THERE IS NO CORRELATION BETWEEN STAGES OF NAFLD ASSESSED BY LIVER BIOPSY AND THE DIAGNOSTIC CRITERIA FOR SARCOPENIA IN ACTIVE POPULATIONS: A CROSS-SECTIONAL STUDY

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RESUMO: Objective: To demonstrate the correlations of the diagnostic criteria for sarcopenia and the levels of Non-alcoholic Fat Liver Disease (NAFLD) assessed by liver biopsy in a physically active population. Methods: Cross-sectional study. Individuals aged ≥18 years, with NAFLD confirmed by liver biopsy, physically active. Sarcopenia assessment followed EWGSOP2: muscle strength by handgrip, Skeletal Muscle Mass by Bioimpedance, and physical performance by usual gait speed. Statistical Analysis: To test differences between groups in continuous variables, Student's T or Mann-Whitney U Test for independent samples. Pearson and Spearman tests were used for correlations. A 5% significance was considered ($p<0.05$). Results: 52 patients with NAFLD included, consisting of 35 women and 15 men. There was no difference in age or anthropometric variables. Were found difference statically significant in platelets (higher in women), basal insulin, HOMA-IR and Quick (higher in men). In sarcopenia, the handgrip strength showed difference in favors of men. There was no statistically significant correlation between the sarcopenia and NAFLD levels. Discussion: sarcopenia has been reported as an independent risk factor for NAFLD and its progressions. The physical exercise is one of the most recommended and more effective treatment for both conditions, so is expected that a non-sedentary individual can reduce both indicators. However, there is no consensus about the best method. Also, the both conditions share heterogeneity in diagnosis, prognosis, reason for develop and risk factors across the literature. Conclusion: For populations where most individuals are physically active, it is not possible to find correlation between sarcopenia diagnostic criteria and the stages of NAFLD.
KEYWORDS: Non-Alcoholic Fatty Liver Disease; Sarcopenia; Exercise.

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NÃO HÁ CORRELAÇÃO ENTRE OS ESTÁGIOS DA DHGNA AVALIADOS POR BIÓPSIA HEPÁTICA E OS CRITÉRIOS DIAGNÓSTICOS PARA SARCOPENIA EM POPULAÇÕES ATIVAS: UM ESTUDO TRANSVERSAL

RESUMO: Objetivo: Demonstrar as correlações dos critérios diagnósticos de sarcopenia e dos níveis de doença hepática gordurosa não alcoólica (DHGNA) avaliados por biópsia hepática em uma população fisicamente ativa. Métodos: Estudo transversal. Indivíduos com idade ≥18 anos, com DHGNA confirmada por biópsia hepática, fisicamente ativos. A avaliação da sarcopenia seguiu o EWGSOP2: força muscular por preensão manual, massa muscular esquelética por bioimpedância e performance física por velocidade usual de marcha. Análise Estatística: Para testar diferenças entre grupos nas variáveis contínuas, teste T de Student ou Teste U de Mann-Whitney para amostras independentes. Os testes de Pearson e Spearman foram utilizados para correlações. Foi considerada significância de 5% ($p<0,05$). Resultados: Foram incluídos 52 pacientes com DHGNA, sendo 35 mulheres e 15 homens. Não houve diferença na idade ou nas variáveis antropométricas. Foram encontradas diferenças estatisticamente significativas em plaquetas (maior em mulheres), insulina basal, HOMA-IR e Quick (maior em homens). Na sarcopenia, a força de preensão manual apresentou diferença em favor dos homens. Não houve correlação estatisticamente significativa entre os níveis de sarcopenia e DHGNA. Discussão: a sarcopenia tem sido relatada como fator de risco independente para DHGNA e suas progressões. O exercício físico é um dos tratamentos mais recomendados e mais eficazes para ambas as condições, pelo que se espera que um indivíduo não sedentário consiga reduzir ambos os indicadores. No entanto, não há consenso sobre o melhor método. Além disso, ambas as condições compartilham heterogeneidade no diagnóstico, prognóstico, razão de desenvolvimento e fatores de risco em toda a literatura. Conclusão: Para populações onde a maioria dos indivíduos é fisicamente ativo, não é possível encontrar correlação entre os critérios diagnósticos de sarcopenia e os estágios da DHGNA.
PALAVRAS-CHAVE: Doença Hepática Gordurosa não Alcoólica; Sarcopenia; Exercício.

NO EXISTE CORRELACIÓN ENTRE LAS ETAPAS DE EHGNA EVALUADAS MEDIANTE BIOPSIA HEPÁTICA Y LOS CRITERIOS DIAGNÓSTICOS DE SARCOPENIA EN POBLACIONES ACTIVAS: UN ESTUDIO TRANSVERSAL

RESUMEN: Objetivo: demostrar las correlaciones de los criterios diagnósticos de sarcopenia y los niveles de enfermedad del hígado graso no alcohólico (EHGNA) evaluados mediante biopsia hepática en una población físicamente activa. Métodos: Estudio transversal. Individuos mayores de 18 años, con EHGNA confirmada mediante biopsia hepática, físicamente activos. La evaluación de la sarcopenia siguió el EWGSOP2: fuerza muscular mediante agarre manual, masa muscular esquelética mediante bioimpedancia y rendimiento físico mediante velocidad de marcha habitual. Análisis estadístico: Para probar diferencias entre grupos en variables continuas, prueba T de Student o U de Mann-Whitney para muestras independientes. Para las correlaciones se utilizaron las pruebas de Pearson y Spearman. Se consideró una significancia del 5% ($p<0,05$). Resultados: Se incluyeron 52 pacientes con EHGNA, 35 mujeres y 15 hombres. No hubo diferencia en la edad ni en variables antropométricas. Se encontraron diferencias estadísticamente significativas en plaquetas (mayor en mujeres), insulina basal, HOMA-IR y Quick (mayor en hombres). En la sarcopenia, la fuerza de prensión manual mostró diferencia a favor de los hombres. No hubo correlación estadísticamente significativa

entre la sarcopenia y los niveles de NAFLD. Discusión: la sarcopenia ha sido reportada como un factor de riesgo independiente para NAFLD y sus progresiones. El ejercicio físico es uno de los tratamientos más recomendados y efectivos para ambas afecciones, por lo que se espera que una persona no sedentaria pueda reducir ambos indicadores. Sin embargo, no hay consenso sobre cuál es el mejor método. Además, ambas afecciones comparten heterogeneidad en el diagnóstico, pronóstico, motivo de desarrollo y factores de riesgo en la literatura. Conclusión: Para poblaciones donde la mayoría de las personas son físicamente activas, no es posible encontrar correlación entre los criterios de diagnóstico de sarcopenia y las etapas de NAFLD.
PALABRAS CLAVE: Enfermedad del Hígado Graso no Alcohólico; Sarcopenia; Ejercicio.

1. BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a disease of great prevalence among the world's populations, that may affect up to a quarter of the individuals, and has an accentuated increase due to several reasons, such as the sedentarism and eating habits. This disease, characterized by fat accumulation in liver cells, can progress to more severe conditions, such as non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and even hepatocellular carcinoma [1-4].

On the other hand, sarcopenia, nowadays, is not anymore recognized as a disease exclusive to aging, as mentioned by Rosenberg, in 1989 [5]. The ICD itself cites sarcopenia as a syndrome characterized by progressive and generalized loss of mass and muscle strength, in addition to a decrease in physical performance [6]. Several studies demonstrate the occurrence of sarcopenia in non-elderly individuals, patients with different pathologies, such as heart and kidney diseases [7, 8], in addition to being associated with other syndromes or conditions, such as obesity [9], osteoporosis [10] and frailty [11].

Lately, authors have reported the relationship between sarcopenia and NAFLD, drawing a line of connection between both conditions, since the pathogenesis of NAFLD may be linked to the physiological pathways of sarcopenia [1, 12, 13]. However, it is not yet clear in the literature whether the fact that the physical activity status of the patient with NAFLD may have any influence on the diagnostic criteria for sarcopenia.

More studies are needed in this matter, trying to connect NAFLD and sarcopenia more than in theory, but in practice, showing how one condition can affect the other, guiding the clinical practice towards a full understanding of the relationship between both conditions. This understanding may open a whole new field of research and treatment, when clinicians do not treat NAFLD in a way and sarcopenia in other, as non-related

diseases, but them both as intimate linked conditions. This study aimed, therefore, to demonstrate the correlations of the diagnostic criteria for sarcopenia and the stages of NAFLD assessed by liver biopsy in a physically active population.

2. MATERIALS AND METHODS

2.1 Study Design

This is a cross-sectional study originating from a cohort study, which included individuals diagnosed with NAFLD of the outpatient Gastroenterology/Hepatology Unit at Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), a tertiary reference center at Southern Brazil. Although there are other ways to diagnose NAFLD, only patients who underwent liver biopsy were included in this study, as this is considered the gold-standard method for this diagnosis.

2.2 Research Place

The clinic, imaging and laboratorial tests were carried out at ISCMPA, as were the fluids collects. The sarcopenia tests were performed at Physical Therapy Laboratory from the Federal University of Health Sciences of Porto Alegre (UFCSPA).

2.3 Ethical Procedures

The study was approved by research ethics committees from UFCSPA (decision letter number 1.894.929); and ISCMPA (decision letter number 1.856.118). All patients read and signed the informed consent form (ICF).

2.4 Inclusion Criteria

All patients aged 18 years or more, with NAFLD confirmed by liver biopsy, treated at the outpatient Gastroenterology/Hepatology Unit between march-2018 and December-2020 were included. in addition, the patients had to be considered physically active, by the International Physical Activity Questionnaire (IPAQ).

2.5 Exclusion Criteria

Were excluded patients with hepatitis B virus, hepatitis C virus, significant alcohol consumption ($\geq$ 20 g/day for women and $\geq$ 30 g/day for men), patients with other chronic liver diseases not caused by NAFLD, secondary causes of NAFLD and patients

with hepatocellular carcinoma. Also, patients sedentary or insufficient active, by IPAQ, were excluded.

2.6 Procedure for data collection and Evaluations

2.6.1 Blood work and liver exams

For this study, blood samples were collected while fasting, by professionals from the Clinical Analysis Laboratory at ISCMPA.

Resistance to insulin action was estimated by calculating the Homeostasis Model Assessment (HOMA-IR) and by the triglyceride-glucose index (TyG) [14, 15]. Sensitivity to insulin action was estimated by calculating the Quantitative Insulin Sensitivity Check Index (QUICK) [16].

Liver biopsy was indicated according to the Guideline of the American Association for the Study of Liver Disease (AASLD), which indicates biopsy in patients with NAFLD at risk of NASH and advanced fibrosis, as part of the care protocol. Liver biopsy was performed using the ultrasound-guided technique using a Tru-cut needle, and the material obtained was analyzed by a professional with experience in the field of liver pathology, covering the relevant histopathological classifications for the assessment of NAFLD. Histopathological analyzes used the NAFLD activity score (NAS) [17, 18].

2.6.2 Sarcopenia assessment

All the assessments followed the recommended by EWGSOP2 [19], it is, muscle strength measured by handgrip strength, Skeletal Muscle Mass (SMM) by Bioimpedance Analysis (BIA), and physical performance by the usual gait speed (UGS).

Muscle strength: assessed by handgrip (Jamar hydraulic hand dynamometer - Sammons Preston Rolyan, IL, USA), which data are presented in Kg. The patients position and test realization followed the recommended by the American Society of Hand Therapy [20].

Skeletal muscle mass: assessed by Bioimpedance Analysis - BIA (Biodynamics 450, Biodynamics Corporation, WA, USA). The patient's preparation and positioning followed the recommended by the European Society for Clinical Nutrition and Metabolism [21]. The data collected was the impedance resistance, and the SMM was calculated using the formula proposed by Janssen et al [22]. Also, the Skeletal Muscle Mass Index (SMMI) was calculated dividing height by weight square (Kg/m²).

Physical performance: assessed by usual gait speed, through the 6-minute walk test, conducted following recommendation by Enright et al [23]. The data was reached dividing the meters walked by 360 seconds (six minutes).

The level of physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) [24]. To be considered active, the individual had to do vigorous exercise three or more days a week, 20 minutes per session, or; do moderate activity or walking five or more days a week, 30 minutes per session, or; walks plus moderate activity plus vigorous activity five or more days a week (adding up to 150 minutes per week). Anything below that was considered sedentary.

2.7 Statistical Analysis

For descriptive analysis, parametric continuous data are presented in mean $\pm$ standard deviation; To test differences between groups in continuous variables, Student's T Test for independent samples (parametric) and Mann-Whitney U Test for independent samples (nonparametric) were used. Pearson (parametric) and Spearman (non-parametric) correlations were used for correlations. A significance level of 5% was considered ($p<0.05$). The analyzes were performed in the statistical software SPSS (IBM SPSS Statistics for Windows, Version 25.0. IBM Corp., Armonk, NY, USA). The sample was divided in women and men, because the data both for sarcopenia and for NAFLD can be very discrepant between those particular groups, and the results could have been affected, either overestimating or subestimating the results.

3. RESULTS

The study included 52 patients with NAFLD, consisting of 35 women (67,3%) and 15 men (32,7%). There was no difference statically significant in age or anthropometric variables.

A statically significant difference was found in platelets (with higher means in women), basal insulin, HOMA-IR and Quick (with higher means in men).

In sarcopenia analysis, only the handgrip strength showed difference statically significant, in favors of men.

Table 1. Sample Characterization (n=52).

Variables (mean±SD)	Women (n=37)	Men (n=15)	p
Age (years)	56.46 ± 9.39	60.33 ± 13.86	,600
Anthropometric Variables			
Weight (Kg)	82.95 ± 14.22	88.55 ± 14.23	,799
Height (cm)	157.27 ± 6.18	172.13 ± 7.62	,694
BMI (Kg/cm²)	33.55 ± 5,44	29.97 ± 4.92	,443
Blood Analysis			
ALT (U/L)	37.17 ± 24.59	48.33 ± 26.04	,468
AST (U/L)	31.31 ± 16.41	37.53 ± 16.64	,710
Albumin (g/L)	4.42 ± 0.82	4.47 ± 0.52	,940
Platelets (mm³)	259.82 ± 84.76	214.79 ± 41.08	,027[1]
Total cholesterol (mg/dL)	193.36 ± 37.00	182.25 ± 43.39	,789
LDL (mg/dL)	48.72 ± 10.14	48.17 ± 9.86	,745
HDL (mg/dL)	109.69 ± 34.52	103.73 ± 40.90	,538
Serum triglyceride (mg/dL)	170.08 ± 62.12	181.33 ± 101.84	,111
Basal glucose (mg/dL)	126.89 ± 57.59	172.17 ± 79.30	,068
Basal insulin (U/mL)	19.89 ± 12.93	22.36 ± 19.47	,000[1]
Leptina	34.63 ± 13.11	37.37 ± 1.66	,181
HOMA-IR	6.08 ± 4.46	9.71 ± 11.56	,037[1]
TyG	0.49 ± 0.03	0.46 ± 0.05	,195
Quick	9.14 ± 0.66	9.41 ± 0.87	,041[1]
C-reactive protein (mg/dL)	7.45 ± 5.60	4.11 ± 5.73	,543
Creatinine (mg/dL)	0.78 ± 0.23	0.91 ± 0.32	,267
Sarcopenia Analysis			
Usual Gait Speed (m/s)	1.05 ± 0.24	1.18 ± 0.32	,842
Grip Strength (Kg/f)	26.8 ± 6.02	39.46 ± 9.32	,026
Skeletal Muscle Mass (Kg)	20.69 ± 4.08	29.63 ± 6.21	,327

Where: n: sample; SD: standard deviation; p: Student T test for independent samples (parametric variables) and Mann-Whitney U test for independent samples (nonparametric variables); Kg: kilogram; cm: centimeter; Kg/cm²: kilogram per square ccentimeter; ALT: Alanine Aminotransferase; U/L: international unities per liter; AST: Aspartate Aminotransferase; g/L: grams per liter; mm³: cubic milimeteres; mg/dL: miligrams per deciliter; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; HOMA-IR: Homeostasis Model Assessment; TyG: triglyceride-glucose index; QUICK: Quantitative Insulin Sensitivity Check Index; m/s: meter per second; Kg/f: kilogram of strength
Source: Prepared by the authors

At table 2 are presented the correlations between the stages of NAFLD (Steatosis, NASH and fibrosis) obtained through liver biopsy, and the three diagnostic criteria for sarcopenia, as recommended by EWGSOP2. There was no statistically significant correlation between the assessments of sarcopenia

Table 2. Correlation Between NAFLD levels assessed by liver biopsy and sarcopenia's diagnostic criteria (n=52).

	Women (n=37)						Men (n=15)					
	Steatosis		NASH		Fibrosis		Steatosis		NASH		Fibrosis	
	p	r	p	r	p	r	p	r	p	r	p	r
Muscle Strength[1]	,657	,080	,250	,200	,483	,162	,068	,543	,300	-,327	,787	,168
Muscle Mass[2]	,095	-,291	,515	-,112	,424	,184	,653	-,127	,725	-,099	,463	-,376
Physical Performance[3]	,354	,164	,981	-,004	,071	,402	,476	,217	,505	,204	,499	,405

Where: n: sample; NASH: non-alcoholic steatohepatitis; p and r: significance and correlation by Pearson (parametric) or Spearman (non-parametric) correlation. [1]muscle strength assessd by handgrip strength; [2]muscle mass assessed by bioimpedance analysis; [3]physical performance assessed by usual gait speed.
Source: Prepared by the authors

4. DISCUSSION

In general, is expected that the sarcopenia and the NAFLD be very connected, once, following Chun et al [25], the NAFLD and the sarcopenia share some pathophysiological pathways. For example, the insulin resistance has been repeatedly reported as a risk factor for both conditions, as is the metabolic syndrome.

Besides, sarcopenia has been reported as an independent risk factor for NAFLD and its progressions, because muscle mass is considered a key factor for the insulin-mediated glucose metabolism in human body. A minor amount of muscle mass can result in less fatty liver oxidation, which can lead to an accumulation of ectopic fat in the liver [12, 26].

The physical exercise is one of the most recommended and more effective treatment for both conditions, so is expected that a non-sedentary individual can reduce both indicators in NAFLD and sarcopenia [19, 27], however it is not clear what kind of physical exercise can be better for both conditions. When we talk only about sarcopenia, a systematic review of systematic reviews [28] showed that be included in any exercise program can be beneficial, though the resistance training showed better results for muscle strength and mass, and combined modalities for physical performance. For NAFLD patients, Carneros et al [29] relates that aerobic training with high volume or intensity can be better to reduce the liver fat. However, some studies with resistance training [29, 30] showed reductions in fat, AST and ALT levels.

However, even though there is no consensus in the literature about the most appropriate training model for NAFLD or for sarcopenia, but some models that cause different effects on the indicators, it is clear that there are more studies in the area of NAFLD using aerobic exercises, while in the field of sarcopenia, the most common training

applied in RCTs are based in resistance training [4, 19, 28, 31]. Having this in mind, we face a problem: to combine exercise modalities than can both be good for sarcopenia and for NAFLD.

For example, however there is some authors who relates benefits in sarcopenia regarding aerobic exercises [32, 33], Ferreira et al [34] shows in a cross-sectional study that this modality is not able to reduce the prevalence for sarcopenia. It is, although it can be beneficial, it is not capable of change the syndrome status.

In other hand, Babu et al [31] related in a systematic review that only the aerobic training reduced the liver parameters of NAFLD, such as intrahepatic lipids, ALT and AST, while resistance training only acts indirectly on NAFLD parameters, reducing, for example, triglycerides and total cholesterol (them both, by the way, also reduced with aerobic training). These findings may explain, at least in part, why this study showed a discrepancy between NAFLD levels and diagnostic criteria for sarcopenia.

Gonzales et al [13], in its systematic review, have reached to a conclusion that physical exercises are beneficial for sarcopenia in NAFLD patients, but the liver function or the NAFLD levels were not evaluated, which means that they do not take in account the NAFLD in those patients.

Other condition in common between sarcopenia and NAFLD that can be found in literature is the heterogeneity in diagnosis, prognosis, reason for development and risk factors. For example, sarcopenia can be developed by a several reasons, from simple aging (primary sarcopenia), to sedentarism, obesity, hospitalization or long-term care facilities inclusion, poor nutrition, or the development of other health conditions (secondary sarcopenia) [19, 28, 32, 35, 36].

Meanwhile, NAFLD is a multifactorial disease, such as genetic, bad nutrition (mainly rich in fat, processed foods and sugar-sweetened beverages), sedentarism, viral hepatitis, diabetes, metabolic syndrome, polypharmacyamong others [3, 4, 13, 27, 37-39]. This high range of causes can lead the individual to different symptoms and levels of both conditions, making a generalization of interventions shallow and unsafety.

So, albeit some authors relate an intimate connection in appearance and development of sarcopenia and NAFLD, because them both share some physiopathological pathways [12, 25, 26], it may not be true when the disease are already installed.

See, in this study, for example, all patients were included because already were patients of NAFLD. And it is true for almost all references across the literature. The

patients included in sarcopenia studies were already sarcopenic, while those included in NAFLD studies where already in this condition. So, maybe to answer the exact correlation between these two conditions, are necessary the conduction of longitudinal studies, as cohort studies, that follow the patients along their lives, in order to get the moment of developing one (or both) condition.

5 CONCLUSION

For populations where most individuals are physically active, it is not possible to find a correlation between sarcopenia diagnostic criteria and the stages of NAFLD. Also, for this sample, to have steatosis, NASH of liver fibrosis do not impact the muscle strength, the skeletal muscle mass quantity and the physical performance, when the patient in physically active.

Clinic and research Impacts: Those findings highlight that, in some cases, despite the evidence of a relationship, there is no correlation between sarcopenia and NAFLD stages. From these results, is possible to say that a complete physical assessment must to be made, as the patients' physical habits, in order to direct the NAFLD treatment in different ways, either if the patient is sedentary or inactive; or if the patient is physically active.

Limitations: As possible limitations, we can highlight that for some analyses, our sample could be higher, in order to have a bigger power in the statistical tests. Also, we do not had access to a more reliable test to assess the SMM, such as DXA, CT or MRI. Finally, it was not investigated which modalities of physical activities the individuals were included, nor for how long.

Future studies: We advise that future studies can be conducted with higher samples, in order to determine which variables are more affected for the physical exercise, in which age group, gender, or even what exercise modality can be more beneficious for NAFLD and sarcopenia at the same time.

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