical status of the individual with end-stage chronic disease (NACIF et al., 2014).

Patients on the LTx waiting list can evolve with several complications, with malnutrition being one of the most frequent clinical outcomes (EASL, 2019; FERREIRA et al., 2009; ANASTÁCIO; CORREIA, 2016). Depending on the nutritional assessment method used, the prevalence of malnutrition in patients with liver cirrhosis can range from 50% to 90% (EASL, 2019; GARCÍA-RODRÍGUEZ et al., 2017; JUAKIEM et al., 2014). Therefore, in an attempt to reverse the malnutrition situation (ANASTÁCIO et al., 2011), nutritional therapy becomes an integral part of care for patients on the LTx waiting list (PLAUTH et al., 2019; ANASTÁCIO; CORREIA, 2016).

Some studies that evaluated food intake in patients with liver cirrhosis showed caloric, and protein intake below recommended nutritional recommendations (DAPHNEE et al., 2018; CHAPMAN et al.; 2019; PALMESE et al., 2019a; MIZUBUTI, et al., 2021), thus reinforcing the need for research to assess and describe which factors can impact adherence to proposed nutritional interventions.

Numerous physiological factors caused by liver disease can influence the reduction of food intake in this group of patients (ANASTÁCIO; CORREIA, 2016; FERREIRA

et al. 2009; JUAKIEM et al., 2014). Loss of appetite, early satiety, complications such as hepatic encephalopathy (HE), which can alter the level of consciousness, causing irregular eating throughout the day, long fasting periods for laboratory procedures, metabolic disorders, and ascites are examples (JUAKIEM et al., 2014; ANASTÁCIO; CORREIA, 2016; FERREIRA et al. 2009).

In addition to physiological factors, eating behavior can interfere with food intake (TARAGANO; ALVARENGA, 2019; TURANO; ALMEIDA, 1999). With the advancement of research, it has been shown that biological knowledge is insufficient to understand the complexity of eating habits, as well as eating behavior and the relationship between disease and the individual (BOOG, 2005; PINTO; CAMPOS; SIQUEIRA, 2018). To promote an adequate nutritional intervention that provides greater adherence to the recommendations, the patient's perception and feelings involved in food need to be observed and considered for adherence to be adequate. Food has more than a nutritional character; it also has social meanings (OLIVEIRA, 2008). Food choice permeates cultural, social, environmental, and psychological aspects, being an intricate and necessary process for health research, especially for nutrition (JOMORI; PROENÇA; CALVO, 2008; CAVALCANTI; DIAS; COSTA, 2005).

Based on the above, investigations need to assess patients' perceptions of food and the factors involved in adherence to nutritional guidelines. Few studies have verified the factors that affect nutritional treatment in patients on the waiting list for liver transplantation. Therefore, this study aimed to identify and understand the factors and perceptions that interfere with adherence to the proposed nutritional intervention during 12 weeks of nutritional monitoring in patients on the waiting list for liver transplantation.

2. MATERIALS AND METHODS

2.1 Contextualization

This study is part of a double-masked longitudinal randomized clinical trial with supplementation of beta-hydroxy-beta-methylbutyrate (HMB) or active control. There was prescription and dietary follow-up for 12 weeks with 44 patients on the waiting list for LTx. Patients were evaluated monthly in relation to clinical, anthropometric, body composition, functionality, and dietary variables. More research details can be found in the original article (FERREIRA et al., 2023).

2.2 Qualitative study

2.2.1 Type of study

This is a qualitative study with patients on the waiting list for liver transplantation who underwent nutritional monitoring from November 2021 to February 2022.

Patients on the liver transplant waiting list who were completing or had completed outpatient nutritional monitoring from 2021 onwards were invited to participate in an interview. This period was selected to avoid memory bias, thus minimizing the systematic error by forgetting events or previous experiences in detail (SPENCER; BRASSEY; MAHTANI, 2017).

The Research Ethics Committee of UFMG approved the project after submission of an addendum to Parecer nº 3.134.996 (Annex B). All participants signed the Termo de Consentimento Livre e Esclarecido (Annex C).

2.2.1.1 The Thematic Analysis

Thematic analysis was adopted, as a method that identifies, analyzes, and reports patterns (themes) in the data. This method minimally organizes and describes the data set in detail (BRAUN; CLARKE, 2006). The researcher plays an active role in identifying patterns/themes, selecting which ones are of interest, and reporting them to readers (BRAUN; CLARKE, 2006).

The thematic analysis used is based on the essentialist method, also called realistic, in which it reports experiences, meanings, and the reality of the participants (BRAUN; CLARKE, 2006). From this, the selection of themes within the data can be identified in two ways in thematic analysis: the inductive and theoretical.

The theoretical form was used in the present work. The theoretical thematic analysis evaluates how to determine themes carried out in previous research related to the object of study. Thus, analysis involves searching a set of data, be it a series of interviews or focus groups, or texts to find repeated patterns of meaning (BRAUN; CLARKE, 2006). This method follows a structured process in six phases that start with the search for patterns of meaning and questions of potential interest in the data, which may also happen during data collection. It ends with reporting the content and meaning of the patterns (analysis themes) in the data. (BRAUN; CLARKE, 2006). Still, the analysis can proceed to the next phase and, if necessary, return to the previous phase, the process being recursive. The stratification of the phases and the description of each one is presented in Table 1.

Table 1. Phases of thematic analysis by Braun and Clarke (2006)

Phase	Process description
1. Getting familiar with your data	Transcribe the data, read, reread the data, and write down the initial ideas.
2. Generating initial codes	Code interesting aspects of data systematically across the database, grouping relevant data for each code.
3. Searching for themes	Grouping codes into potential themes, gathering all relevant data for each potential theme.
4. Review topics	Verify that themes work against coded extracts and the entire dataset; generate a thematic map of the analysis.
5. Definition and naming of themes	Refine the specifics of each theme and the general story that the analysis tells; generate clear definitions and names for each theme.
6. Production of the report	Selection of vivid examples; final analysis of selected extracts, relating the analysis to the research question and literature; scientific account of the analysis.

Adapted from Braun and Clarke, 2006.

2.2.2 Study location

This study was carried out in the transplant sector of the Bias Fortes Ambulatory of the Alfa Institute of Gastroenterology of the Hospital das Clínicas of the Federal University of Minas Gerais (UFMG). Video calls were also made, depending on the possibility and availability of the patient.

2.2.3 Participants

Active patients on the waiting list for liver transplantation who underwent nutritional monitoring for 12 weeks in the liver transplantation sector of the Hospital das Clínicas of UFMG were included. Patients over 18 years of age, cognitively capable of answering the interview questions, who agreed to participate in the study and who are completing or completing nutritional monitoring were included. Those patients who had completed nutritional monitoring before 2021 were excluded.

2.2.4 Intervention

All patients who met the clinical trial inclusion criteria and were within the period selected for data collection were invited to participate in the study. Faced with their agreement, interviews were scheduled to be carried out on the day of the medical appointments at the outpatient clinic either in person or by video call, in case there was no scheduled medical appointment or due to some unforeseen event that prevented the in-person interview. The conversation was conducted by the researcher himself in a silent room and assurance that there would be no external interruptions so that the interviewee felt comfortable, and his privacy was assured.

The interview was scripted following the characteristics of a semi-structured interview. According to Manzini (1990/1991), the semi-structured interview is "focused on an objective on which we create a script with main questions, complemented by other questions inherent to the momentary circumstances of the interview". That is, in the semi-structured interview, the answer is not conditioned to a standardization of questions formulated by the researcher, as in the structured interview. The guiding questions were divided into topics: personal aspects and aspects that encompass the patient's relationship with food (Appendix B). The dialogues were recorded by the researcher's cell phone recorder with backup and stored immediately after the interview in two cloud storage locations.

Data saturation was used to determine sample size. This tool is used to establish or finalize the final size of a sample under study, interrupting the capture of new components (FONTANELLA; RICAS; TURATO, 2008).

2.2.5 Analysis of qualitative data

As the interviews progressed, the questions were analyzed in order to generate a better interaction with the interviewees. After the application of eight interviews, the transcription process was started, carried out in full of the interviews. Transcriptions were performed by the researcher himself with the help of another researcher who was aware of this study and previously instructed.

After transcribing all the interviews, the process of reading and rereading the data and writing down the initial ideas began (Phase 1 - Familiarization with the data). Afterwards, the systematic grouping of relevant information was started (Phase 2 - Generating initial codes) and potential themes were determined for these groupings (Phase 3 - Searching for themes), thus, the themes and subtopics were reviewed for consistency with the excerpts grouped into two levels, at this stage, followed the flowchart based on the ideas of Braun and Clarke (2006) and prepared by Souza (2019), (Phase 4 - Review topics).

After the review carried out in phase 4, the themes raised were evaluated and refined to respect the analysis of the study and clear names for the themes were identified, as well as the subtopics (Phase 5 - Definition and naming of themes). Then, the final analysis of themes, sub-themes and excerpts was carried out and the scientific production process began (Phase 6 - Production of the report).

The speeches cited in the results were kept in their original form, with colloquial language (QUEIROZ, 1983) and the excerpts were anonymously highlighted to illustrate the results, the patients were identified with the acronym p (patient) + (number from 1 to 14).

3. RESULTS AND DISCUSSION

Of the 20 patients who were invited to participate in the research, four refused to participate. Data saturation was achieved after interviews with 12 participants, so two more interviews were carried out to ensure that no new information emerged, totaling 14 complete interviews, with an average duration of 24 minutes and 15 seconds.

Most participants were male (71.4%; n=10), with a mean age of 54.5 ±13.5 years. Ethanol cirrhosis was the main indication for liver transplantation, representing 50.0% of the sample (n=7) and the mean MELD value was 13±4.6. The most frequent family income was between 1 and 2 minimum wages, which corresponded to 50.0% of the sample (n=7). As for education, 35.7% (n=5) had completed high school and 92.9% (n=13) lived in an urban area.

Five main themes were identified after analysis, which describe factors and perceptions that can interfere with adherence to nutritional intervention. Table 3 represents a summary of the themes and sub-themes that emerged from the interviews, in order to allow a better observation of the data.

Table 3. Factors and perceptions of patients on the waiting list for liver transplantation research participants about nutritional intervention at the Ambulatório Bias Fortes between September/2021 and April/2022 - Belo Horizonte, MG

Themes	Subtopics
Family relationships	Autonomy to make food choices Family concern/pressure
Disease perception	Knowledge about aspects of the disease
Physiological factors	Clinical complications Anorexia Change in eating patterns Hospitalization
Understanding about nutrition	Implementing the diet Benefits of nutritional treatment Conflicting nutritional guidelines Long-term nutritional guidelines Influence on the disease knowledge about nutrition
Social aspects	Increase in food prices Absence from work due to illness

3.1 Family relationships

The participants presented different perspectives in relation to their family members. It is noted that the majority did not have autonomy to make food choices, from purchase to meal preparation. It is also possible to assess the importance of family support for coping with the disease and continuing the treatment.

3.1.1 Autonomy to make food choices

Due to the majority of the sample being male, low autonomy in care can be observed due to cultural aspects. Women are responsible for preparing food, as mentioned by Pilla (2015): "When the topic is health and nutrition of the family, it is women who are usually responsible for the well-being of the other members of the group." Thus, even if family members did not accompany the patients to nutritional consultations and were informed about the nutritional intervention, it was they who determined which foods would be offered and, in the absence of this support, patients had difficulty making assertive decisions regarding their diet.

p3 - "There are days when the mother goes out, I stop eating when I'm out in the fields, then I'm on my own, I have to manage"

p13 - "I learned to make some things with food, I don't do much because I have a wife here who is the ox foot, let's say, but I don't harm her at all, I don't force her to do anything, she does what she wants and everything"

p13 - "The two of them go (purchase of the month) [...] to the grocery store, the day to day, I go. Got it? But, I leave the house and ask what she wants to bring"

p4 - "she made the list, but like, her list, she doesn't like to eat a lot, you know, I like to eat zucchini, I like to eat a eggplant, I like to eat squash, I like to eat yams, and so, she I don't like to eat these things anymore, you know"

p10 - "My wife prepares it, so usually I don't even see her do it. It's already arrived and it's ready"

3.1.2 Family concern/pressure

Similarly, to the study conducted by Spillman et al. (2021), which observed barriers and facilitators to following dietary and physical activity advice in their qualitative study with post-TxH patients, family members were essential factors in encouraging the food intake of the interviewed patients, from preparing meals respecting the nutritionist's guidelines, to the need to stay well to take care of their children:

p10 - "The wife who turned to do this, she arranged things. It wasn't complicated, no. Apparently it wasn't, she didn't complain."

p1 - "Can't lose hope, because especially me who has two young children who need me, I have to fight, can't give up treatments, although there are days when you don't want to know about anything, you don't even want to get out of bed, everything seems bad to you."

p2 - "They tell us to eat these leaves, there are some leaves there, that my wife always makes me eat. Says it's good, we eat, I don't know if… right… [...] I don't really like leaves."

p14 - "The thing is they just make it and I eat it."

p5 - "because (patient's spouse name) always cared about that."

p4 - "Because Mrs. (spouse's name), she's very… she even goes a little over the line, you know? Like… she wants everything to be perfect, scolds me a lot, sometimes I even say 'hey, I'm not a kid anymore, you know'."

3.2 Disease perception

3.2.1 Knowledge about disease aspects

Several patients demonstrated low concern with the diagnosis and course of liver disease:

p2 - "[...] I didn't receive anything with sadness, nothing, because I'm not afraid, not even of dying [...] things happen and we have to accept them, right?"

p10 - "When I found out, it was actually a relief because I thought it was cancer."

p4 - "[...] I was a little careless, didn't worry too much."

p12 - "I didn't get scared."

In addition, some patients reported difficulties in getting diagnosed and some beliefs related to the occurrence of cirrhosis:

p1 - "[...] I feel like my liver is swollen."

p13 - "[...] when it started, I didn't know what the disease was."

p14 - "About the pepper, I really like pepper and they said, 'no.' Because I thought this spot, this tumor, could be from eating too much pepper."

Knowledge about the disease and its aspects can be a crucial factor in implementing treatments to improve nutritional status and consequently, prognosis. By

evaluating the findings of this study in relation to this factor, it is possible to infer that, in order for nutritional treatment to be effective, it is important for the patient to understand the health-disease process, so that there can be a change in behavior regarding illness and food intake.

When evaluating the knowledge of liver transplant candidates, Oliveira et al. (2016) found that 37.1% and 45.2% of patients had insufficient understanding of liver disease and liver transplantation, respectively. Additionally, 41.9% of patients had insufficient understanding of the pre-TxH treatment. As a result, tools have been developed to assess patients' knowledge of the disease (MEDEIROS et al., 2018), and their use can be an alternative in clinical practice to better understand the patient's level of knowledge about liver disease, contributing to more appropriate management of the disease and its complications, such as malnutrition.

3.3 Physiological factors

3.3.1 Clinical complications

The complications of the disease such as ascites, weakness, and apathy were one of the factors that made it impossible for some patients to eat:

p8 - "If I consume any liquid, or even the position, if I sit for too long, or lie on my back, I can't..."

p5 - "I have been much more in rest now... I stopped having a normal life in that sense, of activity... If someone asked me to stand on one leg, I couldn't do it"

p6 - "Anything brings me down, the day that I am down is the day that I don't want to eat, when I am feeling good, I eat a lot, even exceed the diet."

p2 - "I'm losing my appetite, I don't know if it's because my belly is too big...then the belly started growing, and I ended up losing my appetite... this swollen belly really interferes, a lot! And it seems like I'm always full, not eating anything."

The stabilization of the disease, reducing imminent complications, favored the improvement of appetite, which can enable the ingestion of food within the recommended amount:

p7 - "Everything is normal, the appetite is normal, also due to the situation I'm in now because I'm much better, exams are fine, no drains."

This excerpt shows that clinical complications are determinant factors for the adherence to nutritional intervention to be effective. Gastrointestinal symptoms have been associated with reduced quality of life and increased morbidity (KALAITZAKIS et al., 2006), which may justify the reports about the need to rest and the feeling of exhaustion. The reduction of food intake is one of the consequences of these aggravations (AQEL et al., 2005).

3.3.2 Anorexia

The lack of appetite was consistently reported among the interviewees:

p8 - "[...] I started to have a decrease in food intake because everything was bad for me, the food...I didn't feel like having lunch, dinner, even breakfast, a bread with butter, it was bad for me"

p2 - "[...] how can I eat this here if I don't have an appetite?"

p6 - "[...] today I eat, as they say, so as not to have problems in the exams and not be hospitalized, but...there are days when you eat, there are days when you don't eat, there are days when you don't want any food"

p1 - "I stop eating, I eat a fruit, I eat salad, until I feel better, but I don't force my body"

p2 - "[...] the food is terrible, I have no appetite [...] I don't feel like eating"

Anorexia is a common symptom in patients with liver cirrhosis. This result showed that adhering to nutritional intervention is a complex step, since there is no appetite for food to occur and, even so, some patients reported eating to avoid worsening the disease despite the lack of hunger.

Recognizing this symptom at the time of intervention is essential to provide effective guidance. The cause of anorexia in patients with cirrhosis has been associated with deficiencies in micronutrients such as zinc and magnesium (MADDEN; BRADBURY; MORGAN, 1997; LIM; JACOB; 1972; GRÜNGREIFF; REINHOLD; WEDEMEYER, 2016) and abnormalities in appetite-regulating hormones such as ghrelin and leptin (OCKENGA et

al., 2000; MARCHESINI et al., 2004). These studies point to possible ways to improve the reduction of appetite through supplementation of deficient micronutrients and pharmacological correction of ghrelin. Therefore, identifying deficiencies at the beginning of treatment is an alternative for better adherence, as well as periodic conversation with the multiprofessional team is fundamental for effective and complementary interventions to be instituted.

3.3.3 Change in dietary patterns

Changes in taste were a frequent topic in the data analysis, with increased food consumption, preference for a certain taste or loss of taste being noticed:

p7 - "[...] sometimes my taste disappeared a bit with regard to seasonings and everything"

p2 - "[...] I'm eating more fruits because I like fruits, what I'm eating is... all these fruits, you know? Fruit is good, but actual food... I used to eat well, but not anymore"

p3 - "Lately, I've been eating a lot of sweet things, I don't know why"

p7 - "[...] but there was a time when my body really wanted sugar, so I started eating sweets, sweets, sweets"

p4 - "[...] when I got home, I would take a shower, have dinner, and then I would indulge"

p4 - "After I stopped drinking, I started binge eating [...] I think I missed something, I wasn't drinking anymore"

p10 - "Before I found out and started treatment, I didn't even like beef. I liked coffee and beans. Now I like beef and I don't like either beans or coffee."

The altered taste perception among patients with hepatic cirrhosis is already a studied subject (GRÜNGREIFF; REINHOLD; WEDEMEYER, 2016). Considering this point, the preference for more caloric foods is recurrent, which can affect adherence to nutritional guidelines. Generally, sugar-rich foods have an increased calorie content and do not provide the necessary micronutrients for proper organ function (BRASIL, 2017; BRASIL, 2014). Another point is the altered taste perception with regard to zinc deficiency, commonly found in patients with hepatic cirrhosis, since the liver is responsible for the metabolism of this mineral (GRÜNGREIFF; REINHOLD; WEDEMEYER, 2016).

Patients with hepatic cirrhosis usually have an exhausting daily routine. Going to medical appointments, ambulatory procedures, restrictions, use of multiple medications, hospitalizations, and the complications of cirrhosis that are accompanied by chronic pain, insomnia, stress, muscle weakness, discomfort, and reduced mobility are everyday examples (ANASTÁCIO; CORREIA, 2016; ANASTÁCIO et al., 2011; VILSTRUP et al., 2014; LIU; CHUNG, 2021). Therefore, the consumption of carbohydrates, such as excessive sweet foods, can be a desire, even unconscious, to feel better (WURTMAN; WURTMAN, 1995). Carbohydrates increase the release of serotonin, a hormone responsible, among other factors, for mood control, while protein does not have the same effect (WURTMAN; WURTMAN, 1995), which justifies the need for carbohydrate intake.

Moreover, when it comes to patients with cirrhosis, in which one of the main causes in the world is alcohol abuse (TSOCHATZIS, 2014), as well as in this work. Ceasing alcohol consumption is one of the main measures to be taken during the treatment of hepatic cirrhosis and for entering the transplant waiting list. However, alcohol abstinence can lead to the use of another substance or even food to replace the alcohol addiction, called "substitutive dependence," which can be excess food or more caloric food (ALARCON et al., 2021; KIM et al., 2021). These justifications for taste changes reinforce the importance of taking these inhibiting factors into account when starting the process of dietary changes.

3.3.4 Hospitalization

The length of hospital stay has been reported as a factor affecting food intake and worsening malnutrition:

p10 - "[...] I stayed in the hospital for 11 days and during those 11 days I lost up to 11 kg"

p11 - "[...] when I was hospitalized I didn't feel hungry at all. The most delicious dish could be served and I still wouldn't feel hungry."

p7 - "[...] hospital food is not pleasant, it's not nice"

p7 - "As for appetite, I got disgusted with chicken because during the 27 days I stayed at the hospital, they must have sent chicken 22 days, so I started to feel sick."

This result demonstrates that in addition to food intake below recommendations in daily life, hospitalization can worsen this condition, as well as contributing to the higher prevalence of malnutrition already extensively present in patients with advanced hepatic cirrhosis (EASL, 2019; GARCÍA-RODRÍGUEZ et al., 2017; JUAKIEM et al., 2014). It is now known that hospital malnutrition can be a factor in several complications of the patient's clinical condition, such as poor immune response, increased risk of developing pressure injuries, and a higher risk of mortality (TOLEDO, 2018). Currently, malnutrition varies between 20 and 50% in adults, with many already presenting this condition at the time of hospital admission (TOLEDO, 2018).

3.4 Understanding about nutrition

3.4.1 Implementing the diet

Among the various factors that can affect adherence to the nutritional treatment developed after analysis, the difficulty in implementing the meal plan was a frequently mentioned aspect, as it was considered inflexible and difficult to understand:

p3 - "[...] very strict"

p3 - "[...] it's not easy to follow it precisely"

p10 - "At first, I found it difficult to do. It's kind of complicated to do things at the right time. It was a bit difficult."

p10 - "No. It's not the same (as the meal plan). It's very difficult."

p6 - "There are days when I'm motivated, I do it, and there are days when I'm not."

p1 - "[...] now I understand the diet better, now that the diet is over, I understand it better, right?"

However, simple and applicable guidelines for daily routines were also mentioned, even though they were not followed ideally:

p13 - "[...] it was very easy, even though we were a little scared about the changes"

p13 - "[...] it was normal, I accepted it, followed everything, my wife followed everything, it was normal, it was easy, it didn't change anything, that's it"

p14 - "It was easy. I didn't follow it exactly, but..."

p12 - "There was no organization, I did it and that's it"

Dietary factors were also perceived, such as considering the prescribed amount of food excessive:

p13 - "I ate too much at breakfast, then at 9 am, then lunch, 3 pm, and dinner time. All of that."

p14 - "I found it too much."

In addition, implementing nutritional guidelines and the meal plan was not a habit:

p14 - "We didn't... we didn't put it into practice..."

p7 - "[...] we didn't have to... change the menu, we usually ate what we were eating before and that was it."

The reduction of palatable foods from the patients' point of view was an obstacle to adhering to the guidelines:

p14 - "[...] I don't eat anything fried... "oh, let's try to cut out fried food", but I like fried steak, I don't really like vegetables and that stuff, so my diet stays exactly the same. [...] A lot of things have to go, though, fried food is definitely a no-no, but the things I like, that's what I eat."

p5 - "[...] salt, that's really troublesome [...] you have to avoid a lot of salt. Because I used to love spicy food."

p6 - "It's difficult, you have the diet there and sometimes you just can't follow it, to be honest, there are days when you slip up...because it's really hard, eating food without salt just doesn't work either."

p3 - "If I don't like something, I don't eat it."

Considering that nutritional recommendations for the treatment of patients with chronic liver disease are necessary, but sometimes far from the reality in which the

patient has lived for years up to that point, giving importance to cultural, social, and economic factors that permeate dietary behavior is essential for adherence to treatment. Sodium restriction, although listed in society recommendations as part of the treatment for patients with decompensated cirrhosis and moderate ascites, is generally associated with a reduction in calorie intake and can harm nutritional status (EASL, 2019).

3.4.2 Benefits of nutritional treatment

The benefits of health during nutritional treatment have been recognized in different ways, such as weight improvement, appetite improvement, perception of appetite, and eating foods that were not eaten before:

p13 - "[...] she would say things like 'Eat kale (patient's name), eat kale', so I made a lot of kale, had kale for lunch and dinner, and it really makes sense, nutrition helps a lot."

p9 - "And then I went to the doctor (nutritionist), and she really lifted me up. Because if she hadn't...if my nutrition hadn't improved, the way I was losing weight, I wouldn't have been able to cope."

p9 - "The first time I saw the doctor (nutritionist), when I came back, I had already gained a little weight, had already improved, it was a small step, but I had already improved a lot, and thank God we're here."

p7 - "[...] it was good because it's something that sometimes I eat...what I ate last week, sometimes I don't even remember, so you end up writing it down (the R3D), you know more or less what you ate, and you see the result, then, there I saw that my appetite was practically normal, right?"

p5 - "[...] I even weighed 68 and a half with her, so that means from 48 I went to 68, which means I gained more than 20 kg, more than 20kg for example, so...she said now you're at a normal weight [...] keep eating normally [...] while she could do it, she did it."

p5 - "And my weight is maintaining, everything...and today I'm feeling nothing, thank God, I'm feeling good."

p12 - "I really liked it and learned to eat better with those food plans she gave me."

p10 - "Beef is stronger, I think I couldn't handle it, I think that was it. After I started the treatment, I started eating beef. It was great for me."

p10 - "Then I started gaining weight, but then I lost weight, gained weight, lost weight...and when I did the treatment with the nutritionist, then I started to improve my weight, to maintain it a little."

The recognition of benefits was also presented, regardless of palatability:

p7 - "There are things that are good for health and sometimes not good in my palate, but sometimes I have to eat them to be able to help in relation to improvement, even to strengthen the liver, right?"

p7 - "[...] I believe the more green, the better, we try, even though it's not my favorite dish, but we have to eat it, it's determinant [...], the food that brings protein, brings muscle, everything, is fundamental."

However, not observing results or benefits with nutritional intervention was also mentioned:

p1 - "I don't know if it didn't give me as much result because I'm not in good health."

p1 - "I didn't feel anything different, but I didn't feel anything strange, neither worse nor better."

Understanding the benefits that nutritional treatment proposes is an integral part of adherence to what is said. Just as understanding the disease and its aspects for commitment to medical treatment, the same applies to nutrition, given that low adherence to recommendations has been associated with a higher incidence of malnutrition, increased morbidity, and mortality (NEY et al., 2015; MAHARSHI, 2015; KALAFATELI, 2015).

5.4.3 Conflicting Nutritional Guidelines

Misguided and outdated guidelines were reported:

p13 - "Today you can eat meat, but only a little"

p9 - "I ate what the clinic told me, it didn't fill my stomach, and they, the people at the clinic, they overdid it with the food. They took away my biscuits, butter, any type of seasoning. They took everything away from me, so I started losing weight, and that's when I came back here and the doctor got angry. That's when he sought out the (clinic's nutritionist). He was very angry: 'why did

they take away the milk? You don't need to take that away.' the nutritionist there took everything away"

p13 - "[...] I also eat meat, but just a little [...]"

p14 - "In the past, it was said that red meat was harmful to the liver. That's not true, is it?"

p14 - "But the doctor (name of the doctor) said, meat, eggs, and milk should be removed"

p11 - "[...] before, the doctor was telling me to eat everything"

It is now known that protein intake should not be limited, even in cases of hepatic encephalopathy (AMODIO et al., 2013). However, reports of advice to restrict sources of protein are still observed, contradicting the guidelines for nutritional therapy of patients with DHC (AMODIO et al., 2013; EASL, 2019; PLAUTH et al., 2019). Like Spillman et al. (2021), participants value advice more when highlighted by doctors, and conflicting advice can reduce the chances of adherence to guidelines, as well as reduce the reliability of healthcare professionals, especially nutritionists. Therefore, Adamski et al. (2018) evaluated the role of doctors in nutritional guidance and considered that doctors need to play a role in reducing the impact of poor nutrition on health, recognizing when and where the diet is the main underlying factor in poor health, and developing the knowledge and skills to offer advice and/or the confidence to refer to those who do. This survey demonstrates the importance of the multidisciplinary team and the role of each professional in treatment.

3.4.4 Long-term nutritional guidelines

After the 12-week nutritional intervention, some patients reported that they stopped following the guidelines:

p6 - "[...] it was easier to follow the diet strictly while I was being monitored."

p1 - "Now I understand better, it became clearer, some things she explained in the beginning, I don't remember anymore, but I'll try to follow the pattern."

p3 - "[...] when I started with the (nutritionist), I followed things more, but now, it's a little out of routine, I don't do everything she asked."

p3 - "I wanted to ask if since the treatment is over, am I allowed to eat everything now?"

The perception that the completion of the intervention would be a determining factor for returning to the previous eating habits shows that long-term nutritional guidelines may not be effective without systematic monitoring. Therefore, it is important to investigate tools/interventions that help develop adaptive skills so that patients can make effective and long-lasting behavior changes (SPILLMAN et al., 2021).

Some patients have shown to be in a stage of behavior maintenance, that is, they maintain the changes for a considerable amount of time (PROCHASKA et al., 1996):

p13 - "I'm doing it, I'm... there was a banana cake recipe it seems. [...] She made a lot for me, she still makes this banana cake today."

3.4.5 Influence on the disease

The patients' perceptions regarding the influence of food on the health-disease process were very valuable and diverse. Some only addressed less healthy foods as harmful influencers, while others only discussed healthy foods, usually recommended in the nutritional intervention:

p8 - "[...] if I am on an empty stomach, it's past feeding time, we feel a lot of pain, okay, sometimes even the lack of water also, this also influences a lot, in my case, in my problem, not for other people, but specifically for me, it influences a lot."

p6 - "[...] but it's much better with nutritional monitoring, you feel more secure, you know that... you can't deviate from the rule."

p7 - "[...] it's not enough for the doctor to say you can't eat, you have to see that it's going to improve you. As I want to improve, I do what the doctor asks me to do and that's it."

p1 - "When I have something too heavy, too difficult to digest, I feel more pain. Then I feel uncomfortable. My stomach gets higher at the top, I feel uncomfortable."

p3 - "Normal lunch, rice, beans, meat, salad, right. Nothing that harms me, I'm not harming myself."

p3 - "[...] if I overdo it, it does affect me, I feel full, my stomach feels bad, but I don't vomit, my body feels a little bad, I feel full."

p13 - "[...] although for some time a... I don't even like to remember... so much that

appeared, I even forgot now, how it is, alcoholic cirrhosis. So from the moment I started to see what the disease was, then yes, I cut everything, cut... I was very radical with everything, with my diet, with drinking and everything, I only ate healthy things, and I still live like that today."

p13 - "Thank God, I'll tell you the truth, I haven't felt anything yet because I don't know why this is the diet that I continue with, it doesn't harm my intestine, it doesn't harm my liver or anything, I don't eat anything to harm my liver."

p13 - "[...] if I eat too much fatty food, it's also harmful, right? And for example, if I eat any food that's too heavy or... let's say... too much pasta as well, I don't think it's good [...] I avoid all of that, but if I go back [...] I think... well, to relax, let's say, to relax in everything, then I believe it harms."

p9 - "We have to have a mature mindset, right? If you don't eat the right food, you're going to die. So, I tried to eat the right food. Was it difficult for me to eat at first? Yes."

p7 - "[...] like the doctor said, 'It seems that if my liver doesn't want to react, it doesn't have the strength to regenerate, to strengthen and everything.' So, in this I had to be even more careful with my diet, it helped a lot because the exams started to improve."

3.4.6 Knowledge about nutrition

The results of the analysis indicated shallow or non-existent knowledge about nutrition:

p10 - "[...] I don't know how to answer you. (when asked about healthy lifestyle)"

p14 - "Ah, I don't think so. I thought... I suspected... but as I said, about the pepper, but the doctor said no..."

p2 - "Well, I think... I don't understand, that's up to you, but it's... the person eats a more or less amount, doesn't need to be, maybe not too much. And I'm not eating anything"

p1 - "There are foods there that I've never eaten in my life, you know. [...] I'll add whatever I can, but there are foods that I won't add"

The relationship between nutrition and quality of life has been extensively studied. Nutritional education, therefore, becomes an essential factor since healthy eating is an indisputable fact for promoting and maintaining health (OLIVEIRA, 2008). Therefore, in order for a nutritional intervention to be beneficial, it is important to

ensure that the patient has knowledge of the importance of nutrition for the health-disease process.

3.5 Social Aspects

3.5.1 Increased in food prices

Access to food is crucial for meeting nutritional recommendations for patients. Despite this, the findings of this study showed that difficulty in buying food has been a hindrance.

p7 - "[...] Brazilians don't have many options, it depends on the financial situation, that's the issue, when we can eat well, we do"

p5 - "Nowadays when you go to the supermarket, the price is... too expensive, you can't afford it, even rapadura (sugar cane candy) became ridiculously expensive"

It is known that in recent years, and especially with the effects of the COVID-19 pandemic on the Brazilian economy, consumer prices have varied monthly, with food and beverages having the highest variation (IBGE, 2022). It is important to take into account access to food when developing the nutritional plan and guidelines, but in addition, working with patients on the best ways to use and buy food can be an alternative for this factor.

3.5.2 Absence from work due to illness

Patients on the waiting list for TxH are usually absent from their work activities:

p4 - "[...] oh, following a meal plan, for me... it's not easy, you know, because in the current situation that the country is going through, this inflation... and I'm not able to work"

p10 - "I only work as a freelancer. It's been nine months since I last received payment"

However, some government aid can provide a sum of money for the patient to maintain themselves in a basic way, which can consider the proposed nutrition plan less

essential at the moment. Therefore, considering the patient's social support on the waiting list for transplantation is of utmost importance as it gives greater chances of adherence to medical and nutritional treatment (MALDONADO, 2019).

3.6. Limitations and strengths of the study

The limitations of the study include the conduct of the research in a single transplant outpatient clinic where the practice may not be representative across all centers. It would be valuable to analyze these findings with research involving other transplant centers. The researcher was from the nutrition team at the site and participants knew they were being interviewed by a nutrition student. This may have led to a bias in their responses due to social desirability.

The strengths of this research include the development of the script with contributions from teachers with adequate experience to ensure that all relevant topics were addressed. The sampling method of saturation ensured that participants with a variety of nutritional intervention support needs were included.

4. CONCLUSIONS

This study was able to identify and understand the factors and perceptions that interfere with adherence to nutritional intervention in patients on the waiting list for liver transplantation. The qualitative approach allowed for more substantial contact with the patient, encompassing understanding of the factors involved in adherence to nutritional prescription.

The factors that interfered with adherence to nutritional intervention were identified in five themes: family relationships, perception of the disease, physiological factors, understanding of nutrition, and social aspects. Thus, it was possible to identify patient motives and perceptions that impacted adherence during nutritional follow-up.

Understanding patients' perceptions of nutritional treatment was essential to gain a deeper understanding of the patient's relationship with food. Thus, respecting the factors that permeate the act of eating, even in the health-disease process, can influence the success of nutritional intervention.

From these results, approaches that take these factors into consideration can make nutritional interventions more effective. Family and social support, the use of tools that assess the degree of understanding of the disease and nutrition, symptom screening, the application of tools that assess levels of behavior change, the definition of personalized goals according to the stage of change, support from the multiprofessional team, as well as the development of instruments that aid in prolonged adherence, are recommended to improve adherence to nutritional treatment.

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ANNEX B

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O Sr (a) está sendo convidado (a) como voluntário (a) para participar do estudo "Identificação de fatores que afetam a adesão à intervenção nutricional em estudo clínico com pacientes em lista de espera para o transplante hepático" pela pesquisadora discente Nathália Pereira de Souza, graduanda em Nutrição, sob orientação da doutoranda Samanta Catherine Ferreira e professora doutora Lucilene Rezende Anastácio, para o trabalho de conclusão de curso, requisito parcial para a obtenção do título de bacharel em Nutrição pela Universidade Federal de Minas Gerais.

O estudo tem como objetivo identificar as possíveis causas que podem afetar a adesão à intervenção nutricional de pacientes em fila de espera para o transplante hepático em estudo clínico, assim, poder desenvolver melhorias no tratamento para minimizar a baixa adesão.

Para participar, será realizada uma entrevista pela pesquisadora discente com o (a) sr (a), que seguirá um roteiro já estabelecido, com perguntas sobre o diagnóstico da doença e sintomas e estilo de vida. A entrevista será gravada em áudio e vídeo. O tempo da entrevista será de aproximadamente 30 minutos. As entrevistas serão transcritas e armazenadas, em arquivos digitais, mas somente terão acesso os pesquisadores do estudo.

Risco e desconforto: risco de constrangimento na entrevista.

Sigilo: serão garantidas a confidencialidade e a privacidade das informações por você prestadas. Qualquer dado que possa identificá-lo será omitido na divulgação dos resultados da pesquisa, e o material será armazenado em local seguro.

Benefícios: Ao participar do estudo você poderá contribuir para que novos métodos sejam empregados na melhora da adesão ao tratamento nutricional de pacientes pré-transplante hepático. Isto pode contribuir na evolução do tratamento, com importante melhora dos resultados.

Sua participação é voluntária, isto é, ela não é obrigatória, e você tem plena autonomia para decidir se quer ou não participar, bem como retirar sua participação a qualquer momento. Você não será penalizado de nenhuma maneira caso decida não consentir sua participação, ou desistir da mesma. Contudo, ela é muito importante para a execução da pesquisa. A qualquer momento, durante a pesquisa, ou posteriormente, você poderá solicitar à discente pesquisadora informações sobre sua participação e/ou sobre a pesquisa, poderá entrar em contato com a discente nos telefones abaixo e também poderá procurar os Comitês de Ética em Pesquisas (COEP).

Este termo de consentimento encontra-se impresso em duas vias originais, sendo que uma será arquivada pelo pesquisador responsável, na Faculdade de Farmácia da UFMG, e a outra será fornecida ao Sr. (a). Os dados, materiais e instrumentos utilizados na

pesquisa ficarão arquivados com o pesquisador responsável por um período de 5 (cinco) anos na sala 2074 da Faculdade de Farmácia da UFMG e após esse tempo serão destruídos. A pesquisadora tratará a sua identidade com padrões profissionais de sigilo, atendendo a legislação brasileira (Resoluções No 466/12; 441/11 e a Portaria 2.201 do Conselho Nacional de Saúde e suas complementares), utilizando as informações somente para fins acadêmicos e científicos.

Eu, _____, portador do documento de identidade _____ fui informado (a) dos objetivos, métodos, riscos e benefícios da pesquisa "Identificação de fatores que afetam a adesão à intervenção nutricional em estudo clínico com pacientes em lista de espera para o transplante hepático", de maneira clara e detalhada e esclareci minhas dúvidas. Sei que a qualquer momento poderei solicitar novas informações e modificar minha decisão de participar se assim desejar.

( ) Concordo que os meus dados coletados sejam utilizados somente para esta pesquisa.

Declaro que concordo em participar desta pesquisa. Recebi uma via original deste termo de consentimento livre e esclarecido assinado por mim e pelo pesquisador, que me deu a oportunidade de ler e esclarecer todas as minhas dúvidas.

_____

(Participante)

_____

(Assinatura)

_____

(Pesquisador)

_____

(Assinatura)

_____

(Testemunha)

_____

(Assinatura)

Belo Horizonte, ____ de _____ de 20__.

ANNEX C - SEMI-STRUCTURED INTERVIEW GUIDE

SEMI-STRUCTURED QUESTIONNAIRE

Initial Question (open-ended): Tell me a little about yourself. (Ask the informant to talk about their history and lifestyle.)

Follow-up Questions:

Personal Aspects

1. How was it for you when you found out about the liver disease diagnosis? (explore)
2. What changed in your life after this discovery? (explore based on what comes up, including if it relates to food)
3. And regarding your diet? Did any changes happen after the diagnosis? (explore in depth what changes occurred)
4. How was it for you to deal with the dietary changes brought about by the disease? (explore in depth the feelings, difficulties, and perceptions involved)
5. How did you adapt to these dietary changes due to the disease? (explore in depth how they coped and organized themselves with the changes over time, the main difficulties, coping strategies, support points, and feelings involved)
6. Do you have any symptoms of the disease that interfere with your food choices? (explore: which ones? How have you been dealing with it? Are there any foods or food groups that are more difficult to consume? Feelings involved? Coping strategies?)
7. What is your daily routine like? (explore aspects of daily life that can hinder adherence)
8. What do you understand by a healthy lifestyle? What does the informant know about healthy eating and related topics? (information)
9. What is the dynamic of meal preparation at home like? (explore patient autonomy in food choices)

10. What is the dynamic of food shopping at your home like? (explore patient autonomy in food choices)

Aspects that guide the patient's relationship with food

11. Do you think that food can influence the development of the disease? (explore). In relation to the nutritional counseling you are currently receiving, how has the experience been? (explore in depth, especially the difficulties and feelings).
12. How have you been organizing yourself to put into practice the dietary guidelines provided in this nutritional treatment? (explore in depth, especially the difficulties, coping strategies, and feelings)

13. Also, in relation to the nutritional counseling you are currently receiving, how is it for you to have to follow a predetermined meal plan?