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PROGRAMA DE PÓS-GRADUAÇÃO:

CIÊNCIAS EM GASTROENTEROLOGIA E HEPATOLOGIA

BRUNA CHERUBINI ALVES

PERFIL NUTRICIONAL, METABÓLICO E RISCO CARDIOVASCULAR EM PACIENTES PÓS-TRANSPLANTE HEPÁTICO

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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação: Ciências em Gastroenterologia e Hepatologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para a obtenção do título de Mestre em Ciências em Gastroenterologia e Hepatologia.

Orientadora: Profa. Valesca Dall'Alba
Co-orientador: Prof. Mário Reis Álvares-da-Silva

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SUMÁRIO

RESUMO

No pós-transplante hepático (pós-TxHep), complicações da doença cardiovascular (CV) têm sido cada vez mais prevalentes e aparecem entre as principais causas de morte nessa população. Sabe-se que alterações metabólicas e nutricionais podem estar associadas ao aumento de risco CV. Assim, o objetivo deste trabalho foi avaliar o risco CV e suas associações com o estado nutricional, ingestão alimentar e o perfil metabólico em pacientes pós-TxHep.

Este estudo transversal incluiu pacientes adultos pós-TxHep. Pacientes transplantados há menos de 1 ano e com histórico de insuficiência hepática fulminante, perda de enxerto hepático ou insuficiência renal crônica pós-TxHep não foram incluídos. Os pacientes passaram por avaliação clínica, nutricional e laboratorial. A avaliação nutricional compreendeu a ingestão alimentar, através de Registro Alimentar de três dias, antropometria e dinamometria. A medida da espessura da camada íntima-média carotídea (EIMC) foi avaliada por ultrassonografia Doppler e considerada alterada quando maior que 1 milímetro.

Foram avaliados 69 pacientes transplantados há 2,8 (1,4 - 6,3) anos, sendo a maioria do sexo masculino (61%). Encontrou-se alta prevalência de desnutrição e sarcopenia, apresentada por 45% dos pacientes com área muscular do braço abaixo do percentil 15, e 71% com força do aperto de mão abaixo do percentil 30. Em contraste, 72% dos pacientes estavam com excesso de peso e 35% apresentaram Índice de Massa Corporal (IMC) maior que 30 kg/m^2. Pacientes com EIMC alterada (54%) apresentaram maior LDL colesterol (P = 0,01), maior proporção de proteína-C reativa ultrassensível (PCR-us) maior que 1mg/L (P = 0.02) e maior ingestão de ácidos graxos saturados e *trans* (P = 0.01).

Em conclusão, este estudo mostrou alta prevalência de EIMC alterada em uma amostra de pacientes pós-TxHep com sobrepeso e sarcopenia, associada a níveis mais elevados de LDL colesterol, PCR-us maior que 1mg/L e maior ingestão de ácidos graxos saturados e *trans*. Este estudo reforça que é necessário fornecer medidas preventivas, incluindo a melhoria da qualidade dietética, para todos os pacientes pós-transplante hepático, a fim de minimizar o risco CV.

Palavras-chave: pós-transplante hepático; espessura da íntima média carotídea; placa aterosclerótica; perfil metabólico; avaliação nutricional.

ABSTRACT

In post-liver transplantation (post-LT), complications of cardiovascular (CV) disease have been increasingly prevalent and have become one of the main causes of death in this population. It is known that metabolic and nutritional imbalance may be associated with increased CV risk. Thus, the aim of this study was to evaluate CV risk and its associations with nutritional status, food intake and metabolic profile in post-LT patients.

This cross-sectional study included adult post-LT patients, who underwent clinical, nutritional and laboratory evaluation. Patients who have undergone LT for less than 1 year, and with history of fulminant hepatic failure, loss of liver graft or chronic renal failure after LT were not included. The nutritional evaluation included food intake, through a three-day Food Record, anthropometry and dynamometry. The carotid intima-media thickness (CIMT) was assessed by Doppler ultrasonography and considered abnormal when greater than 1 millimeter.

A total of 69 patients transplanted 2.8 (1.4 - 6.3) years ago were evaluated, being the majority male (61%). There was a high prevalence of malnutrition and sarcopenia, presented by 45% of patients with arm muscle area below the 15^{th} percentile, and 71% with handgrip strength below the 30^{th} percentile. In contrast, 72% of the patients were overweight and 35% had Body Mass Index greater than 30 kg/m^2. Patients with altered CIMT (54%) had higher LDL cholesterol ($P = 0.01$), higher proportion of high-sensitive C-reactive protein (hs-CRP) greater than 1mg/L ($P = 0.02$) and higher intake of saturated and *trans* fatty acids ($P = 0.01$).

In conclusion, this study showed a high prevalence of abnormal CIMT in a sample of post-LT patients with overweight and sarcopenia, associated with higher

levels of LDL cholesterol, hs-CRP greater than 1mg/L, and higher intake of saturated and *trans* fatty acids. This study reinforces that it is necessary to provide preventive measures, including improvement of dietary quality, for all patients after liver transplantation, in order to minimize CV risk.

Keywords: post-liver transplantation; carotid intima-media thickness; atherosclerotic plaque; metabolic profile; nutritional assessment.

LISTA DE ABREVIATURAS

25OHD – 25-hydroxyvitamin D

AC – arm circumference

AFA – arm fat area

ALP – alkaline phosphatase

ALT – alanine aminotransferase

AMA – arm muscle area

AST – aspartate aminotransferase

BMI – body mass index

BP – blood pressure

CIMT – carotid intima media thickness

CP – carotid plaque

CV – cardiovascular

EIMC – espessura da íntima-média carotídea

ERF – Escore de Risco de Framingham

FRS – Framingham Risk Score

GGT – gamma glutamyl transferase

GI – glycemic index

GL – glycemic load

HCFMUSP – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo

HDL – HDL cholesterol

HS – handgrip strength

hs-CRP – high-sensitive C-reactive protein

IMC – Índice de Massa Corporal

IPAQ – International Physical Activity Questionnaire

LDL – LDL cholesterol

LT – liver transplantation

METs – MET-minutes/week

PAC – placa aterosclerótica carotídea

PCR-us – proteína C-reativa ultrassensível

pós-TxHep – pós-transplante hepático

pré-TxHep – pré-transplante hepático

MS – metabolic syndrome

SM – síndrome metabólica

TC – total cholesterol

TG – triglyceride

TS – triceps skinfold

TxHep – transplante hepático

WC – waist circumference

1. INTRODUÇÃO

O transplante hepático (TxHep) é o procedimento realizado quando não há outra alternativa de tratamento clínico e cirúrgico na hepatopatia avançada, progressiva e irreversível (1). O número de TxHep cresce no Brasil, que já possui 61 equipes atuantes e ocupa o 2º lugar em número de TxHep no mundo (2).

A sobrevida pós-TxHep tem aumentado devido aos avanços no tratamento clínico e cirúrgico da doença hepática. Conforme o Registro Brasileiro de Transplantes, a sobrevida pós-TxHep é de 74% ao final de 1 ano e de 68% ao final de 5 anos pós-TxHep, considerando os transplantes de fígado realizados a partir de 2010 (2). Em países nórdicos, a sobrevida parece ser ainda maior, chegando a 87% ao final de 5 anos (3).

Concomitante ao aumento da sobrevida, a incidência de doença cardiovascular (CV) também aumenta no pós-TxHep (4,5). E ainda, diversos estudos já apontam a doença CV como uma das principais causas de morte nessa população. A alta prevalência de doença CV e seus fatores de risco no pós-TxHep podem ser explicados por um estilo de vida desequilibrado, caracterizado pelo retorno ao hábito alimentar inadequado e pela inatividade física, além do uso crônico de imunossupressores, que pode ser outro agravante. (5–7).

Assim, o presente estudo teve como principal interesse avaliar os pacientes pós-TxHep quanto ao risco CV e detectar o desenvolvimento de processo aterosclerótico, assim como identificar fatores associados à doença CV, incluindo inadequações do estado nutricional, na ingestão alimentar e no perfil metabólico. A identificação destes fatores é de grande relevância, uma vez que poderá nortear condutas mais efetivas de aconselhamento dietético.

2. REFERENCIAL TEÓRICO

2.2. Transplante Hepático

2.2.1. História e Atualidade no Brasil

A primeira tentativa de transplante hepático (TxHep) foi em Denver nos Estados Unidos (EUA) por Thomas Starzl e sua equipe em 1963. No entanto, somente em 1967, com os primeiros quatro transplantados sobreviventes, Starzl foi à imprensa conseguir apoio da população para a doação de órgãos a fim de aumentar o número de beneficiados com este procedimento. A partir daí até 1972 a tentativa de TxHep foi realizada em todo mundo, sendo aqui no Brasil, procedido pelo Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP). Somente em 1985 foi realizado o primeiro TxHep com êxito no Brasil, também no HCFMUSP (8), e, em 1991, no estado do Rio Grande do Sul na Santa Casa de Misericórdia de Porto Alegre.

Atualmente, o Brasil tem o maior sistema público de transplantes do mundo e o segundo maior em volume de transplantes de fígado (2,9). Em 2015, foram realizados 1809 transplantes hepáticos (incluindo pediátricos) no Brasil, sendo o estado do Rio Grande do Sul responsável por 8% desses.

O primeiro TxHep realizado no Hospital de Clínicas de Porto Alegre foi no ano de 1996. De 2015 a outubro de 2016, foram realizados 59 transplantes de fígado nesta instituição.

2.2.2. Indicações

O TxHep é um procedimento cirúrgico realizado em pacientes com hepatopatia avançada, progressiva e irreversível, sem outras alterativas clínicas e cirúrgicas e perspectiva de vida inferior a 1 ano devido à doença hepática (1). Em outras palavras, o TxHep é uma intervenção que salva vidas em pacientes com cirrose descompensada,

certas malignidades e distúrbios genéticos associados ao metabolismo hepático desordenado. A indicação mais frequente de TxHep é na cirrose descompensada, causada principalmente pelo vírus da hepatite C, seguido da cirrose alcoólica. No entanto, acredita-se que a cirrose causada pela doença hepática gordurosa não alcoólica em breve será a principal indicação de TxHep (10) .

2.2.3. Sobrevida

Avanços no tratamento clínico e cirúrgico da doença hepática têm aumentado a sobrevida dos indivíduos pós-TxHep. Jain et al. em seu estudo, o qual avaliou uma coorte de 4000 indivíduos pós-TxHep mostrou que a sobrevida em 18 anos pós-TxHep foi de 48%, sendo maior nas crianças, nos indivíduos do sexo feminino e naqueles que receberam o órgão após 1990 (11). Além disso, este mesmo estudo mostrou que em pacientes adultos o índice de sobrevivência foi de 80% ao final de 1 ano e de 67% ao final de 5 anos. Similar a este resultado, outra coorte americana constituída de 17044 indivíduos que passaram por transplante ortotópico, indicou uma sobrevida média de 83% em 1 ano, 70% em 5 anos e 62% em 8 anos de pós-TxHep, e esta prevalência varia conforme a doença de base, sendo maior na cirrose biliar primária e menor no câncer (12). Em relatório mais atual dos Estados Unidos, foi encontrada sobrevida de 80 e 85% em 1 ano e 65 e 70% em 5 anos, considerando fígado doado após morte circulatória e cerebral do doador respectivamente (13). Este mesmo relatório refere que a taxa de sobrevida é menor em pacientes infectados pelo vírus da hepatite C (13). Já o Registro Brasileiro de Transplantes, recentemente apresentou dados de sobrevida de 74% em 1 ano e 68% em 5 anos pós-TxHep, considerando os transplantes de fígado realizados a partir de 2010 (2). Outro estudo, em países nórdicos, mostrou taxas de sobrevida pós-TxHep maiores: de 87% em 5 anos, 74% em 10 anos e 53% em 20 anos (3).

2.3. Risco Cardiovascular no Transplante Hepático

Devido ao aumento da sobrevida de pós-TxHep, eleva-se também a prevalência de doença cardiovascular (CV) nesses indivíduos (4,5). A doença CV está entre as três principais causas de morte em pacientes pós-TxHep. No estudo de coorte de Jain et al. (11), complicações da doença CV foram as maiores causas de morte, abaixo de infecções e câncer relacionados ao enxerto. No estudo de Aberg et al., em países nórdicos, mostrou que a doença CV foi responsável por 15% da mortalidade desses pacientes em uma média de 8,2 anos pós-TxHep (3).

Muitos estudos já mostram uma alta prevalência de síndrome metabólica (SM), fator de risco estabelecido para doença CV e aterosclerose, em pacientes pós-TxHep. De Luca et al. referem que a SM está presente em 39 a 50% dos pacientes pós-TxHep, variando conforme critério diagnóstico utilizado (14). Da mesma forma, os fatores de risco relacionados à SM também apresentaram um aumento da prevalência pós-TxHep, como diabetes mellitus tipo 2, hipertensão arterial, obesidade, dislipidemia e hipertrigliceridemia (14,15). Prevalências de 13% a 38% de diabéticos, 36% a 69% de hipertensos, mais de 69% de hipertrigliceridemia, e mais de 52% de baixos níveis de HDL colesterol são encontradas em pacientes pós-TxHep (6). Sabe-se que o aumento desses fatores de risco CV pode se dar por estilo de vida inadequado, como tabagismo, dieta inapropriada e sedentarismo (5,16,17). Além desses fatores ligados ao estilo de vida, os pacientes pós-TxHep podem ter outro agravante, como o uso crônico de imunossupressores que podem contribuir para o ganho de peso e resistência insulínica (5,7).

2.4. Espessura da Íntima-Média Carotídea

Já é bem estabelecido que tanto o espessamento arterial como a aterosclerose são importantes fases pré-clínicas da doença CV (18). Assim, a medida ultrassonográfica das carótidas, para avaliar a espessura da camada íntima-média carotídea (EIMC), bem como a presença de placa aterosclerótica carotídea (PAC) tem sido considerada um método útil para reclassificação de risco CV na prática clínica, além de ser um teste rápido, de baixo custo, não invasivo, e com boa reprodutibilidade.(19–21).

De acordo com o *Mannheim Carotid Intima-Media Thickness and Plaque Consensus*, PAC é definida como a presença de estruturas focais das artérias carótidas comum que invadem pelo menos 0,5 mm do lúmen arterial ou 50% do valor circundante da EIMC, ou demonstrada pela medida da EIMC >1,5 mm (21).

A medida da EIMC >1.0 mm já é considerada fator agravante de risco CV, conforme a Sociedade Brasileira de Cardiologia, e pode reclassificar o paciente em risco intermediário para alto risco (22). Apesar dos pacientes pós-TxHep apresentarem altas taxas de mortalidade por doença CV, ainda não há estudos que avaliem a EIMC nessa população.

2.5. Estado Nutricional no Transplante Hepático

O fígado é um órgão que desempenha papel fundamental no metabolismo de nutrientes, por ser responsável pela regulação da síntese, armazenamento e absorção destes. A disfunção hepática é geralmente associada à grave desnutrição proteica, e ainda, os pacientes com cirrose hepática grave experimentam um estado catabólico grave (23). Assim, a desnutrição é uma complicação comum na doença hepática em estágio terminal, que, além de impactar na qualidade de vida, está associada a um risco aumentado para o desenvolvimento de complicações da cirrose, como a encefalopatia

hepática. Além disso, a desnutrição na doença hepática grave pode prejudicar o resultado do TxHep e influenciar negativamente na sobrevida (24).

A causa da desnutrição em pacientes com cirrose hepática é multifatorial e inclui hipermetabolismo, ingestão dietética insuficiente devido a náuseas e vômitos, restrições dietéticas de sal e proteína, anorexia, presença de ascite e/ou encefalopatia, má absorção devido à insuficiência pancreática, supercrescimento bacteriano intestinal e/ou colestase, e ainda, efeitos secundários da terapia medicamentosa e distúrbios metabólicos relacionados à doença hepática (24,25).

A perda involuntária de massa e função muscular, descrita como sarcopenia, sucede concomitantemente à desnutrição na cirrose descompensada e no pré-TxHep e também contribui para a morbi-mortalidade dessa população (26,27). Estudo em nossa população de pacientes com cirrose hepática mostrou uma prevalência de 63% de perda de força do aperto de mão medida através da dinamometria (28). De fato, estima-se que a sarcopenia esteja presente em 40 a 70% dos pacientes cirróticos, variando conforme o método utilizado para diagnóstico e o estágio em que a doença se encontra (26,27).

Entretanto, no pós-TxHep, o que tem sido mais indagado é o excessivo ganho de peso nesta fase. Os pacientes pós-TxHep não recuperam somente o peso perdido durante a fase da doença hepática, mas sim, passam a exceder o peso adequado. Observa-se prevalências de mais de 40% de obesidade e aproximadamente 70% de sobrepeso e obesidade após 03 anos de transplante (6,29). Este ganho de peso em excesso e aumento da obesidade nos pacientes pós-TxHep é preocupante não só por expor os pacientes a um maior risco de desenvolver esteatohepatite no fígado enxertado, como também por aumentar o risco CV.

Acredita-se que esse ganho de peso esteja associado a diversos fatores. Após o transplante, o paciente se encontra ansioso para recuperar o peso perdido, além disso,

redescobre o apetite e se torna apto a comer em maiores quantidades, retornando ao hábito alimentar antigo após meses de restrição (5,30). Importante salientar que as recomendações nutricionais nas fases pré, peri e pós-TxHep são bastante diferentes, e falhas nessa abordagem podem também contribuir para o ganho de peso.

Outro fator que pode influenciar no ganho de peso é a inatividade física. Embora saiba-se que a capacidade para exercer atividade física melhora consideravelmente após meses de TxHep, ainda é observado limitações na capacidade física em alguns pacientes pós-TxHep. E ainda, muitos pacientes não retornam ao trabalho após o transplante, e a longo prazo, apresentam um nível de atividade física menor que a população geral (30–32).

3. JUSTIFICATIVA

Atualmente, a sobrevida dos pacientes que passaram por TxHep tem aumentado devido a avanços clínicos e cirúrgicos. Concomitante ao aumento da sobrevida, se encontra o aumento da prevalência de doença CV, já considerada uma das maiores causas de morte nessa população (4,5). Assim, cresce o interesse em avaliar o risco CV, identificando o processo aterosclerótico nas artérias carótidas, e suas associações com perfil metabólico e nutricional.

4. QUESTÃO DE PESQUISA

O estado nutricional e o perfil metabólico de pacientes pós-TxHep com alteração da medida da EIMC são diferentes dos pacientes sem alteração de EIMC?

5. HIPÓTESE

Pacientes pós-TxHep com EIMC alterada apresentam mais sobrepeso/obesidade, ingestão alimentar mais inadequada e pior perfil metabólico.

6. OBJETIVOS

6.1. Objetivo Geral:

Determinar a EIMC em pacientes pós-TxHep e avaliar sua associação com risco cardiovascular e estado nutricional.

5.2 Objetivos Específicos:

Avaliar e comparar os pacientes pós-TxHep com e sem alteração da EIMC quanto a:

- Perfil metabólico
- Escore de Risco de Framingham (ERF)
- Presença de síndrome metabólica
- Estado nutricional
- Prática de atividade física

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8. ARTIGO ORIGINAL

Intitulado: ***Obesity, sarcopenia and high cardiovascular risk co-exist in post-liver transplantation setting: results of a cross-sectional study***

Encaminhado ao periódico**:** ***Liver Transplantation***

Obesity, sarcopenia and high cardiovascular risk co-exist in post-liver transplantation setting: results of a cross-sectional study

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Key words: liver transplantation; carotid intima-media thickness; atherosclerotic plaque; metabolic profile; nutritional assessment.

Abbreviations: 25OHD, 25-hydroxyvitamin D; AC, arm circumference; AFA, arm fat area; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, arm muscle area; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CIMT, carotid intima media thickness; CP, carotid plaque; CV, cardiovascular; FRS, Framingham Risk Score; GGT, gamma glutamyl transferase; GI, glycemic index; GL, glycemic load; HDL, HDL cholesterol; HS, handgrip strength; hs-CRP, high-sensitive C-reactive protein; IPAQ, International Physical Activity Questionnaire; LDL, LDL cholesterol; LT, liver transplantation; METs, MET-minutes/week; MS, metabolic syndrome; TC, total cholesterol; TG, triglyceride; TS, triceps skinfold; WC, waist circumference.

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ABSTRACT

Cardiovascular (CV) disease is one of the major causes of death in post liver transplantation (LT), possibly associated with metabolic and nutritional changes. The aim of this study was to evaluate LT patients as to the carotid intima-media thickness (CIMT) and its association with nutritional status, food intake, metabolic profile and CV risk factors such as metabolic (MS) and Framingham Risk Score (FRS). In this cross sectional study, 69 adult patients, who have undergone LT for at least 1 year [males 61%, 59 (51 – 64) years; LT for 2.8 (1.4 – 6.3) years] underwent clinical, laboratory, and dietary evaluation. Dietary intake, nutritional and functional assessment were evaluated by 3-day-diet-record, anthropometry and dynamometry respectively. CIMT was evaluated by Doppler ultrasonography and considered abnormal if >1.0 mm. High prevalence of malnutrition was found, such as 45% of arm muscle area < percentile 15 and 71% of handgrip strength < percentile 30. In contrast, excess weight was present in 72% and BMI greater than 30 kg/m^2 in 35% of LT patients. Patients with abnormal CIMT (54%) presented higher LDL cholesterol, higher prevalence of hs-CRP ≥1mg/L and higher intake of saturated and trans fatty acids (P <0.05 for all). **Conclusion**: this study showed a high prevalence of an abnormal CIMT in a sample of overweight and sarcopenic LT patients, which was associated with higher LDL-cholesterol levels, hs-CRP ≥1mg/L and higher intake of saturated and trans fatty acids. This study reinforces that it is required to provide strong preventive measures, including

improvement of dietary quality, for all post-LT patients in order to minimize CV risk in the future.

INTRODUCTION

Liver transplantation (LT) is a lifesaving procedure for patients with decompensated cirrhosis, certain malignancies, and genetic disease associated with disordered liver metabolism. In 2015, 1,809 liver transplants (including pediatric) were performed in Brazil, which is the second largest LT program worldwide.

Advances in medical and surgical treatment lead to an increase in survival of transplanted individuals. Studies show a median survival of nearly 90% at 01 year and, 75% at 5 years post-LT (1,2). Increasing LT survival has enabled some complications to emerge, like metabolic syndrome (MS) and malignancies (3).

Moreover, the incidence of cardiovascular (CV) disease has increased in the last few years in LT patients. Cardiovascular complications are among the top three causes of death in post-LT patients, after cancer and graft-related diseases (1,2). High prevalence of CV disease and its risk factors after LT could possibly be explained by inappropriate lifestyle, characterized by the return to previous dietary habits after pre-transplant dietary restrictions, and by physical inactivity (4). In addition, immunosuppressants themselves promote several metabolic disturbances (5).

It is well established that both arterial stiffness and atherosclerosis are important preclinical stages of CV disease (6). Therefore, ultrasonographic measurement of arteries to assess the carotid intima-media thickness (CIMT) as well as the presence of a carotid plaque (CP) has been considered a useful method for CV risk reclassification in clinical practice (7,8). The aim of this study was to evaluate LT patients as to CIMT and its association with nutritional status, food intake, metabolic profile and CV risk factors such as MS and the Framingham Risk Score (FRS).

METHODOLOGY

This cross-sectional study included adult transplanted patients treated at an outpatient clinic of the Gastroenterology Division of Hospital de Clínicas de Porto Alegre, Brazil, from July, 2014 to April 2016. Patients who have undergone LT for less

than 1 year, and with history of fulminant hepatic failure, loss of liver graft or chronic renal failure after LT were not included.

The Ethics and Research Committee at HCPA approved the protocol, and patients were included only after reading, understanding and signing an Informed Consent Form.

Anthropometric assessment:

The body weight and height of patients were obtained using an anthropometric scale, with measurements recorded to the nearest 100 g for weight and to the nearest 0.1cm for height. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) square. Data before LT, including dry weight, were assessed by electronic medical records.

Waist circumference (WC) was measured at the midpoint between the iliac crest and the lowest rib. Arm circumference (AC) and triceps skinfold (TS) were measured at the midpoint between the olecranon and acromion processes. A flexible, non-stretch fiberglass tape measure and a Lange skinfold caliper were used to assess those measurements. Arm fat area (AFA) and arm muscle area (AMA) were calculated according to the following formulas (9,10):

$$AFA\ (cm^2) = \left[\frac{AC\ (cm)^2}{4 \times \pi}\right] - [\frac{AC\ (cm) - (\pi \times TS(cm))}{4 \times \pi}]^2$$

Male:

$$\text{AMA}\ (cm^2) = \frac{[AC\ (cm) - (\pi \times TS(cm))]^2}{4 \times \pi} - 10$$

Female:

$$\text{AMA}\ (cm^2) = \frac{[AC\ (cm) - (\pi \times TS(cm))]^2}{4 \times \pi} - 6{,}5$$

Functional assessment

Functional assessment consisted in determining the handgrip strength (HS) of the non-dominant hand by dynamometry, using a Jamar® mechanical dynamometer. Patients were positioned sitting down with a straight back and no armrests and with

elbow flexion at 90º. The test was repeated three times at 1-minute intervals and the maximum score recorded was used for analysis. Results were compared to reference values found in the study of Schlüssel et al. (11,12).

Laboratory assessment:

Blood samples were obtained after a 12-h fast, after inclusion in the study. The following tests were then performed: total cholesterol (TC), HDL cholesterol (HDL) and triglyceride (TG) by enzymatic colorimetric method (Bayer Advia 1800 System); Glucose by hexokinase enzymatic method (Advia 1800); Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by UV kinetic method (Advia 1800), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) by colorimetric kinetic method (Advia 1800), albumin by colorimetry (Advia 1800); high-sensitive C-reactive protein (hs-CRP) determined by ultrasensitive nephelometric method (Dade Behring Marburg, Marburg, Germany), and 25-hydroxyvitamin D [25(OH)D] by chemiluminescence (Liaison). The LDL cholesterol (LDL) was determined indirectly by the Friedewald formula: LDLc = TC - HDL-C - (TG / 5).

Dietary intake assessment

The patient's usual diet was assessed by 3-day-diet-record (two non-consecutive weekdays and one-weekend day). Macro-, micronutrients and calories were assessed using the NutriBase 2007 software (Clinical Nutrition Manager v.7.14; Cybersoft). Nutrient data were expressed in crude amounts (g/day, mg/day mcg/day or IU/day) or in grams per kilogram of body weight. The dietary glycemic index (GI) was estimated by the weighted GI value of each consumed food and expressed as percentage. Dietary glycemic load (GL) was calculated as the product of dietary GI and total carbohydrate intake divided by 100, using glucose as reference food (13).

Physical activity assessment

Habitual physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) long form (14). The IPAQ long form asks details about the specific types of activities undertaken within each of the four domains: Work, Active Transportation, Domestic and Garden (Yard Work) and Leisure-Time. From IPAQ it was possible to determine the level of physical activity and the metabolic equivalent

task, expressed in MET-minutes/week (METs), which expresses the weekly energy expenditure. Less than 600 METs were considered low physical activity (15).

Blood pressure measurement

Blood pressure (BP) was measured twice using a digital sphygmomanometer (HEM 433INT, Omron) after 10 minutes of rest, with patients in the sitting position.

Framingham Risk Score

The FRS estimates the probability of myocardial infarction or death from coronary heart disease in a 10-year period in subjects without previous diagnosis of clinical atherosclerosis. FRS is based on the following variables: sex, age, systolic BP, CT, HDL, smoking and diabetes (16).

Metabolic Syndrome

According to a Joint Scientific Statement described by Alberti et al. (17), participants were considered as having MS if at least 3 of the following findings were present: [1] WC greater than 88 cm for female and 102 for male, according to American Heart Association/National Heart, Lung, and Blood Institute; [2] elevated triglycerides (≥150 mg/dL) or drug treatment for elevated triglycerides; [3] reduced HDL (<40 mg/dL for male and <50 mg/dL for female) or drug treatment for reduced HDL; [4] Elevated blood BP (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment; [5] elevated fasting glucose (≥100 mg/dL) or insulin or hypoglycemic drug treatment.

Carotid Intima-Media Thickness and Plaque

Doppler ultrasonography of carotid arteries was performed to measure the CIMT and/or to detect the presence of CP. According to the Mannheim Carotid Intima-Media Thickness and Plaque Consensus (8) and Brazilian Cardiology Society (18), CIMT was considered increased when >1.0 mm, and presence of CP was defined as focal structures encroaching at least 0.5 mm into the arterial lumen or 50% of the surrounding CIMT value, or demonstrated CIMT >1.5 mm. This examination was performed by a single vascular medicine specialist. Patients with an abnormal carotid (increased CIMT or CP) are at increased CV risk, so they were grouped for analysis and compared with patients with a normal carotid.

Sample size estimation

The sample size was calculated based on the previous study of Kawamoto et al. (19), which compared the prevalence of patients with visceral obesity according to CIMT measurement. Thus, for an association between visceral obesity and increased CIMT, a sample of 64 patients is required, considering an alpha error of 5% and a power of 90%.

Statistical Analysis

Statistical analysis was performed using PASW Statistics (version 18.0, IBM SPSS Statistics). Variables with a normal distribution were expressed as mean ± SD, and asymmetrically distributed data were presented as median and interquartile range. Comparisons were analyzed by Student's t-test or Mann-Whitney's U test for continuous variables, and by Chi square test for categorical variables. Pearson or Spearman correlation coefficients were used for bivariate correlation. P-values <0.05 were considered statistically significant.

RESULTS

Initially, 72 post-LT patients were enrolled. Since 3 of them had a history of CV event after LT, they were excluded from analyses. Therefore, our sample consisted of 69 patients, who were mostly Caucasian (92.7%). The main causes of liver disease in these patients were hepatitis C virus (68.1%) and alcoholic cirrhosis (23.2%). Most of them had received tacrolimus-based immunosuppression (87.0%).

Clinical, anthropometric and metabolic profiles of post-LT patients according to CIMT are shown in Table 1. A considerable prevalence of malnutrition, loss of strength and protein/muscle depletion was found according to HS and AMA. The proportion of AMA below percentile 15 was higher in the male than female gender (83.9% *vs* 16.1%; *P* <0.001), moreover 30.9% of males are below percentile 5 which indicates severe malnutrition. A positive correlation was detected between HS and METs (r = 0.271; P = 0.024). In contrast, a large number of obese was detected in this population. The majority of patients (81.1%) gained weight after LT, and it was positively correlated with years after LT (r = 0.284; P = 0.018). Data from dietary intake according to CIMT are presented in Table 2.

More than a half (50.7%) of these post-LT patients presented with MS. The proportion of components of MS is shown in Figure 1. MS was positively associated with weight gain after LT ($P = 0.040$) and years after LT ($P = 0.005$).

According to the FRS, 31.9% of post-LT patients were at high CV risk (FRS >20%), and it was positively associated with hs-CRP ($P = 0.028$). Those with high CV risk have a higher prevalence of MS ($P = 0.004$), higher proportion of low physical activity ($P = 0.013$), and a trend for lower METs ($P = 0.055$) compared to those with moderate and low cardiovascular risk (FRS $\leq$ 20).

Still concerning CV risk, a prevalence was found of 43.5% of patients with CP. CIMT was weakly correlated with FRS ($r = 0.285$; $P = 0.018$). Not only high CV risk (FRS >20%), but also moderate CV risk (FRS >10%), was associated with the presence of CP ($P = 0.036$ and $P = 0.012$ respectively). The proportion of patients who present CP increases with the increase in the FRS, as indicated in Table 3.

Patients who had undergone LT more than 2 years previously, seemed to have a worse metabolic profile, such as higher systolic and diastolic BP and WC ($P < 0.04$ for all), a trend for higher fasting glucose ($P = 0.054$) and BMI ($P = 0.052$), and also, a higher prevalence of MS ($P = 0.025$) and a trend for high CV risk, considering FRS >20% ($P = 0.058$).

Regarding 25OHD, lower levels were found in patients with high and moderate CV risk according to FRS comparing to those with low risk ($P = 0.019$ for both). Also, a negative correlation was found between 25OHD and hs-CRP ($r = -0.279$; $P = 0.020$), stronger in those with abnormal CIMT (Figure 2). And also, a negative correlation was found between albumin and hs-CRP ($r = -0.292$; $P = 0.015$).

DISCUSSION

To the best of our knowledge, the present study was the first one to document the CIMT measurement in adults post-LT. We found a high prevalence of patients with increased CIMT and CP, and MS. Patients with abnormal CIMT presented a worse metabolic profile, especially lipid and inflammatory. Moreover, an increased intake of saturated and trans fatty acids was observed in these patients.

In this study, post-LT patients presented a high prevalence of malnutrition, especially muscle mass depletion, assessed by AMA and HS. It agreed with other studies which have indicated that muscle wasting from metabolic abnormalities of

cirrhosis still persists after LT (20,21). On the other hand, obesity was also very prevalent in this population. Anastácio et al., reported that 53% of patients weighed more than their weight before liver disease within one year after LT, which corroborated the impression that the weight gain after LT corresponds to an increase of fat mass, besides the recovery of their nutritional status after liver disease (22). These results are consistent with the described prevalence of sarcopenia in obese patients with non-alcoholic fatty liver disease, related to the higher levels of myostatin in such cases (23,24).

Similarly to our results, considering all patients, Richards et al. described a median weight gain of 9.5 kg and a prevalence of 30.6% of obesity (BMI $\geq$ 30 kg/m^2) at 3 years after LT (25). The excessive weight gain after LT is concerning, because it would increase the risk of MS and its associated complications, such as diabetes, CV disease, renal disease, and *de novo* NASH in the graft. The reasons why patients gain weight and lots of them become obese after LT are not elucidated, but it is believed that it could be a result of immunosuppression and overeating after recovering their appetite and prior eating habits after a long period of restrictions. These findings highlight the fact that nutritional monitoring is important immediately after LT, since the changes in weight happen soon (3).

The high prevalence of MS found in this study is in agreement with other studies that have described a prevalence of 44% to 58% in post-LT (26,27). A Brazilian study conducted by Anastacio et al. with 148 post-LT patients also found 50% of MS in post-LT, although using different WC criteria from ours (28). Our study observed an association between MS, weight gain and years after LT. Agreeing with that, a recent study with 455 LT patients showed that the prevalence of SM was 38.8% at 1 year after LT and increased between 44% and 45% after 3 to 5 years, and it was associated with the increase in BMI (29).

According to FRS, our study found a prevalence of 37.7%, 30.4% and 31.9% for low, moderate and high CV risk respectively. Another study found a similar prevalence to ours (40.0% for low risk; 29.6% for moderate risk and also 29.6% for high risk) (30). Ribeiro et al. also assessed the FRS in patients who underwent LT for more than 1 year, and found a lower prevalence of moderate risk (16.5%) and similar prevalence at high risk (29.6%) (31). As many components of MS are considered for FRS, such as HDL, BP and diabetes, its association is not very surprising.

Comparing patients according to abnormal CIMT, even though many studies have described a close association between MS and its components (19,32,33), we did not identify a significantly worse metabolic profile in the patients with abnormal CIMT, except for LDL, which was higher. It agreed with Kozakova et al. and Leng et al. who also found a higher LDL without difference in other blood lipids, in subjects with CP (34,35). Contributing to this, a study with young adults demonstrated that apolipoprotein B, which is the main protein in LDL, increased the relative risk of abnormal CIMT (32). It is interesting to note that median levels of LDL found in LT-patients with abnormal CIMT, are still near/below optimal levels related to potential atherogenicity (36).

Surprisingly, the patients with abnormal CIMT presented lower indicators of obesity. Likewise, two Chinese studies compared subjects according to the presence of atherosclerotic plaque and did not find a difference in BMI nor abdominal obesity (34,37). Furthermore, another study, from 14 European countries, did not identify a difference in BMI, WC and fat mass in subjects with or without CP (35). Interestingly, a study with 421 obese subjects that evaluated CIMT and body composition by dual-energy X-ray absorptiometry concluded that lean mass, and not fat mass, might contribute to increase CIMT, and, the explanation can be that increasing lean mass may influence the CV phenotype, leading to a small increase in CIMT (38).

Nowadays, the role of inflammation in the progression of CV disease is much discussed and it is especially important after LT. Alvares-da-Silva et al. (39) recently demonstrated that LT recipients present higher levels of proinflammatory cytokines and endothelial biomarkers than controls, highlighting the influence of inflammation on CV disease. The same group showed similar results before studying a sample of HCV non-cirrhotic patients (40). The circulating marker of inflammation hs-CRP appears to contribute to the identification of people at risk of developing CV disease. Furthermore, the association between hs-CRP levels and CV risk by FRS in our study showed a significantly higher prevalence of hs-CRP ≥1.0 mg/L (that also reflects CV risk and chronic low-grade inflammation) and a trend to higher median values of hs-CRP in patients with abnormal CIMT and CP. It corresponds to a study which observed that CIMT increased with increasing hs-CRP levels (41). In addition, another study indicated that increased hs-CRP was independently associated with abnormal CIMT (considered ≥ 0.7 mm), and it may be a good marker to detect early atherosclerosis independent of LDL levels (42) In this respect, our patients with abnormal CIMT had

hs-CRP inversely correlated to 25OHD. It supports other studies that have linked lower levels of 25OHD to inflammation. Recently, it was proposed that insufficient 25OHD concentrations may contribute to inflammation, as evidenced by higher circulating IL-6, and homocysteine (43). However, low 25OHD levels could only be an epiphenomena, as several studies show no evidence of an association between 25OHD and markers of carotid atherosclerosis, such as CIMT, and also, most clinical trials with vitamin D supplementation show inconsistent results related to hs-CRP (44,45).

Against our expectations, patients with abnormal CIMT did not present a significantly elevated proportion of high CV risk by FRS, even though there was a correlation between the measure of CIMT and FRS. Besides that, we found that 42.3% of low risk patients were diagnosed with abnormal CIMT. This finding is in accordance with other studies that also found an increased risk through carotid IMT and CP in low risk subjects classified by FRS (7,46,47). Hargens et al. support the view that there is a potencial for FRS to misclassify CV risk (46).

It has been already proved that saturated and trans fatty acids are associated with increased CIMT in epidemiological studies (48,49). Concurring with that, our post-LT patients also demonstrated a higher intake of those fatty acids. Concerning CV disease, studies have proposed that the adoption of a Mediterranean diet and replacing saturated fatty acids, trans fatty acids and carbohydrates by polyunsaturated fatty acids would be associated with a lower risk of CV disease (50,51).

We have to acknowledge some limitations in the present study. First, we grouped abnormal CIMT and CP together to compare them with normal CIMT. We did not expect to find such a large proportion of patients with CP, as the median time after LT is not much longer. We know that CIMT and CP are different structures regarding localization, natural history and predictive value for vascular events, but both share common risk factors for atherosclerosis (8). Besides, increased CIMT has been considered a predictor of CP and might occur in an earlier phase of the atherosclerotic process (52). Therefore, we believe that both increased CIMT and CP are at higher CV risk than those with normal CIMT. We did not have access to a metabolic profile before LT to determine if patients really developed MS after-LT. Also, the weight before LT was taken from medical records, and it could have been measured at different moments. Due to the instrument used to assess physical activity, we believe that there may have been an overestimation caused by the Domestic and Garden (Yard Work) domain, concealing patients with a low level of physical activity.

In conclusion, this study showed a high prevalence of an abnormal CIMT in a sample of overweight and sarcopenic LT patients. Abnormal CIMT was associated with higher LDL-cholesterol levels, hs-CRP ≥ 1mg/L and higher intake of saturated and trans fatty acids. This study underscores that it is necessary to provide strong preventive measures, including improvement of dietary quality, for all post-LT patients in order to minimize the CV risk in the future.

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TABLE 1. Clinical, anthropometric and metabolic profiles of post liver transplantation patients according to carotid intima-media thickness

	Normal CIMT	Abnormal CIMT*	P-value
N	32	37	
Gender (% male)	59.4	62.2	0.813 [a]
Age (years)	55 (48 – 64)	61 (57 – 65)	0.059 [b]
Years after LT	1 (4 – 9)	2 (1 – 4)	0.055 [b]
Smoking history (%)	43.7	67.7	0.055 [a]
Weight gain (kg)	13.3 ± 10.7	8.1 ± 10.0	**0.039** [c]
BMI < 60 y (kg/m^2)	28.4 (26.3 – 34.7)	27.6 (23.7 – 32.3)	0.521 [b]
BMI ≥ 60 y (kg/m^2)	29.2 (27.6 – 34.9)	26.6 (24.8 – 29.9)	0.058 [b]
WC (cm)	103.1 ± 15.1	101.2 ± 11.4	0.549 [c]
Increased WC (%)	65.6	59.5	0.627 [a]
HS < P30 (%)	62.5	78.4	0.187 [a]
HS < P10 (%)	50.0	56.8	0.633 [a]
AMA < P15 (%)	37.5	51.3	0.333 [a]
AFA > P90 (%)	43.7	18.9	**0.036** [a]
Systolic BP (mmHg)	125.6 ± 13.4	125.1 ± 12.2	0.882 [c]
Diastolic BP (mmHg)	76.2 (70.6 – 80.9)	76.5 (71.7 – 80.2)	0.993 [b]
TC (mg/dL)	152 (130 – 177)	168 (155 – 194)	0.065 [b]
LDL (mg/dL)	72.1 ± 35.7	101.9 ± 39.1	**0.014** [c]
HDL (mg/dL)	41 (35 – 60)	48 (36 – 62)	0.647 [b]
TG (mg/dL)	114 (89 – 151)	100 (78 – 167)	0.475 [b]
Glucose (mg/dL)	99 (90 – 116)	99 (90 – 114)	0.471 [b]
hs-CRP*	1.10 (0.27 – 3.43)	2.35 (1.26 – 3.39)	0.064 [b]
hs-CRP ≥ 1 mg/L (%)**	50.0	79.4	**0.018** [a]
25OHD (ng/mL)	21.7 (17.3 – 29.7)	25.8 (17.3 – 34.2)	0.749 [b]
Albumin (g/dL)	4.4 ± 0.3	4.2 ± 0.4	0.111 [c]
ALT (U/L)	36 (25 – 57)	36 (23 – 72)	0.964 [b]
AST (U/L)	30 (22 – 57)	38 (22 – 56)	0.544 [b]
GGT (U/L)	86 (45 – 199)	94 (42 – 263)	0.818 [b]
ALP (U/L)	96 (82 – 152)	99 (90 – 144)	0.993 [b]

MS (%)	59.4	43.2	0.230 [a]
Moderate/high CV risk (%)	53.1	70.3	0.213 [a]
METs	2410 (661 – 4314)	1782 (1020 – 3531)	0.749 [b]

Results presented as %; median (p25 – p75) or mean ± SD.

[a]Qui-square test; [b]Mann–Whitney–Wilcoxon *U* test; [c]Student's *t*-test.

*increased CIMT + CP; **excluded those with hsCRP ≥ 10 mg/L as previously described (53)

CIMT: carotid intima-media thickness; LT: liver transplantation; BMI: body mass index; WC: waist circumference; HS: handgrip strength; AMA: arm muscle area; AFA: arm fat area BP: blood pressure; TC: total cholesterol; HDL: HDL cholesterol; LDL: LDL cholesterol; TG: triglycerides; hs-CRP: high-sensitive C-reactive protein; 25OHD: 25-hydroxyvitamin D; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase ; ALP: alkaline phosphatase; MS: metabolic syndrome; Moderate/high CV risk (%): Framingham Risk Score > 10%; METs: MET-minute/week

TABLE 2. Daily Dietary intake of post liver transplantation patients according to carotid intima-media thickness

	Normal CIMT	Abnormal CIMT*	P-value
	32	37	
Energy (kcal/kg)	23.8 (12.3 – 50.7)	27.0 (10.8 – 49.2)	0.084 [a]
Carbohydrates (g/kg)	2.86 ± 1.07	3.39 ± 1.20	0.062 [b]
Protein (g/kg)	1.22 (0.33 – 3.27)	1.21 (0.51 – 2.38)	0.950 [a]
Lipid (g/kg)	0.95 (0.48 – 1.92)	1.01 (0.33 – 2.21)	0.106 [a]
Saturated FA (g/kg)	0.28 ± 0.11	0.35 ± 0.16	**0.032**
Monounsaturated FA (g/kg)	0.29 (015 – 0.72)	0.38 (0.23 – 0.45)	0.119 [a]
Polyunsaturated FA (g/kg)	0.24 (0.09 – 0.46)	0.21 (0.06 – 0.62)	0.691 [a]
Trans FA (g/kg)	0.000 (0.000 – 0.015)	0.002 (0.000 – 0.220)	**0.011** [a]
Cholesterol (mg)	250.0 (154.7 – 316.1)	255.9 (170.0 – 313.3)	0.715 [a]
Fiber (g/kg)	21.4 (0.0 – 46.9)	20.3 (8.1 – 52.3)	0.623 [a]
Glycemic index (%)	59.5 ± 5.6	56.7 ± 7.0	0.069 [b]
Glycemic load (g)	106.9 ± 42.9	111.8 ± 44.3	0.641 [b]

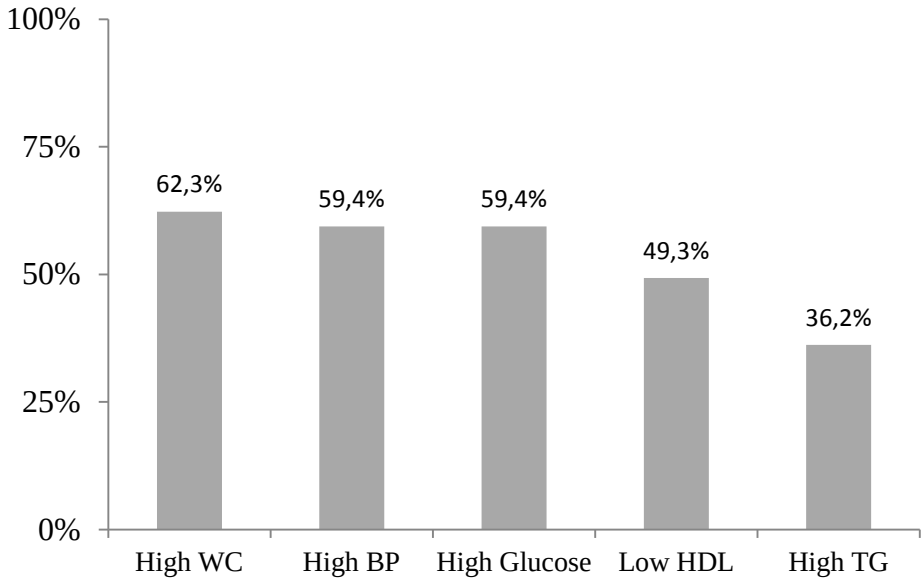
Results presented as median (min – max) or mean ± SD;

[a]Mann–Whitney–Wilcoxon *U* test; [b]Student's *t*-test.

*increased CIMT + CP

FA: fatty acids

FIGURE 1. Proportion of components of metabolic syndrome in post liver transplantation patients



High WC: waist circumference >88 for female and >102 for male; High BP: systolic blood pressure ≥130 and/or diastolic BP ≥85 mmHg or antihypertensive drug treatment; High Glucose: glucose ≥100 mg/dL or insulin or hypoglycemic drug treatment; Low HDL: HDL cholesterol <40 mg/dL for male and < 50 mg/dL for female) or drug treatment for reduced HDL; High TG: triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides.

TABLE 3. Presence of carotid plaque according to Framingham risk score in post liver transplantation patients*.

		<10%	10-20%	>20%	Total
CP	No	20 (77%)	11 (52%)	8 (36%)	39
	Yes	6 (23%)	10 (48%)	14 (63%)	30
Total		26	21	22	69

Results presented as n (%). Qui-square test * $P = 0.019$

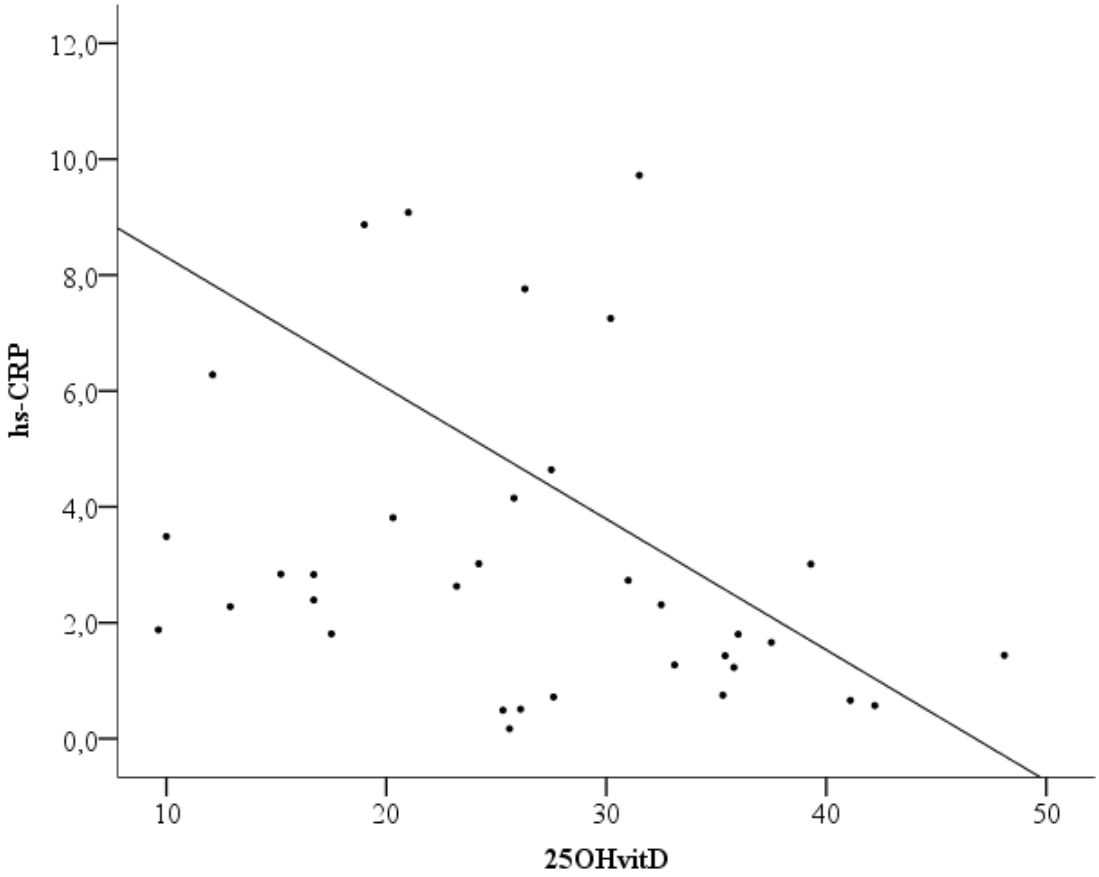


FIGURE 2. Correlation between hs-CRP and 25OHD in post liver transplantation patients with abnormal CIMT (>1.0 mm) or CP (r = -0.455; P = 0.005)

9. CONCLUSÃO

O presente estudo demonstrou elevada prevalência de EIMC alterada em pacientes pós-TxHep, bem como alta prevalência de desnutrição e sarcopenia, apesar da média de IMC apresentar excesso de peso nesta amostra.

A EIMC alterada foi associada a maiores níveis de LDL colesterol, e maior ingestão de ácidos graxos saturados e *trans* saturados. Não houve associação entre EIMC alterada e ERF, SM e atividade física. No entanto, ERF se associou com presença de PAC. Apesar de ter sido encontrado associação negativa entre EIMC alterado e indicadores de obesidade (AGB > p90 e ganho de peso pós-TxHep), não houve diferença entre EIMC alterado e IMC.

Nesse sentido, faz-se necessário a adoção de medidas que visem à melhoria da qualidade da alimentação destes pacientes, com monitoramento nutricional, a fim de prevenir o ganho de peso inadequado e contribuir para minimizar o risco CV.

10. PERSPECTIVAS FUTURAS

Todos os pacientes pós-TxHep que participaram desta pesquisa seguem sua rotina de atendimento com a assistência médica no Ambulatório de Transplante Hepático do HCPA e foi oferecido acompanhamento em ambulatório de Nutrição para todos pacientes que tivessem interesse.

O seguimento de pacientes no período pós-transplante é de grande importância, não apenas no pós-TxHep imediato, mas especialmente na fase mais tardia, a fim de monitorar o estado nutricional e a saúde cardiovascular. Novos estudos, com delineamentos de longo prazo seriam úteis para avaliar entre outros aspectos, a recidiva da doença hepática, especialmente aqueles infectados pelo vírus da hepatite C, que são os mais prevalentes na nossa população.