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MINIREVIEWS

Understanding fatigue in primary biliary cholangitis: From pathophysiology to treatment perspectives

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Abstract

Fatigue is considered one of the most frequent and debilitating symptoms in primary biliary cholangitis (PBC), affecting over 50% of PBC patients. One in five patients with PBC suffer from severe fatigue, which significantly impairs quality of life. Fatigue is made up of a central and a peripheral component, whose pathophysiology is still greatly unresolved. Central fatigue is characterised by a lack of self-motivation and can manifest both in physical and mental activities (lack of intention). Peripheral fatigue includes neuromuscular dysfunction and muscle weakness (lack of ability). Peripheral fatigue could be explained by an excessive deviation from aerobic to anaerobic metabolism leading to excessive lactic acid accumulation and therefore accelerated decline in muscle function and prolonged recovery time. As opposed to itching, and with the exception of end-stage liver disease, fatigue is not related to disease progression. The objective of this review is to outline current understanding regarding the pathophysiology of fatigue, the role of comorbidities and contributing factors, the main tools for fatigue assessment, the failed therapeutic options, and future treatment perspectives for this disabling symptom. Since fatigue is an extremely common and debilitating symptom and there is still no licensed therapy for fatigue in PBC patients, further research is warranted to understand its causative mechanisms and to find an effective treatment.

Key Words: Fatigue; Primary biliary cholangitis; Treatment; Pathophysiology; Central fatigue; Peripheral fatigue

Core Tip: Fatigue is considered one of the most frequent and debilitating symptoms in primary biliary cholangitis, affecting over 50% of patients. The objective of this review is to outline current understanding regarding the pathophysiology of fatigue, the role of comorbidities and contributing factors, the main tools for fatigue assessment, the failed therapeutic options, and future treatment perspectives for this disabling symptom. Since fatigue is an extremely common and debilitating symptom and there is still no licensed therapy for fatigue in PBC patients, further research is warranted to understand its causative mechanisms and to find effective treatment.

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INTRODUCTION

Fatigue is considered one the most frequent and debilitating symptoms in primary biliary cholangitis (PBC), affecting over 50% of patients with PBC[1]. As opposed to itching, and with the exception of end-stage liver disease, fatigue is not related to disease progression[1,2]. One in five patients with PBC suffer from severe fatigue, which significantly impairs quality of life[3]. The severity of chronic fatigue symptoms in PBC predicts liver-related mortality and liver transplantation outcome[4]. Latitude and sun exposure might influence PBC phenotype, including fatigue status[5].

The objective of this review is to outline current understanding regarding the pathophysiology of fatigue, the role of comorbidities and contributing factors, the main tools for fatigue assessment, the available treatments, and future therapeutic options for this disabling symptom.

DEFINITION AND PATHOPHYSIOLOGY

Fatigue is defined as an overwhelming sense of tiredness, lack of energy, and a feeling of exhaustion[6]. Its pathophysiology in PBC is still unresolved. It can be considered as made up of two different entities: Peripheral and central fatigue. Peripheral fatigue includes neuromuscular dysfunction and muscle weakness (lack of ability)[7]. Central fatigue is characterised by a lack of self-motivation and can manifest both in physical and mental activities (lack of intention)[7].

Peripheral fatigue

Anti-mitochondrial autoantibodies (AMA), which specifically target pyruvate dehydrogenase complex (PDC), are a hallmark of PBC[8]. In these patients, anti-PDC antibodies are mainly directed against the inner lipoyl domain of the PDC-E2 component, which has an alpha-lipoic acid covalently bound to a specific lysine residue, that is an absolute requirement for its enzymatic activity. The PDC-E2 component is loosely bound to the inner membrane of mitochondria. Immune reactivity against the lipoylated substrate of PDC-E2-also found in some bacteria and yeasts and mimicked by some xenobiotics-has been suggested to be the cause of PBC, as in patients with PBC, this antigen is aberrantly expressed on the surface of intrahepatic biliary epithelial cells[8]. On the other hand, as AMA highly inhibit mammalian PDC, and moderately and weakly inhibit yeast and bacteria PDC, loss of tolerance is most probably the underlying mechanism which induces PBC[9]. Since PDC is ubiquitous, a reason for the tissue specificity of epithelial damage which is found in PBC could be that secretory IgA anti-PDC, not IgG, is responsible for epithelial cell damage. IgA undergoing transcytosis across the intrahepatic biliary or salivary epithelium might bind to nascent PDC components while being transported to the mitochondria and may export them to the epithelial cell surface. Depletion of these critical proteins would result in chronic metabolic damage to the epithelial cell[9].

In fatigued PBC patients, there seems to be an excessive deviation from aerobic to anaerobic metabolism leading to excessive lactic acid accumulation and therefore accelerated decline in muscle function and prolonged recovery time. Various studies support this conclusion: Fatigued PBC patients

perform worse than non-fatigued patients on hand grip test with no association with liver disease severity[10]; when bioenergetics of muscle function was assessed using $_{31}$P magnetic resonance spectroscopy in PBC patients, non-PBC patients with chronic fatigue syndrome, patients with primary sclerosing cholangitis, and controls, only patients with PBC showed increased post-exercise muscle acidosis and prolonged adenosine diphosphate and phosphocreatine recovery time suggesting mitochondrial dysfunction[11]. pH recovery appeared to be related to fatigue severity[11]. How AMA can induce PDC depletion or dysfunction in muscles of patients with PBC remains uncertain.

It should also be noted that the reduction of AMA through B-cell depletion with rituximab did not have any effect on fatigue, suggesting the existence of other fatigue-inducing pathophysiologic mechanisms than antibody-mediated damage[12]. In addition, peripheral fatigue measured by twitch interpolation did not differ between PBC patients and controls, although patients with PBC were not differentially assessed based on fatigue symptoms[13]. Twitch interpolation can supposedly distinguish central from peripheral fatigue as it allows to assess whether all motor units have been recruited by the central nervous system or not[13]. In centrally fatigued patients, central activation is low, and a smaller number of motor units are stimulated[13].

Central fatigue

Patients with PBC often report cognitive symptoms, such as memory impairment, and higher rates of sleep-wake disturbance with delayed sleep timing, worse sleep quality, and excessive daytime somnolence[14], seemingly unrelated to liver disease severity[13,15]. Evidence supporting the central origin of fatigue in PBC patients is mostly made up of small-scale studies and its pathophysiology is unknown. Treatment for excessive daytime somnolence with modafinil was ineffective[16]. Mosher *et al* [17] studied the resting-state functional connectivity (rsFC) of deep grey matter brain structures (putamen, thalamus, amygdala, and hippocampus) using resting-state functional magnetic resonance imaging in 20 non-cirrhotic PBC patients compared with 21 matched controls. PBC patients exhibited significant alterations in rsFC levels as compared to controls. Fatigue, itch, and verbal working memory performance were associated with alterations of deep grey matter rsFC, possibly reflecting chronic immune-mediated signalling from the liver to the brain in PBC patients[17]. In a study by McDonald *et al*[13], twitch interpolation and paired-pulse trans-cranial magnetic stimulation were used to study central nervous system function in PBC patients and its relationship to fatigue symptoms. PBC patients had significantly lower levels of central activation[13]. Interestingly, no differences were found between transplanted and non-transplanted patients. However, a volitional contribution could justify the results and could not be excluded; central activation might be reduced as a protective mechanism to avoid exhaustion (due to peripheral fatigue?).

Altered central neurotransmission has been a leading hypothesis to explain the development of fatigue in PBC patients, involving both serotonergic and noradrenaline pathways. Unfortunately, no specific treatment to stimulate the serotonin pathway (ondansetron, fluvoxamine, or fluoxetine) has brought positive results[18,20].

Large-scale clinical studies are warranted that assess whether fatigue in PBC patients is predominantly central or peripheral, or both, in order to concentrate future research in the right direction.

ROLE OF COMORBIDITIES AND CONTRIBUTING FACTORS

There are many conditions and therapies which can cause fatigue or deteriorate existing weariness; in fatigued PCB patients, a complete assessment should be performed, and any detected condition should be addressed. Among these conditions, we can find autoimmune diseases such as hypothyroidism, anaemia, type II diabetes, nocturnal pruritus, autonomic dysfunction, dehydration, restless leg syndrome, and concurrent medications such as anti-hypertensive therapy. Depressive symptoms in PBC patients seem to be the consequence rather than the cause of fatigue, as the prevalence of a depressive disorder in patients with PBC does not seem to be higher than that in the general population[21].

A complete list of additive factors to fatigue burden is presented in Table 1.

ASSESSMENT OF FATIGUE

Although fatigue is a ubiquitous symptom in medical practice, one single questionnaire might not fit the purpose of measuring fatigue in a specific group of patients. Each assessment tool should be validated not to compromise the quality of research. In a systematic review by Kim *et al*[22], the authors found that, between 1990 and 2019, patient reported outcomes in PBC had been mostly assessed with unlabelled, nonspecific versions of numeric ratings or Likert scales and that fatigue has been measured with over ten different instruments although ideally, the use of questionnaires should be standardised to allow comparison.

Table 1 Conditions and drugs contributing to fatigue burden[1,2]

Conditions	Drugs
Addison disease; Anaemia; Autonomic dysfunction; Cancer; Chronic Lyme disease; Dehydration; Depression; Diabetes; Heart failure; Hypothyroidism; Infectious/inflammatory state; Myasthenia gravis; Multiple sclerosis; Obstructive sleep apnoea; Parkinson's disease; Pregnancy; Renal failure; Restless legs syndrome; Tuberculosis	Antibiotics; Antidepressants; Anti-hypertensive therapy; Muscle relaxants; Opioids; Sedative-hypnotics

In a recent systematic review, Machado *et al*[6] evaluated existing fatigue scales commonly used to assess fatigue in patients with various medical conditions. Eleven fatigue scales were identified and analysed: Five were unidimensional [Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Brief Fatigue Inventory, Fatigue Severity Scale (FSS), Numerical Rating Scale-Fatigue, and Visual Analog Scale-Fatigue (VAS-F)] and six multidimensional [Fatigue Impact Scale (FIS), Checklist Individual Strength (CIS), Chalder Fatigue Scale (CFS), Multidimensional Assessment of Fatigue, Multidimensional Fatigue Inventory Scale, and Piper Fatigue Scale][6]. Unidimensional scales can be useful to assess severity or as screening tools, whereas multidimensional scores are more informative and can evaluate affective, cognitive, somatic, and behavioural manifestations of fatigue.

FACIT-F and FSS can be used as screening tools as they present a cut-off point to differentiate patients with fatigue *vs* non-fatigue. Eight of the previously reported scales (FACIT, FSS, BFI, CIS, MAF, MFI, FIS, and CFS) are able to detect disease progression or response to treatment[6].

Of all the above-mentioned fatigue-specific scales, the Fatigue Impact Scale is the only one which has been validated in PBC[23,24]. It was initially validated in 1994 by Fisk *et al*[25] in patients with multiple sclerosis and mild hypertension and was then found to be highly acceptable and consistent also in patients with PBC. It takes approximately 5 to 8 minutes to be completed and has a coefficient of reproducibility of 13% of the mean (vs 33% for the VAS-F)[23]. FIS measures the impact of fatigue on 40 aspects of daily life over the previous month. Patients are required to grade from zero to four how impaired has each aspect been to give a maximum score of 160 (severely fatigued). FIS assesses the impact of fatigue on psycho-social, cognitive, and physical activities[23].

However, the PBC-40 is the only instrument which can claim to be truly representative of PBC-related fatigue as it was originally developed for PBC patients. Jacoby *et al* [5] developed the PBC-40 in 2005 to assess PBC patients' quality of life. It investigates the impact of the disease in six domains: Fatigue, pruritus, social, cognitive, and other symptoms. The patients rate 40 items on a five-point scale, with a higher score indicating a worse quality of life. It has also been adapted in shorter versions. As it includes a fatigue subscale with proven content validity, it is the ideal instrument for studies on PBC-related fatigue. None of the proposed questionnaires specifically differentiate between peripheral and central fatigue.

Fatigue can also be assessed by measuring objective (*e.g.*, brain imaging, serological, and physical performance measures), as well as patient reported outcomes, but no consensus has been reached with regard to objective or combined assessments in PBC[7]**.** In the literature, there are a certain number of objective methods to distinguish central from peripheral fatigue. Peripheral fatigue, or impairment of muscle excitation, is most commonly evaluated with electromyography[26]. Serum lactate and IL-6 have been identified as the most accurate and valid biomarkers to measure muscle fatigue, although they are influenced by workload conditions and timing of testing with respect to exercise[27]. Other non-invasive methods have been employed for the detection of peripheral fatigue (*e.g.*, acoustic myography) [28]. On the other hand, central fatigue can be assessed either with percutaneous nerve stimulation[29] or transcranial magnetic stimulation during maximal contractions[30]. If the stimulation evokes an extra-force, it means that not all muscle units have been recruited, suggesting that central fatigue is present[30].

LIFESTYLE ADJUSTMENTS AND DEVELOPING COPING MECHANISMS

Patients need to be advised and supported to develop coping strategies while retaining ownership of the problem. Pacing strategies (using available energy to its best advantage) and timing strategies (fatigue is worse later in the day typically so arranging key tasks for earlier in the day can make them less demanding) are recommended[3]. Awareness and understanding from carers should be promoted [3].

EFFECT OF MAIN DRUGS FOR PBC ON FATIGUE

Ursodeoxycholic acid (UDCA) at a daily dosage of 13-15 mg/kg is the first line treatment for PBC. Although UDCA slows liver disease progression, increases transplant-free survival, and reduces mortality, it does not improve fatigue[1,31]. In China, a phase IV trial (NCT03345589) is being conducted

to compare the efficacy of an intermediate dosage of UDCA of 18–22 mg/kg/day and the standard dose over 6 mo in achieving biochemical remission. Unfortunately, since Angulo *et al* found no symptom improvement with an UDCA dosage increase to 23-25/mg/kg/day, the same is to be expected with the intermediate dosage[32].

Obeticholic acid (OCA) is a semi-synthetic hydrophobic bile acid analogue which can be used in patients who experience an inadequate response or are intolerant to UDCA. It is administered at an initial dose of 5 mg which can be titrated to 10 mg according to tolerability at 6 mo[1]. Fatigue is not responsive to OCA therapy[33]. OCA is associated with a dose dependent exacerbation in pruritus which can impair sleep and worsen fatigue[33].

Fibrates are a readily available but unlicensed treatment option for patients with PBC[34]. In the BEZURSO trial, a multicentre, double-blind, placebo-controlled, phase III clinical trial, 100 patients with inadequate response to ursodeoxycholic acid were randomly assigned to receive benzafibrate at a daily dose of 400 mg or placebo. After a 24 mo follow-up, 15% of patients in the benzafibrate group *vs* 9% in the placebo group reported an improvement in fatigue so benzafibrate could be the first therapeutic drug for PBC which has an effect on fatigue[35]. However, in this trial, no validated metrics were used to assess fatigue, as it was only categorised as absent, intermittent, or continuous. Further studies are required to confirm these results.

Budesonide is a synthetic corticosteroid with a high first-pass metabolism in the liver, which was found to improve liver histology and biochemistry in PBC patients with interface hepatitis on biopsy [36]. A recent phase-III, double-blind, randomised trial comparing budesonide combined with UDCA and UDCA only did not detect any improvement in liver histology, nor was fatigue alleviated[37].

FAILED THERAPEUTIC OPTIONS

Modafinil is an approved treatment for daytime somnolence due to narcolepsy, sleep apnoea, and fatigue related to shift work sleep disorder. A randomised, double-blind, placebo-controlled study was conducted to assess the efficacy of modafinil for the treatment of fatigue in PBC did not show a significant improvement *vs* placebo[16], despite positive results from an uncontrolled study. The use of modafinil should therefore be limited to patients with formally diagnosed sleep disorders.

As previously mentioned, rituximab, which could have influenced fatigue severity by reducing circulating anti-PDC antibodies, did not significantly reduce fatigue in a single-centre randomised controlled trial with 57 participants[38]. The anaerobic threshold improved, possibly due to an effect on muscle bioenergetics dysfunction, but this did not lead to reduced fatigue symptoms. Interestingly, in two small sample studies on the use of plasmapheresis in PBC, in one study all patients who suffered from fatigue (4/5) reported reduced symptoms after treatment[39] and in the second study on 13 patients, the reduction of the PBC-40 fatigue domain score was statistically significant (30 *vs* 38, P = 0.004)[40].

Ondansetron (a 5HT1 A receptor antagonist) did not determine an improvement in fatigue in a crossover study[20], nor did the use of selective serotonin reuptake inhibitors (fluoxetine and fluvoxamine) show any effect on fatigue in randomised controlled trials[18,19].

The empirical use of antioxidant therapy (vitamins A, C and E, selenium, methionine, and ubiquinone) had no effect on fatigue scores in a randomised, placebo-controlled crossover trial[41].

LIVER TRANSPLANTATION

In the last few decades, there has been a decrease in the need for liver transplantation (LT) in PBC, most probably due to the introduction of UDCA as standard therapy[42]. According to current guidelines, liver transplant for fatigue in PBC is not appropriate as fatigue persists after transplantation in most patients[1]. Montali *et al*[5] conducted a prospective study to assess the impact of LT on fatigue. Although fatigue scores were significantly lower after LT, nearly half of LT recipients reported ongoing fatigue (44% of the total cohort and 47% of patients with low Model for End Stage Liver Disease score). These results have been confirmed in later studies[43].

FUTURE TREATMENT PERSPECTIVES

Seladelpar

Seladelpar is a selective peroxisome proliferator activated receptor delta agonist which has recently been assessed in an open-label, uncontrolled phase 2 study in PBC patients[44]. After 1 year of treatment, PBC-40 fatigue scores improved in 55%-64% of patients. Patients also reported a decrease in itch and sleep disturbance. These results need to be confirmed in a placebo-controlled and randomised trial.

Table 2 Failed therapeutic options and future therapeutic perspectives for fatigue in primary biliary cholangitis

Treatment for fatigue in PBC	Ref.
Failed therapeutic options	
Ursodeoxycholic acid	Angulo *et al*[32], 1999
Obeticholic acid	Hirschfield *et al*[33], 2015
Budesonide	Hirschfield *et al*[37], 2021
Fluoxetine	Talwalkar *et al*[18], 2006
Fluvoxamine	ter Borg *et al*[19], 2004
Ondansetron	Theal *et al*[20], 2005
Rituximab	Khanna *et al*[14], 2019
Modafinil	Silveira *et al*[16], 2017
Methotrexate	Combes *et al*[48], 2005
Oral antioxidant supplementation	Prince *et al*[23], 2003
Lifestyle changes	
Morning bright light treatment	Turco *et al*[15], 2018
Home-based exercise programme	Freer *et al*[46], 2021
Possible future therapeutic options	
Fibrates	Corpechot *et al*[35], 2018
Plasmapheresis	Wunsch *et al*[40], 2021
S-adenosyl-L-methionine	Wunsch *et al*[45], 2018
Seladelpar	Kremer *et al*[44], 2022

PBC: Primary biliary cholangitis.

S-adenosyl-L-methionine

S-adenosyl-L-methionine, added to UDCA, can improve cholestasis in non-cirrhotic PBC patients, probably due to its hepatoprotective effects[45]. In an open label clinical trial on 24 PBC patients, there was a significant improvement in fatigue, assessed with the PBC-40 questionnaire[45].

Although causative mechanisms of fatigue in PBC are still unknown, therapeutic approaches have been sought to alleviate this debilitating symptom.

Home-based exercise programme

Since fatigue in patients with PBC could be caused by muscle bioenergetic abnormalities, as previously mentioned, Freer *et al*[46] have performed a phase 1, single-arm, open-label clinical trial evaluating a novel exercise programme in patients with PBC with moderate-severe fatigue. Thirty-one patients concluded the 12-week home-based exercise programme which consisted of individualised resistance, aerobic exercises, and telephone health calls, although the results have not yet been published[46]. Peripheral muscle excessive acidosis and delayed pH recovery which characterise PBC patients can be improved with repeated single exercise episodes[47]. This programme is of great interest as patients with PBC tend to lead a sedentary lifestyle due to fear of exacerbating fatigue, but muscle fatigability is increased when physical activity is reduced.

Morning bright light treatment

PBC is associated with poor sleep quality and delayed sleep-wake profile which can worsen the burden of fatigue. For this reason, Turco *et al*[15] conducted a pilot study to assess the efficacy of a short course of morning bright light treatment on sleep-wake patterns of fifteen PBC patients, six healthy individuals, and seven cirrhotic patients[15]. In patients with PBC, 15 d of light therapy resulted in subjective sleep quality improvement and a reduction in daytime sleepiness. In addition, sleep onset and get-up time were significantly advanced. Unfortunately, fatigue was not formally assessed, although daytime dysfunction due to somnolence was reported as improved[15].

Failed therapeutic options and future therapeutic perspectives for fatigue in PBC are summarised in Table 2.

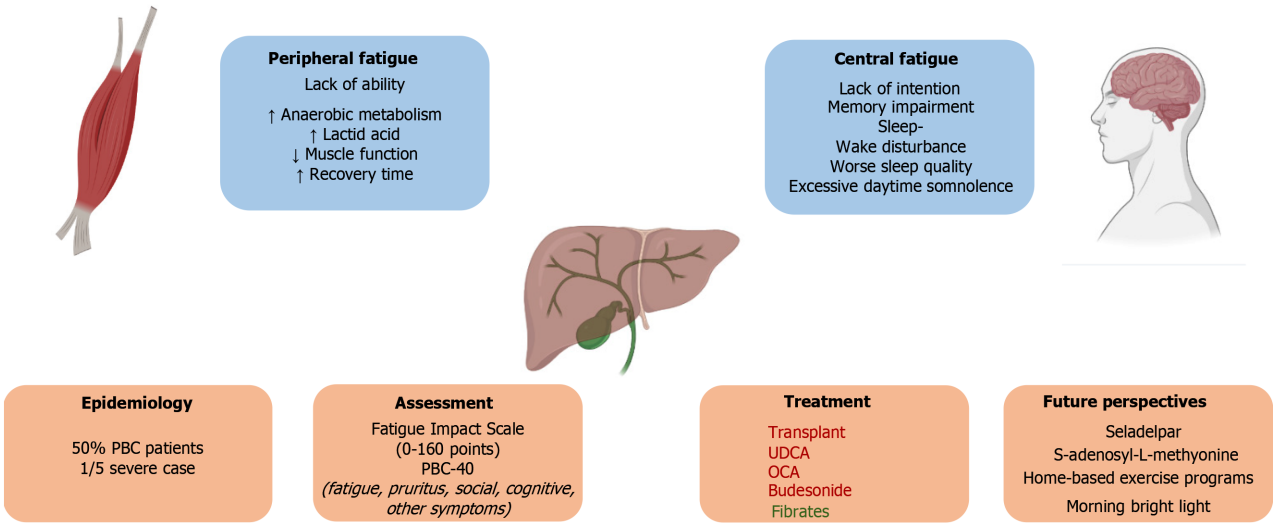

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Figure 1 Fatigue in primary biliary cholangitis: Key concepts. PBC: Primary biliary cholangitis; UDCA: Ursodeoxycholic acid; OCA: Obeticholic acid.

The key concepts presented in this review are illustrated in Figure 1.

CONCLUSION

The pathophysiology of fatigue in patients with PBC is still unresolved and as yet, there is no licensed therapy for fatigue in PBC patients. Since fatigue is an extremely common and debilitating symptom, further research is warranted to understand its causative mechanisms and to find effective treatment.

FOOTNOTES

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