**Name of Journal:** *World Journal of Gastrointestinal Pathophysiology*

**Manuscript NO:** 74490

**Manuscript Type:** LETTER TO THE EDITOR

**Hepatomusculoskeletal disorders: Coining a new term might improve the management of the musculoskeletal manifestations of chronic liver disease**

Tsagkaris C *et al*. Hepatomusculoskeletal disorders

Christos Tsagkaris, Stavros P Papadakos, Dimitrios V Moysidis, Andreas S Papazoglou, Alexandra Koutsogianni, Marios Papadakis

**Christos Tsagkaris,** Public Health and Policy Working Group, Stg European Student Think Tank, Amsterdam, Netherlands

**Stavros P Papadakos, Alexandra Koutsogianni,** Laiko General Hospital of Athens, National and Kapodistrian University of Athens, Athens 18233, Greece

**Dimitrios V Moysidis,** Hippokration University Hospital, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

**Andreas S Papazoglou,** Athens Naval Hospital, Athens 18233, Greece

**Marios Papadakis,** Department of Surgery II, University Hospital Witten-Herdecke, University of Witten-Herdecke, Wuppertal 42283, Germany

**Author contributions:** Tsagkaris C conceptualized this letter; Tsagkaris C, Papadakos SP and Moysidis DV performed the literature search; Tsagkaris C, Papadakos SP and Papazoglou AS wrote the first draft; Moysidis DV, Koutsogianni A and Papadakis M revised the manuscript and wrote the second draft; All authors have further revised, read and approve the final manuscript.

**Corresponding author: Christos Tsagkaris, MD, Academic Fellow,** Public Health and Policy Working Group, Stg European Student Think Tank, Postjeskade 29, 1058 DE, Amsterdam, Netherlands. chriss20x@gmail.com

**Received:** December 25, 2021

**Revised:** April 7, 2022

**Accepted:** June 26, 2022

**Published online:** July 22, 2022

**Abstract**

Chronic liver disease can affect many body systems including the musculoskeletal system. The pathogenetic crosstalk between the liver and organs such as the brain and the kidneys has already been described with compound terms merging the organs affected by the pathology, such as the hepatorenal syndrome. Nevertheless, the musculoskeletal manifestations of chronic liver disease have not been coined with such a term to date. Because of this shortage, documenting the musculoskeletal implications of chronic liver disease in both research and clinical practice is challenging. To fill this gap, the authors propose the term hepatomusculoskeletal disorders, a compound term of Greek origin that encompasses all the body structures involved in the aforementioned pathologic crosstalk.

**Key Words:** Chronic liver disease; Hepatomusculoskeletal disorders; Musculoskeletal system; Hepatology; Pathophysiology; Osteodystrophy

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Tsagkaris C, Papadakos SP, Moysidis DV, Papazoglou AS, Koutsogianni A, Papadakis M. Hepatomusculoskeletal disorders: Coining a new term might improve the management of the musculoskeletal manifestations of chronic liver disease. *World J Gastrointest Pathophysiol* 2022; 13(4): 124-127

**URL**: <https://www.wjgnet.com/2150-5330/full/v13/i4/124.htm>

**DOI**: https://dx.doi.org/10.4291/wjgp.v13.i4.124

**Core Tip:** The authors recommend coining the umbrella term “hepatomusculoskeletal disorders” in response to the need to expand knowledge about chronic liver disorders and capitalize it in the form of practice guidelines.

**TO THE EDITOR**

Chronic liver disease (CLD) is the 11th leading cause of mortality globally accounting for up to 2% of disability-adjusted life years worldwide[1]. It encompasses ailments of infectious (viral hepatitis) and non-infectious (alcohol abuse, non-alcoholic steatohepatitis, cancer) origin leading to progressive structural and functional depletion of hepatic physiology in the form of liver cirrhosis. CLD is associated with multisystem complications involving the kidneys, the heart, the nervous system and the musculoskeletal system[2]. Research in the field has recently sought hematological and electrocardiographic CLD biomarkers addressing CLD’s extrahepatic manifestations as a potential standpoint for the management of the disease and for the identification of novel therapeutic targets[3-5]. Nevertheless, research regarding the musculoskeletal implications of CLD remains limited. Action is needed to expand the existing knowledge and its clinical applications.

The impact of CLD on the musculoskeletal system has been better understood during the last years[6]. The musculoskeletal manifestations can be classified into two categories according to their etiology: (1) On the causative disease which insults the liver; and (2) On the type and the degree of liver disease. In more detail, Hepatitis C is frequently associated with rheumatologic phenomena. Polyarthralgia either in the context of mixed cryoglobulinemia triad of purpura, fatigue and arthralgia or alone as hepatitis C virus (HCV)-induced arthritis is documented frequently[7,8]. Overt arthritis and fibromyalgia are less frequently diagnosed in parallel with HCV infection. Polyarthritis and polyarthralgia are commonly presented as manifestations of hepatitis B virus, hepatitis A virus and hepatitis E virus infections[7] while erosive arthritis is encountered in anti-cyclic citrullinated peptide positive type I autoimmune hepatitis[9]. In regards to the alcoholic liver disease, ethanol exerts direct cytotoxic effects into the muscular system causing alcoholic myopathy while affects bone metabolism causing matrix decomposition and suppression of bone synthesis[10]. Nonalcoholic fatty liver disease is frequently associated with low bone mineral density[11] while in diseases characterized by defective metabolism of metals (*e.g.*, copper in Wilson’s disease and iron in haemochromatosis), arthritis, chondrocalcinosis and muscle stiffness and pain are regularly noticed[7,12]. On the other side, the severity of liver disease impacts the musculoskeletal health. Alterations in endogenous steroid metabolism and the use of proton pump inhibitors and diuretics results in fluctuations of mineral metabolism which result in hepatic osteodystrophy[13]. The defective immune responses due to poor complement system and opsonization sufficiency, portosystemic shunt and bacterial intestinal overgrowth render the patients prone to infections like septic arthritis, osteomyelitis, cellulitis and necrotizing fasciitis[14]. Finally, sarcopenia[15], non-traumatic osteonecrosis[16] and a higher rate of periprosthetic complications[17] are manifestations from the musculoskeletal system that compromise severely the quality of a patient’s life.

On these grounds, healthcare professionals specializing in the management of musculoskeletal conditions (rheumatologists, orthopedic surgeons, physiatrists, physiotherapists, *etc*) can substantially contribute to CLD management. Prevention-wise, patients with CLD history can benefit from regular screening for osteopenia and osteoporosis and from falls’ prevention training[18]. Similarly, physiotherapy to maintain muscle mass, improve patients’ functionality and prevent sarcopenia-associated injury and disability can also be provided[19]. Treatment-wise, orthopedists and rheumatologists need to be aware of septic arthritis in CLD patients presenting with joint pain, and for spondylodiscitis and vertebral tuberculosis - in regions where the disease is endemic-in CLD patients presenting with low back pain[20-22]. Performing orthopedic surgery should also entail special considerations in CLD patients. Given their 3.5-fold higher risk for periprosthetic infections, cellulitis and necrotizing fasciitis, conservative management of fractures or osteoarthritis can be prioritized. In case of surgery, the patients and their formal and informal caregivers need to be instructed about the risk of infection and the need to carefully inspect surgical wounds and areas of plaster casting and seek medical attention when appropriate[23].

To contribute towards this end, musculoskeletal healthcare professionals need updated practice guidelines and relevant training. Developing concrete guidelines in turn requires systematic research in the field, with large scale observational studies and clinical trials confirming the existing knowledge and optimizing the recommended interventions. Currently, it appears that research in the field is heterogeneous, with the majority of studies being observational and having been conducted independently in inconsistent time intervals.

A search for relevant publications on Medline, Scopus and other databases reveals a plethora of terms used to describe CLD musculoskeletal implications. The wording is often alternating (musculoskeletal disorders in patients with CLD, hepatic osteodystrophy) and rather descriptive words addressing particular alterations associated with CLD (sarcopenia, osteosarcopenia, skeletal muscle mass) rather than the phenomenon as a whole[2,24-26]. A term grouping all of the aforementioned together has not been included in the Medical Subject Headings thesaurus and in the International Disease Classification (ICD10) system to date. To the best of the authors’ knowledge, no relevant term can be found in hospital records and documentation systems as well. Therefore, the lack of a consistent nomenclature poses significant obstacles to the appraisal of the existing knowledge, let alone its expansion.

The authors recommend coining the umbrella term “hepatomusculoskeletal disorders” in response to the need to expand relevant knowledge and capitalize it in the form of practice guidelines. The term is a compound word of Greek origin. It emphasizes the implications of liver conditions (hepato-) on muscles (musculo-), bones and connective tissue (skeletal). The composition of the term is similar to other relevant clinical terms such as the hepatorenal or the cardiorenal syndrome. In both these examples, the organs whose pathologies affect each other (liver, heart and kidneys respectively) are merged in a single term. Coining the new term in a similar linguistic format to other terms that are established in clinical practice makes it easily comprehensible to physicians and researchers. Therefore, the proposed term can benefit future research, clinical practice and medical education. Certainly, to address the musculoskeletal implications of CLD sufficiently, several steps involving clinicians, researchers, health bodies, healthcare administrators and stakeholders are required. Nonetheless, the new term can hopefully serve as common ground underlining the need to take relevant action.

**REFERENCES**

1 **Cheemerla S**, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. *Clin Liver Dis (Hoboken)* 2021; **17**: 365-370 [PMID: 34136143 DOI: 10.1002/cld.1061]

2 **Ranjan R**, Rampal S, Jaiman A, Tokgöz MA, Koong JK, Ramayah K, Rajaram R. Common musculoskeletal disorders in chronic liver disease patients. *Jt Dis Relat Surg* 2021; **32**: 818-823 [PMID: 34842121 DOI: 10.52312/jdrs.2021.25]

3 **Surana P**, Hercun J, Takyar V, Kleiner DE, Heller T, Koh C. Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis. *World J Gastrointest Pathophysiol* 2021; **12**: 40-50 [PMID: 34084591 DOI: 10.4291/wjgp.v12.i3.40]

4 **Rajapaksha IG**, Angus PW, Herath CB. Current therapies and novel approaches for biliary diseases. *World J Gastrointest Pathophysiol* 2019; **10**: 1-10 [PMID: 30622832 DOI: 10.4291/wjgp.v10.i1.1]

5 **Tsiompanidis E**, Siakavellas SI, Tentolouris A, Eleftheriadou I, Chorepsima S, Manolakis A, Oikonomou K, Tentolouris N. Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity. *World J Gastrointest Pathophysiol* 2018; **9**: 28-36 [PMID: 29487764 DOI: 10.4291/wjgp.v9.i1.28]

6 **Arora A**, Rajesh S, Bansal K, Sureka B, Patidar Y, Thapar S, Mukund A. Cirrhosis-related musculoskeletal disease: radiological review. *Br J Radiol* 2016; **89**: 20150450 [PMID: 27356209 DOI: 10.1259/bjr.20150450]

7 **Fernandes B**, Dias E, Mascarenhas-Saraiva M, Bernardes M, Costa L, Cardoso H, Macedo G. Rheumatologic manifestations of hepatic diseases. *Ann Gastroenterol* 2019; **32**: 352-360 [PMID: 31263357 DOI: 10.20524/aog.2019.0386]

8 **Zignego AL**, Gragnani L, Giannini C, Laffi G. The hepatitis C virus infection as a systemic disease. *Intern Emerg Med* 2012; **7 Suppl 3**: S201-S208 [PMID: 23073858 DOI: 10.1007/s11739-012-0825-6]

9 **Fusconi M**, Vannini A, Dall'Aglio AC, Pappas G, Cassani F, Ballardini G, Frisoni M, Grassi A, Bianchi FB, Zauli D. Anti-cyclic citrullinated peptide antibodies in type 1 autoimmune hepatitis. *Aliment Pharmacol Ther* 2005; **22**: 951-955 [PMID: 16268969 DOI: 10.1111/j.1365-2036.2005.02686.x]

10 **González-Reimers E**, Quintero-Platt G, Rodríguez-Rodríguez E, Martínez-Riera A, Alvisa-Negrín J, Santolaria-Fernández F. Bone changes in alcoholic liver disease. *World J Hepatol* 2015; **7**: 1258-1264 [PMID: 26019741 DOI: 10.4254/wjh.v7.i9.1258]

11 **Eshraghian A**. Bone metabolism in non-alcoholic fatty liver disease: vitamin D status and bone mineral density. *Minerva Endocrinol* 2017; **42**: 164-172 [PMID: 27973461 DOI: 10.23736/S0391-1977.16.02587-6]

12 **Martinon F**, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; **440**: 237-241 [PMID: 16407889 DOI: 10.1038/nature04516]

13 **Nakchbandi IA**, van der Merwe SW. Current understanding of osteoporosis associated with liver disease. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 660-670 [PMID: 19881518 DOI: 10.1038/nrgastro.2009.166]

14 **Park CH**, Joo YE, Choi SK, Rew JS, Kim SJ. Klebsiella pneumoniae septic arthritis in a cirrhotic patient with hepatocellular carcinoma. *J Korean Med Sci* 2004; **19**: 608-610 [PMID: 15308857 DOI: 10.3346/jkms.2004.19.4.608]

15 **Kalafateli M**, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, de Vos M, Papadimitriou K, Thorburn D, O'Beirne J, Patch D, Pinzani M, Morgan MY, Agarwal B, Yu D, Burroughs AK, Tsochatzis EA. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. *J Cachexia Sarcopenia Muscle* 2017; **8**: 113-121 [PMID: 27239424 DOI: 10.1002/jcsm.12095]

16 **Deleuran T**, Overgaard S, Vilstrup H, Jepsen P. Cirrhosis is a risk factor for total hip arthroplasty for avascular necrosis. *Acta Orthop* 2016; **87**: 231-234 [PMID: 26900635 DOI: 10.3109/17453674.2016.1151122]

17 **Salomon B**, Krause PC, Dasa V, Shi L, Jones D, Chapple AG. The Impact of Hepatitis C and Liver Disease on Risk of Complications After Total Hip and Knee Arthroplasty: Analysis of Administrative Data From Louisiana and Texas. *Arthroplast Today* 2021; **7**: 200-207 [PMID: 33553550 DOI: 10.1016/j.artd.2020.12.016]

18 **Lara-Medrano R,** Alcázar-Quiñones C, Galarza-Delgado DÁ, Baena-Trejo L. Impact of a fall prevention program in the Internal Medicine wards of a tertiary care university hospital. *Med Univ* 2014; **16**: 156-160. Available from: https://www.elsevier.es/en-revista-medicina-universitaria-304-articulo-impact-fall-prevention-program-in-X1665579614675994

19 **Naseer M**, Turse EP, Syed A, Dailey FE, Zatreh M, Tahan V. Interventions to improve sarcopenia in cirrhosis: A systematic review. *World J Clin Cases* 2019; **7**: 156-170 [PMID: 30705893 DOI: 10.12998/wjcc.v7.i2.156]

20 **Hung TH**, Hsieh MH, Lay CJ, Tsai CC, Tsai CC. Increased occurrence of native septic arthritis in adult cirrhotic patients: a population-based three-year follow-up study in Taiwan. *Prz Gastroenterol* 2014; **9**: 342-347 [PMID: 25653729 DOI: 10.5114/pg.2014.47896]

21 **Abdelrahman H**, Shousha M, Bahrami R, Boehm H. Haematogenous Spondylodiscitis in Patients With Liver Cirrhosis: Case Series of 36 Patients. *Spine (Phila Pa 1976)* 2020; **45**: E425-E429 [PMID: 31770341 DOI: 10.1097/BRS.0000000000003326]

22 **Sharma D**, Kc S, Jaisi B. Prevalence of Tuberculosis in Patients with Liver Cirrhosis. *J Nepal Health Res Counc* 2018; **15**: 264-267 [PMID: 29353900 DOI: 10.3126/jnhrc.v15i3.18852]

23 **Jiang SL**, Schairer WW, Bozic KJ. Increased rates of periprosthetic joint infection in patients with cirrhosis undergoing total joint arthroplasty. *Clin Orthop Relat Res* 2014; **472**: 2483-2491 [PMID: 24711129 DOI: 10.1007/s11999-014-3593-y]

24 **Barbu EC**, Chițu-Tișu CE, Lazăr M, Olariu C, Bojincă M, Ionescu RA, Ion DA, Bădărău IA. Hepatic Osteodystrophy: A Global (Re)View of the Problem. *Acta Clin Croat* 2017; **56**: 512-525 [PMID: 29479918 DOI: 10.20471/acc.2017.56.03.19]

25 **Saeki C**, Tsubota A. Influencing Factors and Molecular Pathogenesis of Sarcopenia and Osteosarcopenia in Chronic Liver Disease. *Life (Basel)* 2021; **11** [PMID: 34575048 DOI: 10.3390/Life11090899]

26 **Tokuchi Y**, Suda G, Kimura M, Maehara O, Kitagataya T, Kubo A, Yoshida S, Fu Q, Yang Z, Hosoda S, Ohara M, Yamada R, Suzuki K, Kawagishi N, Nakai M, Sho T, Natsuizaka M, Morikawa K, Ogawa K, Ohnishi S, Sakamoto N. Possible correlation between increased serum free carnitine levels and increased skeletal muscle mass following HCV eradication by direct acting antivirals. *Sci Rep* 2021; **11**: 16616 [PMID: 34400736 DOI: 10.1038/s41598-021-96203-z]

**Footnotes**

**Conflict-of-interest statement:** All authors report no relevant conflict of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** December 25, 2021

**First decision:** February 15, 2022

**Article in press:** June 26, 2022

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Switzerland

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Caballero-Mateos AM, Spain; Kim DJ, South Korea; Rodrigues AT, Brazil; Wu SZ, China **S-Editor:** Wu YXJ **L-Editor:** Filipodia **P-Editor:** Wu YXJ



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**