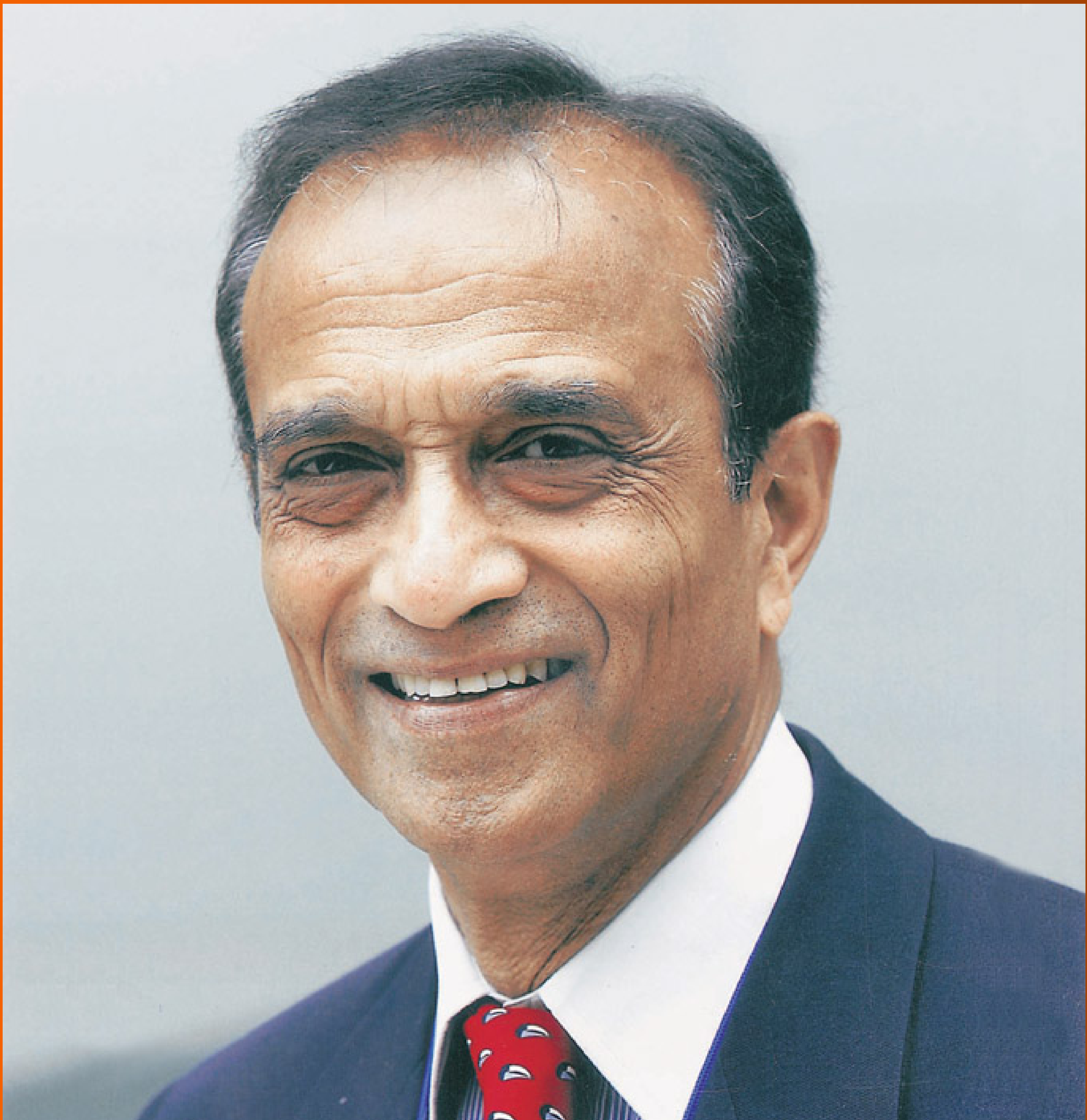
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2019 July 28; 25(28): 3664-3837



Published by Baishideng Publishing Group Inc

WJG World Journal of Gastroenterology

Contents

Weekly Volume 25 Number 28 July 28, 2019

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Rakesh Kumar Tandon, MD, PhD, Doctor, Professor, Department of Gastroenterology, Pushpawati Singhania Research Institute for Liver, Renal and Digestive Diseases, Sheikh Sarai-Phase II, New Delhi 110017, Delhi, India

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 701 experts in gastroenterology and hepatology from 58 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, *etc*. The *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for *WJG* as 3.411 (5-year impact factor: 3.579), ranking *WJG* as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Subrata Ghosh, Andrzej S. Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

EDITORIAL OFFICE
Ze-Mao Gong, Director

PUBLICATION DATE
July 28, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2019 July 28; 25(28): 3669-3683

DOI: 10.3748/wjg.v25.i28.3669

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

OPINION REVIEW

Importance of fatigue and its measurement in chronic liver disease

Lynn H Gerber, Ali A Weinstein, Rohini Mehta, Zobair M Younossi

ORCID number: Lynn H Gerber (0000-0001-7525-680x); Ali A Weinstein (0000-0002-3371-6086); Rohini Mehta (0000-0001-5046-336x); Zobair M Younossi (0000-0001-9313-577x).

Author contributions: Gerber LH, Weinstein AA and Younossi ZM participated in the conceptualization of the paper; Gerber LH, Weinstein AA and Rohini M drafted the manuscript; Gerber LH, Weinstein AA, Rohini M and Younossi ZM edited and finalized the manuscript.

Conflict-of-interest statement: Authors have no conflict of interest to disclose.

Open-Access: This 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 Non Commercial (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: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: April 6, 2019
Peer-review started: April 8, 2019
First decision: May 30, 2019
Revised: June 10, 2019
Accepted: June 22, 2019
Article in press: June 23, 2019
Published online: July 28, 2019

P-Reviewer: Akbulut S

Lynn H Gerber, Zobair M Younossi, Department of Medicine, Beatty Center for Liver and Obesity Research, Inova Health System, Falls Church, VA 22042, United States

Ali A Weinstein, Center for the Study of Chronic Illness and Disability, George Mason University, Fairfax, VA 22030, United States

Rohini Mehta, Beatty Center for Liver and Obesity Research, Inova Health System, Falls Church, VA 22042, United States

Corresponding author: Lynn H Gerber, MD, Professor, Department of Medicine, Fairfax Medical Campus, Inova Health System, 3300 Gallows Rd, Falls Church, VA 22042, United States. ngerber1@gmu.edu
Telephone: +1-703-7764027
Fax: +1-703-7764388

Abstract

The mechanisms of fatigue in the group of people with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are protean. The liver is central in the pathogenesis of fatigue because it uniquely regulates much of the storage, release and production of substrate for energy generation. It is exquisitely sensitive to the feedback controlling the uptake and release of these energy generation substrates. Metabolic contributors to fatigue, beginning with the uptake of substrate from the gut, the passage through the portal system to hepatic storage and release of energy to target organs (muscle and brain) are central to understanding fatigue in patients with chronic liver disease. Inflammation either causing or resulting from chronic liver disease contributes to fatigue, although inflammation has not been demonstrated to be causal. It is this unique combination of factors, the nexus of metabolic abnormality and the inflammatory burden of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis that creates pathways to different types of fatigue. Many use the terms central and peripheral fatigue. Central fatigue is characterized by a lack of self-motivation and can manifest both in physical and mental activities. Peripheral fatigue is classically manifested by neuromuscular dysfunction and muscle weakness. Therefore, the distinction is often seen as a difference between intention (central fatigue) *versus* ability (peripheral fatigue). New approaches to measuring fatigue include the use of objective measures as well as patient reported outcomes. These measures have improved the precision with which we are able to describe fatigue. The measures of fatigue severity and its impact on usual daily routines in this population have also been improved, and they are more generally accepted as reliable and sensitive. Several approaches to evaluating fatigue and developing endpoints for treatment have relied of biosignatures associated with fatigue. These have been used singly or in combination and include: physical performance measures, cognitive performance

S-Editor: Ma RY
L-Editor: Filipodia
E-Editor: Zhang YL

measures, mood/behavioral measures, brain imaging and serological measures. Treatment with non-pharmacological agents have been shown to be effective in symptom reduction, whereas pharmacological agents have not been shown effective.

Key words: Fatigue; Chronic liver disease; Non-alcoholic fatty liver diseases; Non-alcoholic steatohepatitis; Measurement; Patient-reported outcomes

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Fatigue is prevalent, persistent and complex in people with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Fatigue can be analyzed in terms of peripheral and central fatigue, increasing precision of evaluation while elucidating causes and improving treatment. The liver is central to the pathogenesis of fatigue, which in our view, is dependent upon energy regulation. Biosignatures for fatigue are being tested that reflect metabolic and inflammatory pathways of relevance. Non-pharmacological treatments including weight loss, aerobic and resistance exercise are effective in treating fatigue in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Pharmacological agents to date have not been shown to have a significant/reliable effect in reducing fatigue.

Citation: Gerber LH, Weinstein AA, Mehta R, Younossi ZM. Importance of fatigue and its measurement in chronic liver disease. *World J Gastroenterol* 2019; 25(28): 3669-3683
URL: https://www.wjgnet.com/1007-9327/full/v25/i28/3669.htm
DOI: https://dx.doi.org/10.3748/wjg.v25.i28.3669

INTRODUCTION

Fatigue is a critical component of chronic liver disease (CLD)[1]. It is common, complex, confusing and challenging to treat. It is thought to be the hallmark of certain diseases, including autoimmune diseases and chronic congestive heart failure, and is known to accompany many chronic illnesses including cancer, primary biliary cholangitis, sclerosing cholangitis and other cholestatic types of CLD. Relatively recently, investigators have identified that fatigue may also associate with non-alcoholic fatty liver diseases (NAFLD) and non-alcoholic steatohepatitis (NASH)[2]. This lag in recognition of an association with NAFLD/NASH is, in the opinion of the authors, in part because NAFLD/NASH have only recently been described as a clinical entity, and it is considered a "silent" disease with low symptom burden. Additionally, the role of the liver in the pathogenesis of fatigue has not been well understood, and it has been attributed to other causes such as autonomic dysfunction, sedentary behavior and sickness behavior/hypothalamic-pituitary axis dysfunction[2,3].

Our point of view, based on our and others' research with patients with chronic hepatitis C (CHC) and NAFLD/NASH, leads us to a somewhat different perspective. That is, that while the mechanisms of fatigue are protean in the group of people with NAFLD/NASH and CHC, the liver is central in its pathogenesis. It uniquely regulates much of the storage, release and production of substrate for energy generation. It is exquisitely sensitive to the feedback controlling the uptake and release of these energy generation substrates. Metabolic contributors to fatigue, beginning with the uptake of substrate from the gut, the passage through the portal system to hepatic storage and release of energy to target organs (muscle and brain) are central to understanding fatigue in patients with CLD and possibly others.

In addition to energy needs for normal function, the level of inflammation either causing or resulting from CLD contributes to fatigue, although inflammation has not been demonstrated to be causal. It is this unique combination of factors, the nexus of metabolic abnormality and the inflammatory burden of NAFLD/NASH and CHC that creates pathways to different types of fatigue (*i.e.*, central and peripheral fatigue which will be discussed below). These pathways, in our opinion, create guidance for assessment, endpoints for treatments and possible interventions.

Primary fatigue, which is fatigue not associated with an accepted underlying fatigue-causing disease mechanism such as tumor, heart failure, anemia, thyroid dysfunction or medications, is especially difficult to treat. Frequently, depressive symptoms accompany fatigue, and people with CLD are treated for depression or are treated for insomnia. These may be effective in treating primary depression or insomnia but are not shown to be effective for treating fatigue. These observations lead us to support the view that exercise is among the highly specific and effective treatments for fatigue associated with NAFLD/NASH and CHC.

Why are we writing this opinion piece? We are attempting to provide a context in which fatigue is understood and can be clinically evaluated so that it can be distinguished from somnolence, mood disturbance or other co-morbidities often associated with fatigue. New approaches on how to measure fatigue include use of objective measures and patient reported outcomes (PROs). These measures have improved the precision with which we are able to describe fatigue. The measures of fatigue severity and its impact on usual daily routines in this population have also been improved and more generally accepted as reliable and sensitive.

This paper will discuss fatigue in CLD and possible mechanisms, review which treatment approaches may be effective in controlling symptoms and will discuss future opportunities for research that may lead to biosignatures such as performance and serological measures to assess fatigue.

FATIGUE AS A CONSTRUCT

Fatigue is common and experienced by virtually everyone during the course of their lives[4]. However, fatigue is difficult to characterize and define because it encompasses a complex interaction between biological, psychosocial and behavioral processes[5]. Therefore, it is important to differentiate it from other related constructs, such as sleepiness, while still creating clear definitions for fatigue[6]. To follow along with this example, sleepiness is simply the propensity to fall asleep, while fatigue can be overall tiredness that is not corrected by sleep. Clear distinctions can be drawn when exact definitions and terminology are utilized. Fatigue needs to be differentiated from symptoms of somnolence (*i.e.*, the quality or state of being drowsy), dyspnea (*i.e.*, difficult or labored respiration), boredom and weakness.

The most common types of fatigue that are used in the literature are central and peripheral[7]. However, it is important to be aware that these types of fatigue are defined differently across disciplines[8]. Again, clear and exact terminology is important when types of fatigue are discussed. In our research, we have been able to demonstrate clear distinctions between mental (central) and physical (peripheral) fatigue[9]. Central fatigue is characterized by a lack of self-motivation and can manifest both in physical and mental activities. Peripheral fatigue has been classically manifested by neuromuscular dysfunction and muscle weakness[7]. Therefore, the distinction has been about intention (central) *versus* ability (peripheral). It is important to also consider the types of activities. Fatigue can be experienced differently when performing a physical task *versus* performing a mental task[10].

For those with CLD, both dimensions of fatigue have been shown to be present[11]. However, this one categorization may not be sufficient to provide sensitive assessment of fatigue. In our qualitative work, we were able to show additional dimensions of fatigue that might be useful for treatment and research purposes[12]. Capacity across both the central and peripheral domains was an important distinction for patients. Fatigue and energy level were intricately linked and therefore capacity became a way for patients to describe their access to energy (access), their rapid depletion of energy (depletion) and their ability to restore energy once it was used (restoration). We believe that the inclusion of these concepts (access, depletion and restoration) would help to add depth to our understanding of fatigue across the central and peripheral domains. Recently, there have been many reviews of fatigue in the context of liver disease (see Table 1 for a summary of recent reviews). Fatigue has a profound effect on patients' quality of life[2]. There is a need to increase the depth of our understanding of fatigue in order to be able to better treat it.

FATIGUE IN LIVER DISEASE

Prevalence

Estimates of the prevalence of fatigue differ across different studies. However, in the general population it ranges from 5%-7%[13]. For patients within a primary care practice, the prevalence increases to between 10%-25%[13], and in individuals with chronic illness the prevalence ranges widely depending on the illness (from 20%-60%)[14]. In CLD, the prevalence ranges between 50%-85%[11]. Fatigue is the most

Table 1 Summary of recently published reviews specifically on fatigue in liver disease

Article title
Fatigue in chronic liver disease: New insights and therapeutic approaches[3]
Fatigue complicating chronic liver disease[95]
Depression, fatigue and neurocognitive deficits in chronic hepatitis C[96]
Patient-Reported outcomes and fatigue in patients with chronic hepatitis C infection[21]
Future directions for investigation of fatigue in chronic hepatitis C viral infection[97]
Fatigue, depression and chronic hepatitis C infection[98]
Fatigue in cholestatic liver disease-a perplexing symptom[99]
Fatigue in liver disease: Pathophysiology and clinical management[11]
Understanding and treating fatigue in primary biliary cirrhosis (cholangitis) and primary sclerosing cholangitis[19]
Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders[30]
Fatigue in primary biliary cirrhosis (cholangitis)[100]
Complications, symptoms, quality of life and pregnancy in cholestatic liver disease[101]
Fatigue in primary biliary cirrhosis (cholangitis)[102]

commonly reported symptom in CLD, and it is also the symptom that most often gets individuals to visit their doctors[15]. In addition, the severity of fatigue does not seem to be associated with biochemical or histological parameters of liver disease severity, although the data are mixed on this point[16].

Measurement

Although there is a proliferation of measurement tools to assess fatigue, there is no instrument that can provide both specificity and sensitivity for measuring fatigue. The lack of a tool is part of the problem that leads to under diagnosis, under recognition, and under treatment of fatigue in CLD patients. Part of the issue is that the tools that are currently used do not adequately capture the complexity and dimensionality of fatigue[17]. None of the commonly used tools address all aspects of fatigue. Commonly assessed areas include: Descriptions or characterizations of fatigue, feelings of distress associated with fatigue, presumed causes of fatigue and consequences of fatigue[18]. It is important to recognize what components of fatigue are being assessed and what components of fatigue should be assessed. Because there are no tools that address all of these components, it is important for researchers to consider what it is about fatigue that is relevant to the current research or patient and use that to drive the selection of a specific measure[17]. Please see Table 2 for a summary of instruments.

SYMPTOMS OF FATIGUE

Fatigue in liver disease is a well-described syndrome and is recognized as prevalent, persistent and problematic. It is the hallmark of primary biliary cholangitis[19], other forms of cirrhosis[20] and has been associated with CHC[21]. In fact, suggestions have been made that clinically significant fatigue should be an indication for anti-viral therapy[22]. Unlike cancer and myalgic encephalomyelitis/chronic fatigue syndrome (MECFS), there are no specific criteria for a “liver related fatigue” syndrome. However, much of the fatigue literature in hepatology does derive from the excellent work done by the National Cancer Consortium Network in an effort to raise awareness of cancer-related fatigue and to define it[23]. The field has also been influenced by the Centers for Disease Control and Prevention, who has championed the cause of devising criteria for diagnosis of MECFS and the National Institutes of Health, who has spearheaded the need for using common data elements in developing a standard approach to evaluation and performing research into MECFS[24]. These efforts have led to consensus that chronic fatigue is a persistent perception of tiredness that interferes with function, needed and desired activities and is often distressing and difficult to treat[25,26].

One important observation from one of our studies[27] is that the descriptive variables (PRO profiles as well as the serum analytes) differed between people with central fatigue compared with peripheral fatigue. These differences may help in planning treatment.

Chronic fatigue implies fatigue most days for at least a duration of 3 mo. Additionally, it is a multi-dimensional symptom and may be experienced as tiredness

Table 2 Commonly used measures of fatigue

	Type of assessment	Domain(s) assessed	Length	Used in liver disease?
Fatigue assessment scale[103]	5-point Likert scale	Severity	10 items	Rarely
Fatigue severity scale[104]	7-point Likert scale	Severity, Impact	9 items	Often
Fatigue impact scale[105]	5-point Likert scale	Physical, Cognitive, Psychosocial	40 items	Sometimes
Fatigue scale[106]	4-point Likert scale	Physical, Mental	11 items	Rarely
Multidimensional Assessment of Fatigue[107]	Visual analog scale	Severity, Distress, Impact on Activities	14 items	Rarely
Multidimensional fatigue inventory[108]	5-point Likert scale	General, Physical, Activity, Motivation, Mental	20 items	Sometimes
Visual analog fatigue scale[109]	Visual analog scale	Energy, Fatigue	18 items	Rarely
Functional assessment of chronic illness therapy fatigue scale[110]	5-point Likert scale	Severity, Impact	13 items	Often
Sf-36 vitality scale[111]	5-point Likert scale	Energy	4 items	Often
Chronic liver disease questionnaire fatigue scale[112]	7-point Likert scale	Energy	5 items	Often
PROMIS®-fatigue[113]	5-point Likert scale	Severity	Variable[1]	Rarely

[1]PROMIS® is a computer adaptive test where the specific questions and number of questions is tailored to the individual using item response theory techniques. Usually the number of items will range between 4-12.

in the musculoskeletal system, cognitive decline or fuzzy thinking , muscle fatigue, poor recovery from exercise and decreased motivation for usual activities. See Table 3, which was taken from the International Classification of Disease 10th edition for diagnosis of cancer related fatigue.

The experiential aspects of fatigue may be influenced by age, culture, comorbidities, pain, mood, sleep and affect[28]. In fact, there is a significant interest in the possibility of symptom clusters, such as pain, fatigue, anxiety, depression and insomnia having a common etiology or genetic basis[29]. This is understandable given the overlapping nature of many of the symptoms. This presents a diagnostic and therapeutic dilemma because of the overlap between depressive symptoms and fatigue[30]. In fact, it is believed by some investigators that the word “fatigue” may be used interchangeably or may be a residual sign of depression[31,32].

The relationship between depression and/or depressive symptoms and fatigue suggests additional overlap because of the reported findings of changes in serotonin levels and abnormalities with tryptophan pathway regulation that is common in the depression and fatigue literatures[27,33-37]. Not only does this create diagnostic confusion, but it often leads to treatments for depression, which may not be helpful for reducing fatigue.

Additionally, we rely upon patients and research participants to “fit” their symptoms into standardized evaluations that have specific descriptors about level of intensity. Responses are stereotyped and not personalized, and as a result we get a limited amount of information about what individuals are truly experiencing. Our research group attempted to learn about how people with liver disease are likely to express their symptoms of fatigue (as discussed above)[12]. In this study we provided groups with CHC infection an opportunity to describe their fatigue using any adjective or metaphors they chose. They spoke of the dimensions of the fatigue in terms of intensity, frequency and duration. There were references to having limited capacity to do the things they wished to do. Further, that their energy stores often depleted rapidly without having the restorative power to recharge. Or they were unable to access the energy in order to do things they wished or needed to do. The presentation of their perceptions of fatigue and its impact helped us understand what they were experiencing and how central fatigue influences their functioning and well-being. Other investigators have made similar points about how important fatigue is to an individual[38].

Despite the fact that there is no unique signature describing fatigue associated with liver disease, many of the symptoms patients report are consistent with fatigue syndromes previously reported by investigators assessing cancer and MECFS. Interestingly, as in these other diagnoses, fatigue may associate with other symptoms in clusters of pain, anxiety, depression and insomnia. But with recent advances, there

Table 3 Fatigue symptoms for diagnosing pathological fatigue

The symptoms must have been present every (or nearly every) day over a 2-wk period during the past month	
Necessary	Significant fatigue
	Diminished energy
	Increased need to rest disproportionate to level of activity
At least five of these symptoms must be present	Experience of limb heaviness of generalized weakness
	Diminished concentration or attention
	Decreased motivation or interest to engage in usual activities
	Insomnia or hypersomnia
	Experience sleep as unrefreshing or non-restorative
	Perceived need to struggle to overcome inactivity
	Marked emotional reactivity to feeling fatigued
	Perceived problems with short term memory
	Post-exertional malaise for several hours

are published data supporting the constructs of central and peripheral fatigue, whose symptoms and impact are very different. Data are also pointing to serological measures (pro- and anti-inflammatory cytokines and growth factors) that are linked to symptoms of fatigue that can be distinguished using self-reports[9]. A summary of associated symptoms is provided in Table 4.

MECHANISMS OF FATIGUE

Fatigue may be attributed to a mechanism such as neuromotor dysfunction associated with muscle weakness, an organ specific explanation such as hypothyroid state or congestive heart failure. More often, fatigue is used as a non-specific term by patients, and many health care professionals treat it as such without producing a differential diagnosis or seeking a cause for it. Therefore, making the investigation of potential underlying mechanisms of fatigue is an important area.

Central and peripheral fatigue are experienced and measured differently and may be indicators of how the underlying mechanisms of fatigue differ as well. Central fatigue, is mediated by the central nervous system and is characterized by a failure to transmit motor impulses or perform voluntary activities[39], or the inability or reduced ability to perform attentional tasks. Peripheral fatigue, in comparison is a reduction in the ability to exert muscular force after exercise[40] and maintain a maximal force because of muscular limitations[8]. This implies that the source of the fatigue is independent of the muscular apparatus and originates above the neuromuscular junction[41]. A theoretical case can be made for a role for the autonomic nervous system as well[42]. Nonetheless, fatigue has been linked to many specific conditions including: anemia, cancer, cardiac, pulmonary, renal, liver disease, hypothyroid states, nutritional status and medication (Table 4). The assumption is that a deficit or disorder is the cause of the fatigue and correcting the deficit or disorder is likely to reverse the fatigue. When evaluating patients with chronic or "pathological" fatigue, it is advantageous to obtain a full work up to identify possible causative factors of fatigue and/or comorbidities that may contribute to its persistence.

However, there are many possible contributions the liver specifically makes in the pathophysiology of chronic fatigue. One recent review discussed the central role of the liver in metabolism and generation of energy[43]. It creates substrates for the production of ATP responsive to two conditions: (1) When eating and carbohydrate is available, the liver metabolizes glucose into glycogen and fatty acid; and (2) In the fasting state, when it produces energy by metabolizing glycogen *via* glycogenolysis or *via* gluconeogenesis. The liver can also metabolize fatty acid into ketone bodies for energy, but this is less efficient and occurs when glycogen is depleted from the liver[44].

The data supporting the central role of glucose to fatigue has been the result of studies in people with diabetes. This group of patients were studied to assess the relationship between blood glucose level and fatigue as well as the fluctuation in blood sugar levels over time[45,46]. This is an important observation because it supports the view that metabolic homeostasis is likely to be important for sustained physical and cognitive activity and because of the highly correlated conditions of type 2 diabetes and CLD (NAFLD/NASH).

Table 4 Established associations among physical findings, diagnoses and fatigue

Adrenal insufficiency	
Anemia	
Auto-immune diseases	
Cancer	Especially in breast, pancreatic, pulmonary
Cardiac failure	
Deconditioning	
Electrolyte imbalance	
Hypo/hyperthyroidism	
Infection	
Malnutrition	
Medication	Anti-emetics, anti-histamines, anxiolytics, chemotherapy, opioids, radiation, sedatives
Pulmonary	Chronic obstructive pulmonary disease, cystic fibrosis
Renal failure	
Sarcopenia	
Stress	Physiological, hypercortisolism
Symptoms Contributing	Depressive symptoms, insomnia, pain
Syndromes of unknown etiology	Lyme disease, chronic fatigue syndrome
Vitamin deficiency	Especially B complex

The liver is closely connected to extra-hepatic tissues in order to signal energy needs (skeletal muscle, brain), storage (adipose tissue) and substrate (gut). These responses are regulated through hormonal and neuronal networks. The hormonal signaling results from insulin, which stimulates glycolysis and lipogenesis. It suppresses gluconeogenesis and glucagon inhibits the effects of insulin. With respect to the nervous system, both the sympathetic and parasympathetic nervous system are important. The former stimulates and the latter inhibits gluconeogenesis.

In addition, control of liver metabolic processes depends upon several key transcription factors (FOXO1, PGC-1a and others) that control enzyme expression, which in turn controls hepatic metabolic processes[43]. The disruption of energy production and utilization has a profound impact on insulin sensitivity, development of type 2 diabetes and fatty liver. These changes in metabolic status are likely to be related to fatigue.

As mentioned above, the liver is in continual communication with extra-hepatic tissue, and with respect to fatigue it communicates through neuronal and hormonal networks. There are important gastrointestinal hormones that influence hepatic glucose production. Glucagon-like peptide is one that stimulates insulin secretion, and serotonin found in the gut stimulates gluconeogenesis in hepatocytes in the fasting state. Absorption of food and possibly microbiota release substrate through the gastrointestinal tract that send signals to the central nervous system (CNS) *via* the vagus nerve[47-49]. The sympathetic nervous system and parasympathetic nervous system both work through the CNS (hypothalamus) to regulate hepatic glucose production. Sympathetic nervous system activity increases glucose production and mobilizes substrate to extra-hepatic tissue (*e.g.*, muscle, brain) and parasympathetic nervous system inhibits it[50]. Insulin signaling has an effect on the hypothalamus to stimulate interleukin (IL)-6 production, which suppresses gluconeogenesis[51]. The role of this pro-inflammatory cytokine is also thought to contribute to the progression of steatosis to steatohepatitis[52]. IL-6 is involved in inflammatory and metabolic changes that may stimulate synthesis of other cytokines that induce cell migration and initiate healing processes, including fibrosis development of steatohepatitis[53]. Skeletal muscle has endocrine properties and has been shown to be able to secrete myokines, which are inflammatory peptides. Myokines are involved in the inflammatory response, and physical activity plays a key role in down-regulating their release[54].

Many peripheral factors at the gut, liver and skeletal muscle level, central factors involving a variety of hormones including leptin and growth hormone regulate gluconeogenesis and insulin resistance. The latter is critical to the development of NAFLD and/or type 2 diabetes. Both conditions are associated with metabolic imbalances, metabolic stress and energy production inefficiencies (all of which promote insulin resistance in the liver)[55]. The CNS plays a key role in the perception of fatigue. It is likely that changes in neuronal signaling within the brain gives rise to changes in perceptions of fatigue and influences behavior. Swain *et al*[3] suggested in a recent review that there are several possible peripheral pathways by which liver inflammation can relay information to the brain that enhances fatigue perception. Signals include inflammation of: (1) The neural pathways *via* vagal nerve afferents; (2) Direct effect *via* transport through the circulation of pro-inflammatory cytokines; and (3) *Via* immune cells in the liver (Kupffer cells, stellate cells, natural killer cells) and recruited neutrophils, monocytes and macrophages[56]. They further suggested that there is evidence linking the basal ganglia to central fatigue[3]. Others identify a critical role for the hypothalamic pituitary adrenal axis (HPA axis). A recent review of its potential mechanisms that contribute to fatigue in cholestasis is available[57].

Because the HPA axis controls many functions of the liver through neuroendocrine pathways as well as mediating inflammation, it is thought to influence cellular and molecular processes in the liver. Fatigue, asthenia and muscular weakness, which can get worse during stress and infection[58], have been correlated with an impaired stress response due to HPA axis dysfunction. Interactions of the HPA axis with the liver also stimulate release of pro-inflammatory cytokines that stimulate release of glucocorticoids by the adrenals and block bile acid efflux impairing glucocorticoid metabolism[59]. In chronic inflammation, the HPA axis function is suppressed. Some investigators suggest that the common symptoms reported by people with CLD, such as fatigue, asthenia, lack of motivation and depressive symptoms are similar to symptoms associated with chronic fatigue syndrome and are suggestive of suppressed HPA axis[60].

Recent data[33] suggest that the monoamine transmitters are elevated in patients with CHC and persistent fatigue. Specifically, in patients taking direct acting antiviral agents, serotonin levels were significantly decreased at post treatment week 4 compared with baseline. Compared with baseline, there were significant decreases in IL-10 levels at end of treatment and 4 wk post-treatment. Changes in dopamine and tryptophan levels at the end of treatment correlated with increasing emotional health scores. Changes in monocyte chemoattractant protein-1 at end of treatment and IL-8 at 4 wk post-treatment correlated with increasing mental health scores. These data support the view that cytokines are involved in the well-being of patients with CHC. Others have reported significant roles for neurotransmitters, including the tryptophan pathway[34,61].

Borrowing from the literature[25,26] and using our own patient base with CHC and NAFLD/NASH, we have observed that patients display some similar symptoms. These include post-exertional malaise and an aversion to physical exercise/activity. They experience mental fatigue, sleep disruption, mood changes consistent with anxiety, depressive symptoms and decreased quality of life[62,63]. Some have difficulty concentrating and processing information. Most of this resolves with viral eradication shortly after completion of anti-viral therapy[11,27]. However, these symptoms persist in 23%-26% of those who achieve sustained viral eradication (SVR)[27]. When evaluating who within the group with CHC continued to have fatigue after achieving SVR, it was the group that had higher baseline depressive and other affective symptoms[27] and who had a higher number of comorbidities. Additionally, the change in cytokine profile after achieving SVR may be clinically meaningful. High baseline serum levels of interferon-g were associated with fatigue. Reductions in levels of chemokine (C-C motif) ligand 2 were associated with persistent fatigue after 12 wks of SVR. With respect to predictors of fatigue, there are no predictors of central fatigue at baseline if one controls for the diagnosis of depression. However, with respect to peripheral fatigue the best predictors at baseline for peripheral fatigue are IL-10, IL-8 and TNFα. TNFα continues to remain a strong predictor of persistent moderate/severe peripheral fatigue after treatment[27]. The contribution of tryptophan pathways and serotonin to fatigue[27,35] and recently to cognitive deficits[64] demonstrate that there are dynamic changes in the central nervous system within the hypothalamus-hippocampal circuit that cause central fatigue. These changes are associated with increased tryptophan-kynurenic acid pathway activity that causes reduced cognitive function, impaired spatial cognitive memory accuracy and increased hyperactivity and impulsivity[64].

POSSIBLE FATIGUE BIOMARKERS/BIOMARKER SIGNATURES

Current clinical and translational research has led to discussions about possible endpoints for treatment trials and clinical outcomes in managing fatigue. There is interest in the research community to develop objective measures, biomarkers or biomarker signatures for self-reports. According to the National Institutes of Health, "a biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. A biomarker signature is a combination of multiple variables to yield a patient-specific indicator of normal biological processes or responses to an exposure or intervention including therapeutic interventions. Biomarker modalities are diverse, and can include genetic, protein, cellular, metabolomics, imaging, behavioral, and physiologic endpoints"[65].

Fatigue is a symptom or state that is multi-dimensional. Hence measures of and outcomes for treating fatigue would benefit from the use of a multidimensional construct, such as the World Health Organization's International Classification of Functioning, Disability and Health (https://www.who.int/classifications/icf/en/). This provides a framework where one can identify potential contributors to fatigue. For example, anatomic/physiological abnormalities, function, activity and participation in life activities may need to be assessed to thoroughly evaluate fatigue. Potential biomarkers or biomarker signatures for fatigue have emerged with a better understanding of the (1) Fatigue construct; (2) Distinction of central and peripheral fatigue; (3) Potential mechanisms underlying peripheral and central fatigue; and (4) Significant improvement in use of PROs for measuring function and patient experience.

Potential biomarkers/biosignatures for fatigue include: (1) Physical performance: measures such as 6-minute walk times for ambulatory tolerance, up-and-go test for physical mobility, measures of exercise tolerance including gas exchange and strength and local muscle endurance testing; (2) Cognitive performance: measures offer an objective measure of memory, recall, executive functioning and visuospatial processing; (3) Mood/behavioral: measures for depressive symptoms, anxiety, pain and insomnia; and (4) Brain imaging: imaging studies have provided some new insights into brain metabolic activity, but there is no consensus about its meaning with respect to function. Some suggest that functional magnetic resonance imaging is useful in measuring cognitive fatigue[6,40]. These data provide direct support for the Chaudhuri and Behan model of "central" fatigue that suggests these are non-motor functions of the basal ganglia. Some claim there are no associations between fatigue and attention, cognitive performance and brain structure[66]. Others have shown correlations between brain volume[67] and brain health[68]. Despite these differences, imaging is very likely to serve as a biomarker for brain health and possible cognitive function and fatigue in the future[6].

Evidence exists for the role of pro-inflammatory cytokines in CLD. TNFα, IL-1β and IL-6 are elevated during the viremic phase of CHC and decrease after achieving SVR. This observation is temporally related to improved fatigue symptoms[27]. The literature on IL-1 is noteworthy, despite lack of data specifically for NAFLD/NASH and CHC. There are data for type 2 diabetes and because people with NAFLD are often diabetic, the findings may have significant relevance. Cavelti-Weder *et al*[69] assessed the efficacy of a monoclonal anti-IL-1β antibody compared to placebo in 30 type 2 diabetes patients. Fatigue was reported by 53% of patients and significantly correlated to diabetes duration but not to age. After treatment for 1 mo, fatigue decreased in the groups treated with moderate- and high-dose anti-IL-1β but not in the placebo group.

It is likely that a combination of these measures will need to be configured in order to identify endpoints for clinical trials of fatigue and may serve as treatment targets to better manage the symptom.

FATIGUE SPECIFIC TREATMENTS

Non-pharmacological approaches

A significant amount of literature has been written about the treatment of fatigue in MECFS and cancer related fatigue[70-72]. These reviews discuss a variety of non-pharmacological approaches to fatigue management including weight loss, exercise, dietary supplements, acupuncture, insomnia treatment and cognitive and behavioral interventions. These have helped guide treatment for fatigue in CLD.

With respect to CLD however, there are far fewer disease specific interventions that have been tested and shown to be promising. Starting with an approach to this problem is the TrACE model discussed by Swain[3]. This useful approach includes treating the treatable causes of fatigue (*i.e.*, anemia, other comorbidities), ameliorating the modifiable symptoms (*i.e.*, reduce symptom burden of sleepiness, depressive symptoms), coping and empathizing.

There is very little doubt on the effectiveness of exercise and diet/weight loss alone or in combination for treatment of CLD related fatigue[73-77]; and experts have indicated that this type of intervention is worth the effort[78]. Exercise and dietary interventions appear to be effective by mobilizing fat from the liver, increasing insulin sensitivity, improving endothelial function, reducing oxidative stress and decreasing inflammation[54].

Several mechanisms have been postulated. One is that training increases peroxisome proliferator-activated receptor gamma coactivator 1-alpha expression, improves mitochondrial function and leads to reduced hepatic steatosis and inflammation[79]. An excellent review of mechanisms of action of exercise in NAFLD is available[79]. Further, exercise and to some degree increased activity improve all-cause and cardiovascular mortality[80-83]. There is ongoing research to determine the comparative effectiveness of aerobic training *versus* anaerobic training (*e.g.*, resistance training) in NAFLD/NASH. As of now, both are recommended[84].

The mechanisms by which exercise works is beginning to emerge and includes direct effects on metabolic regulation and increased cardiovascular resilience. Recently, the effects of exercise on the tryptophan clearance by activation of kynurenine pathway of tryptophan metabolism (Figure 1), which has been shown to mitigate fatigue[85] were reported. Tryptophan is the substrate for kynurenine (kynurenine pathway) as well as serotonin (serotonin pathway). Kynurenine and serotonin can cross the blood brain barrier and influence mood, cognition and fatigue[86]. Thus, peripheral tissues have a large impact on metabolism of kynurenine and serotonin and their availability to the CNS. Exercise stimulates not only the catabolism of tryptophan but also the clearance of kynurenine as kynurenic acid thereby reducing availability of kynurenine for transport across the blood brain barrier[87]. There is also a general improvement in insomnia, hypertension and mood.

In our experience, people who are sedentary, overweight, working, managing families and often feeling overwhelmed find it hard to commit to an active lifestyle and/or a specific exercise regimen. Self-efficacy and illness understanding are major determinants of lifestyle-modification among NAFLD patients. This information can assist clinicians in improving compliance with lifestyle changes among these patients[88].

Frith *et al*[89] reported that patients with NAFLD have significant fear of failing to meet expectations and lack confidence to proceed with an exercise program, which are factors that are modifiable. A recent study suggested that patients with NAFLD, supported by a Web-based approach, can increase the VO_{2peak} to a similar extent as in-person interventions[90]. They noted that patients with low body fat and low VO_{2peak} benefited the most.

The published literature on predictors for or factors promoting adherence to long-term exercise does not lead to a consensus of how to achieve this. A very good review[91] identified many factors and cited conflicting findings including: poorer health (trending towards increased adherence), depression (trending toward decreased adherence) and life stresses (trending toward decreased adherence). One fairly consistent factor influencing adherence included enabling patients to self-select their exercise programs and have flexibility in the types, duration and locations in which they are implemented[91]. Most of the published literature comes from the cardiovascular, cancer and geriatric populations.

Pharmacological agents

Much of the literature on the pharmacological treatment of fatigue in NAFLD is preclinical and is based on metabolism of tryptophan[92]. In the clinical setting, altered serotonergic neurotransmission has been reported in hepatitis C patients with fatigue, and treatment with serotonin receptor antagonists have been linked with improvements in fatigue as documented in patients with hepatitis C that were treated with ondansetron, a 5-HT3 receptor antagonist[93]. Additionally, s-adenosylmethionine (a methyl donor) is thought to work through the dopamine pathway and has been shown to mitigate symptoms of depression. Clinically, the level of evidence of effectiveness is low, although some therapeutic benefits have been reported in terms of fatigue reduction in people with intrahepatic cholestasis[3,94].

CONCLUSION

Fatigue is prevalent and persistent in people with NAFLD/NASH. Fatigue is a multi-domain construct whose deconstruction into central and peripheral fatigue enables us to better evaluate the condition and identify potential causes and/or correlates. Liver is central to the pathogenesis of peripheral and central fatigue, which in our view is dependent upon energy regulation and crosstalk between the gut, liver, muscle and brain. Measurement of fatigue has improved such that performance (objective) and PROs can effectively be used to identify potential causal factors, treatments and

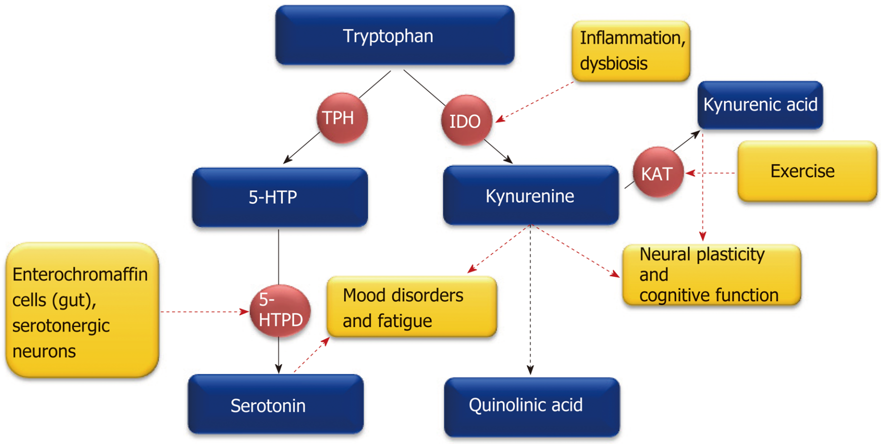


Figure 1 Tryptophan metabolism and the physiological role of its metabolites.

endpoints for treatment. Although further work is needed to provide even more specificity to the fatigue construct and its measurement. Biosignatures for fatigue are being tested and validated that reflect metabolic and inflammatory pathways of relevance. Non-pharmacological treatments have been explored and shown to be effective in NAFLD, NASH, and CHC. These include weight loss and aerobic and resistance exercise. Pharmacological agents to date have not been shown to have a significant, reliable effect in reducing fatigue.

REFERENCES

1 **Poynard T**, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, Ghillani P, Charlotte F, Piette JC, Moussalli J; Multivirc group. Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 2002; **9**: 295-303 [PMID: 12081607]

2 **Newton JL**. Systemic symptoms in non-alcoholic fatty liver disease. *Dig Dis* 2010; **28**: 214-219 [PMID: 20460914 DOI: 10.1159/000282089]

3 **Swain MG**, Jones DEJ. Fatigue in chronic liver disease: New insights and therapeutic approaches. *Liver Int* 2019; **39**: 6-19 [PMID: 29935104 DOI: 10.1111/liv.13919]

4 **Jason LA**, Evans M, Brown M, Porter N. What is fatigue? Pathological and nonpathological fatigue. *PM R* 2010; **2**: 327-331 [PMID: 20656613 DOI: 10.1016/j.pmrj.2010.03.028]

5 **Bower JE**. Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol* 2014; **11**: 597-609 [PMID: 25113839 DOI: 10.1038/nrclinonc.2014.127]

6 Fatigue as a window to the brain. Cambridge, MA: MIT Press, 2005

7 **Cantor F**. Central and peripheral fatigue: exemplified by multiple sclerosis and myasthenia gravis. *PM R* 2010; **2**: 399-405 [PMID: 20656621 DOI: 10.1016/j.pmrj.2010.04.012]

8 **Chaudhuri A**, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* 2000; **179**: 34-42 [PMID: 11054483]

9 **Weinstein AA**, Diao G, Baghi H, Escheik C, Gerber LH, Younossi ZM. Demonstration of two types of fatigue in subjects with chronic liver disease using factor analysis. *Qual Life Res* 2017; **26**: 1777-1784 [PMID: 28224256 DOI: 10.1007/s11136-017-1516-6]

10 **Holtzer R**, Shuman M, Mahoney JR, Lipton R, Verghese J. Cognitive fatigue defined in the context of attention networks. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2011; **18**: 108-128 [PMID: 21128132 DOI: 10.1080/13825585.2010.517826]

11 **Swain MG**. Fatigue in liver disease: pathophysiology and clinical management. *Can J Gastroenterol* 2006; **20**: 181-188 [PMID: 16550262]

12 **Spataro C**, Afdhal S, Weinstein AA, Escheik C, Austin P, Brodie K, Gerber L, Younossi ZM. Fatigue and Hepatitis C: a focus group study. *Qual Res Med Healthc* 2017; 1 [DOI: 10.4081/qrmh.2017.6698]

13 **Bates DW**, Schmitt W, Buchwald D, Ware NC, Lee J, Thoyer E, Kornish RJ, Komaroff AL. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. *Arch Intern Med* 1993; **153**: 2759-2765 [PMID: 8257251]

14 **Swain MG**. Fatigue in chronic disease. *Clin Sci (Lond)* 2000; **99**: 1-8 [PMID: 10887052]

15 **Kant IJ**, Bültmann U, Schröer KA, Beurskens AJ, Van Amelsvoort LG, Swaen GM. An epidemiological approach to study fatigue in the working population: the Maastricht Cohort Study. *Occup Environ Med* 2003; **60** Suppl 1: i32-i39 [PMID: 12782745]

16 **Newton JL**, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, Day CP. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut* 2008; **57**: 807-813 [PMID: 18270241 DOI: 10.1136/gut.2007.139303]

17 **Aaronson LS**, Teel CS, Cassmeyer V, Neuberger GB, Pallikkathayil L, Pierce J, Press AN, Williams PD, Wingate A. Defining and measuring fatigue. *Image J Nurs Sch* 1999; **31**: 45-50 [PMID: 10081212]

18 **Whitehead L**. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manage* 2009; **37**: 107-128 [PMID: 19111779 DOI: 10.1016/j.jpainsymman.2007.08.019]

19 **Jopson L**, Dyson JK, Jones DE. Understanding and Treating Fatigue in Primary Biliary Cirrhosis and

Primary Sclerosing Cholangitis. *Clin Liver Dis* 2016; **20**: 131-142 [PMID: 26593295 DOI: 10.1016/j.cld.2015.08.007]
20 **Kalaitzakis E**, Josefsson A, Castedal M, Henfridsson P, Bengtsson M, Hugosson I, Andersson B, Björnsson E. Factors Related to Fatigue in Patients With Cirrhosis Before and After Liver Transplantation. *Clin Gastroenterol Hepatol* 2012; **10**: 174-181.e1 [PMID: 21839709 DOI: 10.1016/j.cgh.2011.07.029]
21 **Golabi P**, Sayiner M, Bush H, Gerber LH, Younossi ZM. Patient-Reported Outcomes and Fatigue in Patients with Chronic Hepatitis C Infection. *Clin Liver Dis* 2017; **21**: 565-578 [PMID: 28689594 DOI: 10.1016/j.cld.2017.03.011]
22 **Smith ME**, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, Fu R, Nelson HD. Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015; **162**: 841-850 [PMID: 26075755 DOI: 10.7326/M15-0114]
23 **Berger AM**, Abernethy AP, Atkinson A, Barsevick AM, Breitbart WS, Cella D, Cimprich B, Cleeland C, Eisenberger MA, Escalante CP, Jacobsen PB, Kaldor P, Ligibel JA, Murphy BA, O'Connor T, Pirl WF, Rodler E, Rugo HS, Thomas J, Wagner LI. NCCN Clinical Practice Guidelines Cancer-related fatigue. *J Natl Compr Canc Netw* 2010; **8**: 904-931 [PMID: 20870636]
24 **Feldman R**, Gay K, Ala'i S, Esterlitz J, Sheikh M, Tanveer S, Joseph K, Unger E, Whittemore V. A Common Language for Clinical Research Studies: The National Institute of Neurological Disorders and Stroke (NINDS) and Centers for Disease Control and Prevention (CDC) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Common Data Elements (CDEs) (P2.016). *Neurology* 2018; **90**: P2.016
25 **Wessely S**, Chalder T, Hirsch S, Wallace P, Wright D. Psychological symptoms, somatic symptoms, and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in the primary care setting. *Am J Psychiatry* 1996; **153**: 1050-1059 [PMID: 8678174 DOI: 10.1176/ajp.153.8.1050]
26 **Jason L**, Brown M, Evans M, Anderson V, Lerch A, Brown A, Hunnell J, Porter N. Measuring substantial reductions in functioning in patients with chronic fatigue syndrome. *Disabil Rehabil* 2011; **33**: 589-598 [PMID: 20617920 DOI: 10.3109/09638288.2010.503256]
27 **Gerber L**, Estep M, Stepanova M, Escheik C, Weinstein A, Younossi ZM. Effects of Viral Eradication With Ledipasvir and Sofosbuvir, With or Without Ribavirin, on Measures of Fatigue in Patients With Chronic Hepatitis C Virus Infection. *Clin Gastroenterol Hepatol* 2016; **14**: 156-64.e3 [PMID: 26241510 DOI: 10.1016/j.cgh.2015.07.035]
28 **Finsterer J**, Mahjoub SZ. Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Care* 2014; **31**: 562-575 [PMID: 23892338 DOI: 10.1177/1049909113494748]
29 **Miaskowski C**, Barsevick A, Berger A, Casagrande R, Grady PA, Jacobsen P, Kutner J, Patrick D, Zimmerman L, Xiao C, Matocha M, Marden S. Advancing Symptom Science Through Symptom Cluster Research: Expert Panel Proceedings and Recommendations. *J Natl Cancer Inst* 2017; **109** [PMID: 28119347 DOI: 10.1093/jnci/djw253]
30 **D'Mello C**, Swain MG. Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders. *Brain Behav Immun* 2014; **35**: 9-20 [PMID: 24140301 DOI: 10.1016/j.bbi.2013.10.009]
31 **Fava M**, Ball S, Nelson JC, Sparks J, Konechnik T, Classi P, Dube S, Thase ME. Clinical relevance of fatigue as a residual symptom in major depressive disorder. *Depress Anxiety* 2014; **31**: 250-257 [PMID: 24115209 DOI: 10.1002/da.22199]
32 **Targum SD**, Fava M. Fatigue as a residual symptom of depression. *Innov Clin Neurosci* 2011; **8**: 40-43 [PMID: 22132370]
33 **Golabi P**, Elsheikh E, Karrar A, Estep JM, Younossi I, Stepanova M, Gerber L, Younossi ZM. The levels of monoamine neurotransmitters and measures of mental and emotional health in HCV patients treated with ledipasvir (LDV) and sofosbuvir (SOF) with or without ribavirin (RBV). *Medicine (Baltimore)* 2016; **95**: e5066 [PMID: 27861337 DOI: 10.1097/MD.0000000000005066]
34 **Castell LM**, Yamamoto T, Phoenix J, Newsholme EA. The role of tryptophan in fatigue in different conditions of stress. *Adv Exp Med Biol* 1999; **467**: 697-704 [PMID: 10721121]
35 **Jones EA**. Altered central serotoninergic neurotransmission: a potential mechanism for profound fatigue complicating chronic hepatitis C. *Med Hypotheses* 2001; **57**: 133-134 [PMID: 11461159 DOI: 10.1054/mehy.2000.1287]
36 **Müller N**, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry* 2007; **12**: 988-1000 [PMID: 17457312 DOI: 10.1038/sj.mp.4002006]
37 **Dell'Osso L**, Carmassi C, Mucci F, Marazziti D. Depression, Serotonin and Tryptophan. *Curr Pharm Des* 2016; **22**: 949-954 [PMID: 26654774]
38 **Zalai D**, Sherman M, McShane K, Shapiro CM, Carney CE. The importance of fatigue cognitions in chronic hepatitis C infection. *J Psychosom Res* 2015; **78**: 193-198 [PMID: 25433976 DOI: 10.1016/j.jpsychores.2014.11.011]
39 **Chaudhuri A**, Behan PO. Fatigue in neurological disorders. *Lancet* 2004; **363**: 978-988 [PMID: 15043967 DOI: 10.1016/S0140-6736(04)15794-2]
40 **Gandevia SC**, Allen GM, McKenzie DK. Central fatigue. Critical issues, quantification and practical implications. *Adv Exp Med Biol* 1995; **384**: 281-294 [PMID: 8585457]
41 **Taylor JL**, Amann M, Duchateau J, Meeusen R, Rice CL. Neural Contributions to Muscle Fatigue: From the Brain to the Muscle and Back Again. *Med Sci Sports Exerc* 2016; **48**: 2294-2306 [PMID: 27003703 DOI: 10.1249/MSS.0000000000000923]
42 **Austin PW**, Gerber L, Karrar AK. Fatigue in chronic liver disease: exploring the role of the autonomic nervous system. *Liver Int* 2015; **35**: 1489-1491 [PMID: 25588454 DOI: 10.1111/liv.12784]
43 **Rui L**. Energy metabolism in the liver. *Compr Physiol* 2014; **4**: 177-197 [PMID: 24692138 DOI: 10.1002/cphy.c130024]
44 **San-Millán I**, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. *Carcinogenesis* 2017; **38**: 119-133 [PMID: 27993896 DOI: 10.1093/carcin/bgw127]
45 **Fritschi C**, Quinn L. Fatigue in patients with diabetes: a review. *J Psychosom Res* 2010; **69**: 33-41 [PMID: 20630261 DOI: 10.1016/j.jpsychores.2010.01.021]
46 **King P**, Kong MF, Parkin H, Macdonald IA, Tattersall RB. Well-being, cerebral function, and physical fatigue after nocturnal hypoglycemia in IDDM. *Diabetes Care* 1998; **21**: 341-345 [PMID: 9540013]
47 **Wang FB**, Powley TL. Vagal innervation of intestines: afferent pathways mapped with new en bloc

horseradish peroxidase adaptation. *Cell Tissue Res* 2007; **329**: 221-230 [PMID: 17453246 DOI: 10.1007/s00441-007-0413-7]
48 **Wang Y**, Wang Z, Wang Y, Li F, Jia J, Song X, Qin S, Wang R, Jin F, Kitazato K, Wang Y. The Gut-Microglia Connection: Implications for Central Nervous System Diseases. *Front Immunol* 2018; **9**: 2325 [PMID: 30344525 DOI: 10.3389/fimmu.2018.02325]
49 **Bonaz B**, Bazin T, Pellissier S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front Neurosci* 2018; **12**: 49 [PMID: 29467611 DOI: 10.3389/fnins.2018.00049]
50 **Stanley S**, Pinto S, Segal J, Pérez CA, Viale A, DeFalco J, Cai X, Heisler LK, Friedman JM. Identification of neuronal subpopulations that project from hypothalamus to both liver and adipose tissue polysynaptically. *Proc Natl Acad Sci USA* 2010; **107**: 7024-7029 [PMID: 20351287 DOI: 10.1073/pnas.1002790107]
51 **Inoue H**, Ogawa W, Asakawa A, Okamoto Y, Nishizawa A, Matsumoto M, Teshigawara K, Matsuki Y, Watanabe E, Hiramatsu R, Notohara K, Katayose K, Okamura H, Kahn CR, Noda T, Takeda K, Akira S, Inui A, Kasuga M. Role of hepatic STAT3 in brain-insulin action on hepatic glucose production. *Cell Metab* 2006; **3**: 267-275 [PMID: 16581004 DOI: 10.1016/j.cmet.2006.02.009]
52 **Chen Z**, Yu R, Xiong Y, Du F, Zhu S. A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease. *Lipids Health Dis* 2017; **16**: 203 [PMID: 29037210 DOI: 10.1186/s12944-017-0572-9]
53 **Tilg H**, Diehl AM. Cytokines in alcoholic and nonalcoholic steatohepatitis. *N Engl J Med* 2000; **343**: 1467-1476 [PMID: 11078773 DOI: 10.1056/NEJM200011163432007]
54 **Berzigotti A**, Saran U, Dufour JF. Physical activity and liver diseases. *Hepatology* 2016; **63**: 1026-1040 [PMID: 26313307 DOI: 10.1002/hep.28132]
55 **Kitade H**, Chen G, Ni Y, Ota T. Nonalcoholic Fatty Liver Disease and Insulin Resistance: New Insights and Potential New Treatments. *Nutrients* 2017; **9** [PMID: 28420094 DOI: 10.3390/nu9040387]
56 **Koyama Y**, Brenner DA. Liver inflammation and fibrosis. *J Clin Invest* 2017; **127**: 55-64 [PMID: 28045404 DOI: 10.1172/JCI88881]
57 **Petrescu AD**, Kain J, Liere V, Heavener T, DeMorrow S. Hypothalamus-Pituitary-Adrenal Dysfunction in Cholestatic Liver Disease. *Front Endocrinol (Lausanne)* 2018; **9**: 660 [PMID: 30483216 DOI: 10.3389/fendo.2018.00660]
58 **Hayley S**, Lacosta S, Merali Z, van Rooijen N, Anisman H. Central monoamine and plasma corticosterone changes induced by a bacterial endotoxin: sensitization and cross-sensitization effects. *Eur J Neurosci* 2001; **13**: 1155-1165 [PMID: 11285013]
59 **Silverman MN**, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol* 2005; **18**: 41-78 [PMID: 15802953 DOI: 10.1089/vim.2005.18.41]
60 **Demitrack MA**. Neuroendocrine correlates of chronic fatigue syndrome: a brief review. *J Psychiatr Res* 1997; **31**: 69-82 [PMID: 9201649]
61 **Weissenborn K**, Ennen JC, Bokemeyer M, Ahl B, Wurster U, Tillmann H, Trebst C, Hecker H, Berding G. Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment. *Gut* 2006; **55**: 1624-1630 [PMID: 16682431 DOI: 10.1136/gut.2005.080267]
62 **Zalai D**, Carney CE, Sherman M, Shapiro CM, McShane K. Fatigue in chronic hepatitis C infection: Understanding patients' experience from a cognitive-behavioural perspective. *Br J Health Psychol* 2016; **21**: 157-172 [PMID: 26250404 DOI: 10.1111/bjhp.12155]
63 **Dwight MM**, Kowdley KV, Russo JE, Ciechanowski PS, Larson AM, Katon WJ. Depression, fatigue, and functional disability in patients with chronic hepatitis C. *J Psychosom Res* 2000; **49**: 311-317 [PMID: 11164055 DOI: 10.1016/S0022-3999(00)00155-0]
64 **Yamashita M**, Yamamoto T. Tryptophan circuit in fatigue: From blood to brain and cognition. *Brain Res* 2017; **1675**: 116-126 [PMID: 28893581 DOI: 10.1016/j.brainres.2017.09.002]
65 **Biomarkers Definitions Working Group**. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001; **69**: 89-95 [PMID: 11240971 DOI: 10.1067/mcp.2001.113989]
66 **Zenouzi R**, Gablentz J von der, Heldmann M, Göttlich M, Weiler-Normann C, Sebode M, Ehlken H, Hartl J, Fellbrich A, Siemonsen S, Schramm C, Münte TF, Lohse AW. Patients with primary biliary cholangitis and fatigue present with depressive symptoms and selected cognitive deficits, but with normal attention performance and brain structure. *PLoS One* 2018; **13**: e0190005 [PMID: 29320524 DOI: 10.1371/journal.pone.0190005]
67 **Weinstein G**, Zelber-Sagi S, Preis SR, Beiser AS, DeCarli C, Speliotes EK, Satizabal CL, Vasan RS, Seshadri S. Association of Nonalcoholic Fatty Liver Disease With Lower Brain Volume in Healthy Middle-aged Adults in the Framingham Study. *JAMA Neurol* 2018; **75**: 97-104 [PMID: 29159396 DOI: 10.1001/jamaneurol.2017.3229]
68 **VanWagner LB**, Terry JG, Chow LS, Alman AC, Kang H, Ingram KH, Shay C, Lewis CE, Bryan RN, Launer LJ, Jeffrey Carr J. Nonalcoholic fatty liver disease and measures of early brain health in middle-aged adults: The CARDIA study. *Obesity (Silver Spring)* 2017; **25**: 642-651 [PMID: 28169509 DOI: 10.1002/oby.21767]
69 **Cavelti-Weder C**, Furrer R, Keller C, Babians-Brunner A, Solinger AM, Gast H, Fontana A, Donath MY, Penner IK. Inhibition of IL-1beta improves fatigue in type 2 diabetes. *Diabetes Care* 2011; **34**: e158 [PMID: 21949230 DOI: 10.2337/dc11-1196]
70 **Larun L**, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev* 2017; **4**: CD003200 [PMID: 28444695 DOI: 10.1002/14651858.CD003200.pub7]
71 **Berger AM**, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, Cleeland C, Dotan E, Eisenberger MA, Escalante CP, Jacobsen PB, Jankowski C, LeBlanc T, Ligibel JA, Loggers ET, Mandrell B, Murphy BA, Palesh O, Pirl WF, Plaxe SC, Riba MB, Rugo HS, Salvador C, Wagner LI, Wagner-Johnston ND, Zachariah FJ, Bergman MA, Smith C; National comprehensive cancer network. Cancer-Related Fatigue, Version 2.2015. *J Natl Compr Canc Netw* 2015; **13**: 1012-1039 [PMID: 26285247]
72 **Hilfiker R**, Meichtry A, Eicher M, Nilsson Balfe L, Knols RH, Verra ML, Taeymans J. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. *Br J Sports Med* 2018; **52**: 651-658 [PMID: 28501804 DOI: 10.1136/bjsports-2016-096422]
73 **Golabi P**, Locklear CT, Austin P, Afdhal S, Byrns M, Gerber L, Younossi ZM. Effectiveness of exercise in hepatic fat mobilization in non-alcoholic fatty liver disease: Systematic review. *World J Gastroenterol*

2016; **22**: 6318-6327 [PMID: 27468220 DOI: 10.3748/wjg.v22.i27.6318]
74 **Romero-Gómez M**, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol* 2017; **67**: 829-846 [PMID: 28545937 DOI: 10.1016/j.jhep.2017.05.016]
75 **Oseini AM**, Sanyal AJ. Therapies in non-alcoholic steatohepatitis (NASH). *Liver Int* 2017; **37** Suppl 1: 97-103 [PMID: 28052626 DOI: 10.1111/liv.13302]
76 **Hashida R**, Kawaguchi T, Bekki M, Omoto M, Matsuse H, Nago T, Takano Y, Ueno T, Koga H, George J, Shiba N, Torimura T. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. *J Hepatol* 2017; **66**: 142-152 [PMID: 27639843 DOI: 10.1016/j.jhep.2016.08.023]
77 **Katsagoni CN**, Georgoulis M, Papatheodoridis GV, Panagiotakos DB, Kontogianni MD. Effects of lifestyle interventions on clinical characteristics of patients with non-alcoholic fatty liver disease: A meta-analysis. *Metabolism* 2017; **68**: 119-132 [PMID: 28183444 DOI: 10.1016/j.metabol.2016.12.006]
78 **Schweitzer GG**, Klein S. Exercise and NAFLD: Is it worth the effort? *Hepatology* 2017; **66**: 1691-1694 [PMID: 28688146 DOI: 10.1002/hep.29356]
79 **Takahashi H**, Kotani K, Tanaka K, Egucih Y, Anzai K. Therapeutic Approaches to Nonalcoholic Fatty Liver Disease: Exercise Intervention and Related Mechanisms. *Front Endocrinol (Lausanne)* 2018; **9**: 588 [PMID: 30374329 DOI: 10.3389/fendo.2018.00588]
80 **Keating SE**, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *J Hepatol* 2012; **57**: 157-166 [PMID: 22414768 DOI: 10.1016/j.jhep.2012.02.023]
81 **Pugh CJ**, Spring VS, Kemp GJ, Richardson P, Shojaee-Moradie F, Umpleby AM, Green DJ, Cable NT, Jones H, Cuthbertson DJ. Exercise training reverses endothelial dysfunction in nonalcoholic fatty liver disease. *Am J Physiol Heart Circ Physiol* 2014; **307**: H1298-H1306 [PMID: 25193471 DOI: 10.1152/ajpheart.00306.2014]
82 **Yoshimura E**, Kumahara H, Tobina T, Matsuda T, Ayabe M, Kiyonaga A, Anzai K, Higaki Y, Tanaka H. Lifestyle intervention involving calorie restriction with or without aerobic exercise training improves liver fat in adults with visceral adiposity. *J Obes* 2014; **2014**: 197216 [PMID: 24864199 DOI: 10.1155/2014/197216]
83 **Gerber LH**, Weinstein A, Pawloski L. Role of exercise in optimizing the functional status of patients with nonalcoholic fatty liver disease. *Clin Liver Dis* 2014; **18**: 113-127 [PMID: 24274868 DOI: 10.1016/j.cld.2013.09.016]
84 **Bacchi E**, Negri C, Targher G, Faccioli N, Lanza M, Zoppini G, Zanolin E, Schena F, Bonora E, Moghetti P. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 Randomized Trial). *Hepatology* 2013; **58**: 1287-1295 [PMID: 23504926 DOI: 10.1002/hep.26393]
85 **Dantzer R**. Role of the Kynurenine Metabolism Pathway in Inflammation-Induced Depression: Preclinical Approaches. *Curr Top Behav Neurosci* 2017; **31**: 117-138 [PMID: 27225497 DOI: 10.1007/7854_2016_6]
86 **Cervenka I**, Agudelo LZ, Ruas JL. Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. *Science* 2017; 357 [PMID: 28751584 DOI: 10.1126/science.aaf9794]
87 **Strasser B**, Geiger D, Schauer M, Gatterer H, Burtscher M, Fuchs D. Effects of Exhaustive Aerobic Exercise on Tryptophan-Kynurenine Metabolism in Trained Athletes. *PLoS One* 2016; **11**: e0153617 [PMID: 27124720 DOI: 10.1371/journal.pone.0153617]
88 **Zelber-Sagi S**, Bord S, Dror-Lavi G, Smith ML, Towne SD, Buch A, Webb M, Yeshua H, Nimer A, Shibolet O. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. *World J Gastroenterol* 2017; **23**: 1881-1890 [PMID: 28348495 DOI: 10.3748/wjg.v23.i10.1881]
89 **Frith J**, Day CP, Robinson L, Elliott C, Jones DE, Newton JL. Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. *J Hepatol* 2010; **52**: 112-116 [PMID: 19897272 DOI: 10.1016/j.jhep.2009.10.010]
90 **Mazzotti A**, Caletti MT, Brodosi L, Di Domizio S, Forchielli ML, Petta S, Bugianesi E, Bianchi G, Marchesini G. An internet-based approach for lifestyle changes in patients with NAFLD: Two-year effects on weight loss and surrogate markers. *J Hepatol* 2018; **69**: 1155-1163 [PMID: 30290973 DOI: 10.1016/j.jhep.2018.07.013]
91 **Findorff MJ**, Wyman JF, Gross CR. Predictors of long-term exercise adherence in a community-based sample of older women. *J Womens Health (Larchmt)* 2009; **18**: 1769-1776 [PMID: 19951210 DOI: 10.1089/jwh.2008.1265]
92 **Nguyen H**, Wang H, le T, Ho W, Sharkey KA, Swain MG. Downregulated hypothalamic 5-HT3 receptor expression and enhanced 5-HT3 receptor antagonist-mediated improvement in fatigue-like behaviour in cholestatic rats. *Neurogastroenterol Motil* 2008; **20**: 228-235 [PMID: 17919312 DOI: 10.1111/j.1365-2982.2007.01016.x]
93 **Piche T**, Vanbiervliet G, Cherikh F, Antoun Z, Huet PM, Gelsi E, Demarquay J-F, Caroli-Bosc F-X, Benzaken S, Rigault M-C, Renou C, Rampal P, Tran A. Effect of ondansetron, a 5-HT3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut* 2005; **54**: 1169-1173 [PMID: 16009690 DOI: 10.1136/gut.2004.055251]
94 **Frezza M**, Surrenti C, Manzillo G, Fiaccadori F, Bortolini M, Di Padova C. Oral S-adenosylmethionine in the symptomatic treatment of intrahepatic cholestasis. A double-blind, placebo-controlled study. *Gastroenterology* 1990; **99**: 211-215 [PMID: 2188871]
95 **Jones EA**. Fatigue complicating chronic liver disease. *Metab Brain Dis* 2004; **19**: 421-429 [PMID: 15554432]
96 **Yeoh SW**, Holmes ACN, Saling MM, Everall IP, Nicoll AJ. Depression, fatigue and neurocognitive deficits in chronic hepatitis C. *Hepatol Int* 2018; **12**: 294-304 [PMID: 29931590 DOI: 10.1007/s12072-018-9879-5]
97 **Seaman K**, Paterson BL, Vallis M, Hirsch G, Peltekian KM. Future directions for investigation of fatigue in chronic hepatitis C viral infection. *Chronic Illn* 2009; **5**: 115-128 [PMID: 19474234 DOI: 10.1177/1742395309104476]
98 **Wessely S**, Pariante C. Fatigue, depression and chronic hepatitis C infection. *Psychol Med* 2002; **32**: 1-10 [PMID: 11883721]
99 **Kumar D**, Tandon RK. Fatigue in cholestatic liver disease--a perplexing symptom. *Postgrad Med J* 2002; **78**: 404-407 [PMID: 12151655]
100 **Newton JL**. Fatigue in primary biliary cirrhosis. *Clin Liver Dis* 2008; **12**: 367-83; ix [PMID: 18456186 DOI: 10.1016/j.cld.2008.02.010]
101 **Zakharia K**, Tabibian A, Lindor KD, Tabibian JH. Complications, symptoms, quality of life and

pregnancy in cholestatic liver disease. *Liver Int* 2018; **38**: 399-411 [PMID: 28921801 DOI: 10.1111/liv.13591]
102 **Abbas G**, Jorgensen RA, Lindor KD. Fatigue in primary biliary cirrhosis. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 313-319 [PMID: 20458334 DOI: 10.1038/nrgastro.2010.62]
103 **Michielsen HJ**, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. *J Psychosom Res* 2003; **54**: 345-352 [PMID: 12670612]
104 **Krupp LB**, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; **46**: 1121-1123 [PMID: 2803071]
105 **Fisk JD**, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994; **18** Suppl 1: S79-S83 [PMID: 8148458]
106 **Chalder T**, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace EP. Development of a fatigue scale. *J Psychosom Res* 1993; **37**: 147-153 [PMID: 8463991]
107 **Belza BL**. Comparison of self-reported fatigue in rheumatoid arthritis and controls. *J Rheumatol* 1995; **22**: 639-643 [PMID: 7791155]
108 **Smets EM**, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; **39**: 315-325 [PMID: 7636775]
109 **Lee KA**, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res* 1991; **36**: 291-298 [PMID: 2062970]
110 **Webster K**, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003; **1**: 79 [PMID: 14678568 DOI: 10.1186/1477-7525-1-79]
111 **Ware JE**, Snow KK, Kosinski M, Gandek B, Institute NEMCHH. SF-36 health survey: manual and interpretation guide. The Health Institute. *New England Medical Center;* 1993
112 **Younossi ZM**, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 1999; **45**: 295-300 [PMID: 10403745]
113 **Lai JS**, Cella D, Choi S, Junghaenel DU, Christodoulou C, Gershon R, Stone A. How item banks and their application can influence measurement practice in rehabilitation medicine: a PROMIS fatigue item bank example. *Arch Phys Med Rehabil* 2011; **92**: S20-S27 [PMID: 21958919 DOI: 10.1016/j.apmr.2010.08.033]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk:http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

© 2019 Baishideng Publishing Group Inc. All rights reserved.