



Using the NIH symptom science model to understand fatigue and mitochondrial bioenergetics

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Abstract

The symptom of fatigue is prevalent among patients with chronic diseases and conditions such as congestive heart failure and cancer. It has a significant debilitating impact on patients' physical health, quality of life, and well-being. Early detection and appropriate assessment of fatigue is essential for diagnosing, treating, and monitoring disease progression. However, it is often challenging to manage the symptom of fatigue without first investigating the underlying biological mechanisms. In this narrative review, we conceptualize the symptom of fatigue and its relationship with mitochondrial bioenergetics using the National Institute of Health Symptom Science Model (NIH-SSM). In particular, we discuss mental and physical measures to assess fatigue, the importance of adenosine triphosphate (ATP) in cellular and organ functions, and how impaired ATP production contributes to fatigue. Specific methods to measure ATP are described. Recommendations are provided concerning how to integrate biological mechanisms with the symptom of fatigue for future research and clinical practice to help alleviate symptoms and improve patients' quality of life.

Keywords: Adenosine triphosphate, fatigue, PROMIS, symptom science

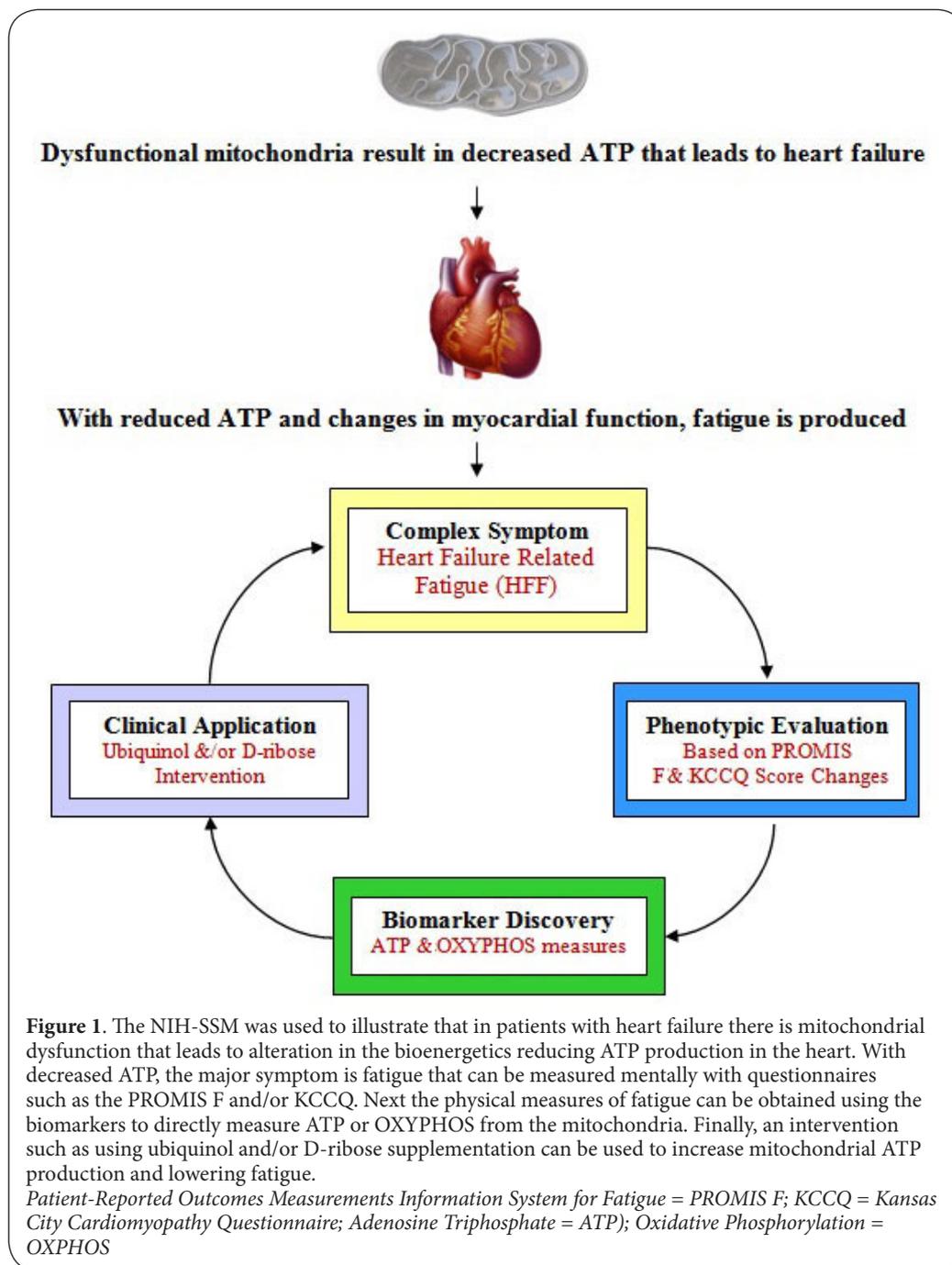
Introduction

Fatigue is commonly described as one's perceived lack of energy or feelings of tiredness [1]. As such, fatigue has been observed as a normal human response to increased physical exertion as well as a physical symptom of underlying disease [2]. Fatigue has been associated with several diseases including cardiovascular and respiratory disorders, cancer, neurologic conditions, diabetes, thyroid abnormalities, rheumatic diseases, psychiatric conditions, and sleep disturbance disorders [3]. Because fatigue can lead to physical debilitation and diminished quality of life for individuals, it is important to assess and manage the symptom of fatigue for early detection of disease, monitoring illness progression, and evaluation of the effectiveness of clinical treatments [4,5]. One common group of patients that have severe fatigue is those suffering from heart failure. Fatigue in patients with heart failure is defined as persistent tiredness and the perception of difficulty performing daily activities because of this fatigue [6].

The National Institutes of Health Symptom Science Model (NIH-SSM) was created to guide the development of precise

treatment decisions when evaluating an individual symptom such as fatigue or symptom clusters. Based on this model demonstrated in **Figure 1**: (1) the person presents with the symptom of fatigue; (2) phenotypic data are collected based on the patient's behavioral (self-reported), biological, and clinical information; (3) biomarkers are determined; and (4) a clinical intervention can be developed and applied [7-9]. Therefore, evaluation of patients with fatigue should incorporate multifaceted measures to assist with identifying the best treatment strategies to optimize energy levels.

Bioenergetics is the branch of biochemistry that focuses on how cells transform energy including how energy is produced, stored, or consumption of adenosine triphosphate (ATP) [10,11]. The ability to generate energy in the mitochondria is related to the production and utilization of the molecule called ATP. ATP is produced within the mitochondria during oxidative phosphorylation [12]. In the mitochondria the metabolism of sugars are completed and approximately 30 molecules of ATP are produced for each molecule of glucose oxidized. ATP is essential for maintaining cellular functions [13]. Thus, if ATP



production becomes compromised, it can result in the patient experiencing fatigue. In this paper, we will be applying the NIH-SSM to the symptom of fatigue, specifically examining the phenotypic characterization of fatigue and its relationship to mitochondrial ATP production.

This literature review is an overview of the current state of knowledge of mitochondrial bioenergetics and its relationship to fatigue. Throughout the review process, we used a synthesis matrix to identify various sources that reveal what is known, and what is not known about the phenotype of fatigue and

mitochondrial performance biomarkers. We will use examples specifically related to patients with heart failure because there is a relationship between fatigue and mitochondrial dysfunction in this complex syndrome. This article will provide new and additional information concerning how to assess and examine fatigue from a mitochondrial perspective.

Review Symptom science model

One of the four priorities of the National Institute of Nursing

Research (NINR) is symptom science that supports the scientific foundation of nursing practice [7]. The NIH-SSM was created by scientists in the intramural research program at NINR to guide research focusing on biological mechanisms of symptoms to characterize symptom phenotypes, identify biomarkers, and develop interventions that are targeted and effective, thus advancing symptom management and care. Symptoms that occur with a single disease or more often with comorbid conditions negatively impact functionality and well-being, contributing to decreased health-related quality of life (QoL). Characterizing symptoms and identifying the biological mechanisms can lead to improved assessment and treatment to improve health, survival, and QoL. The NIH-SSM is a systematic step-by-step process that provides direction to clinicians and researchers to target symptoms that may assist with improving patient care [14]. The outline of this discussion is based upon the symptom science model (Figure 1) for fatigue and will begin with the discussion of the phenotypic evaluation of fatigue, then examine the role of bioenergetics and mitochondrial biomarkers of fatigue, and end with the clinical application of the NIH-SSM and conclusion. We will focus on mitochondrial dysfunction that has been implicated in the development of heart failure leading to the symptom of fatigue. Mitochondria in the cardiac myocytes in patients with heart failure have increased reactive oxygen species and mitochondrial damage that causes the oxidative stress and the reduction of ATP production.

Complex symptom of fatigue

A symptom is a self-reported perception of an individual's experience such as fatigue [14]. The symptom of fatigue is an important clinical concern because it is one of the most common reasons why patients seek healthcare [7]. Fatigue often impacts patient's health outcomes and QoL. Thus, assessment and management of symptoms is a hallmark of nursing practice [8]. The symptom of fatigue for clinicians and researchers can be highly subjective thus, there are multiple definitions of fatigue and many psychometric measures [15]. The ultimate goal for nurses is to reduce and improve the symptom of fatigue.

Phenotypic evaluation of fatigue

Fatigue has most often been measured by researchers and clinicians using validated self-report measures. These mental measures of fatigue are valuable for understanding patients' perspectives concerning their perceived lack of energy [4]. However, physical measures of fatigue are also important to gain a broader assessment of energy levels and assist healthcare providers with making the best treatment decisions. Physical measures of fatigue often include physical assessments and biomarkers. Serum biomarkers have been beneficial in detecting and monitoring the progression of various disease states within the general patient population [1]; thus, examining biomarkers for cellular energy could be

very useful for evaluating and intervening when patients report symptoms of fatigue.

Mental measures of fatigue

Identification of the symptom of fatigue usually depends on the patient's initial self-report. It is critical to have reliable and valid tools and instruments to accurately evaluate the level of the patient's reported fatigue. Various unidimensional and multidimensional questionnaires have been developed and used to assess fatigue [16]. However, there is a major concern related to the patient's interpretation of the questionnaire items because of the subjective nature of one's perception of fatigue. The word choices used on fatigue scales may hold different meaning to patients based on their demographic backgrounds, life experiences, and disease states. Therefore, the tool or instrument used to measure fatigue should be specifically applicable to the patient populations.

Many psychometric measurements of the symptom of fatigue are available to assess self-reported fatigue focusing on mood, activity, energy, and behavior [1,7]. These psychosocial constructs of fatigue influence a person's perception of their health. Some of the commonly used mental measures of fatigue for the general population include the Patient-Reported Outcomes Measurements Information System for Fatigue (PROMIS-F) and POMS. Other mental measures of fatigue for specific patient populations include Kansas City Cardiomyopathy Questionnaire (KCCQ), Functional Assessment of Cancer Therapy: Fatigue (FACT-F), and Quality of Life in Neurological Disorders (Neuro-QoL). These measures are briefly described in Table 1.

The PROMIS is comprised of measures of mental, social, and physical health determinants across a multitude of specific domains for adults and children [17]. The PROMIS for Fatigue (PROMIS-F) item banks assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming exhaustion that may decrease a patient's ability to execute daily activities. The fatigue scale is administered as either a computer adaptive test (CAT) or a short-written form. The PROMIS fatigue instruments are available in many formats to include adults (7 tools, PROMIS-F, PROMIS F-SF 4-13a), adult cancer (1 tool, PROMIS F-Ca), pediatric self-report (4 tools, PROMIS F (v1-2), PROMIS SF(v1-2)10a) and parents serving as proxy reporters for their child (4 tools, PROMIS PPF (v1-2), PROMIS PPF-SF-F(v1-2)10a). Most of the PROMIS fatigue questionnaires rate the frequency of the test items on a 5-point Likert scale with varying combinations of experience and impact questions covering the past 7 days, except for the fatigue short form 7b, which includes questions about only the present day [18].

The POMS measures six distinctive mood states over the past 7 days using a 5-point Likert scale [19,20]. It features two scales related to perceived energy level, the Vigor factor and the Fatigue factor. The Vigor scale consists of eight questions and the Fatigue scale has seven questions.

Table 1. List of psychometric instruments for the measurement of the symptom of fatigue.

Name of Instrument	Number of Questions	Measurements
PROMIS Fatigue CAT	95	This tool includes a range of symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles.
• PROMIS Fatigue Adult Short Form 4a	4	3 experience and 1 impact item related to fatigue
• PROMIS Fatigue Adult Short Form 6a	6	3 experience and 3 impact items related to fatigue
• PROMIS Fatigue Adult Short Form 7a	7	3 experience and 4 impact items related to fatigue
• PROMIS Fatigue Adult Short Form 7b	7	Modified PROMIS Fatigue Adult Shortv1.0-Fatigue 7a to evaluate daily fatigue
• PROMIS Fatigue Adult Short Form 8a	8	4 experience and 4 impact items related to fatigue
• PROMIS Fatigue Adult Short Form 13a	13	6 experience and 7 impact items related to fatigue to evaluate daily fatigue.
• PROMIS Fatigue Adult Cancer	54	All of which are also in the PROMIS Fatigue item bank* but pertain to cancer-related fatigue.
FACT-F	41	Assessing fatigue and anemia-related concerns in people with cancer. 5 domains.
POMS Vigor-Activity	8	Mood of vigorousness, ebullience, and high energy
POMS Fatigue-Inertia	7	Mood of weariness, inertia, and low energy level
KCCQ	15	Physical limitations, social interference, quality of life related to fatigue in patients with heart failure

PROMIS, Patient-Reported Outcomes Measurements Information System; POMS, Profile of Mood States; KCCQ, Kansas City Cardiomyopathy Questionnaire;

*The experience bank contained items measuring intensity, frequency, or duration of fatigue, whereas the impact bank contained items measuring impact on physical, emotional, or social function.

Disease-specific psychometric instruments are customized for a defined subset of the population. Examples of these measurements include the KCCQ, FACT-F, and Neuro-QoL. The KCCQ is a disease-specific assessment of health status for individuals diagnosed with heart failure. The KCCQ form includes 15 questions asking about the past 2 weeks to measure an individual's physical limitations, social interference, and quality of life based on the severity of heart failure symptoms including fatigue, dyspnea, and edema [21]. The FACT-F questionnaire includes 41 questions that assess fatigue and anemia-related concerns in the domains of fatigue, physical health, social and family well-being, emotional health, and functional well-being for those with cancer [22-24]. The Neuro-QoL questionnaire evaluates the physical, social, mental, and functional activities of particular symptoms, behaviors, and feelings as they relate to those with neurological disorders [25]. The Neuro-QoL includes a short and long fatigue form with 8 and 19 questions each, respectively.

Physical measures of fatigue

In addition to the mental measures of fatigue, it is important to use physical methods to evaluate the patient's level of

fatigue. Such physical measures often involve exercise that can induce the patient to experience fatigue caused by the underlying biologic mechanisms related to specific diseases such as heart failure. The cardiac exercise stress test, maximal handgrip strength, and the 6-minute walk test are examples of these measures.

During a cardiac exercise stress test, the patient walks on a treadmill or cycles to increase the heart rate and make the heart work progressively harder [26,27]. Normal vital signs are monitored, and the symptoms of fatigue and chest discomfort are assessed. If there are signs of abnormalities in the electrocardiogram, heart rate, or blood pressure or signs of worsening fatigue or chest pain, this may indicate coronary artery disease [28]. During this type of stress test, fatigue is measured physiologically and classified in three ways: (1) peripheral fatigue; (2) central fatigue; or (3) neuromuscular fatigue [29]. Fatigue is measured at rest, during exercise, and after exercise [30]. However, the criterion used to end a stress test is often the patient's expression of the symptoms of fatigue, dyspnea, leg fatigue, or chest pain [31]. Fatigue symptoms are often recorded at each stage of the exercise stress test using the 11-point Borg scale [30,32]. This scale

ranges from 0 to 10 with 0 being "Nothing at all" to 10 being "Very very severe (maximal)." According to Borg's psychophysiological basis for exertion, perceived fatigue is the best indicator of the degree of physical strain [33]. Often the word "fatigability" is used when describing a patient's symptom of fatigue. However, fatigability is the degree of fatigue with daily activities and differs from fatigue related to muscle endurance during an exercise stress test. A clear definition of fatigability helps standardize the measurements to objectively assess how it changes under a specified activity in terms of duration, intensity, and frequency. It is often measured during performance-based assessment [34].

Maximal handgrip strength (MHGS) can be used to examine exercise performance in healthy older subjects and in patients with chronic fatigue and other diseases. Often exercise stress tests and other maximal performances are not possible for severely tired patients. The MHGS is an alternative measure of fatigue when ergometric cycle or treadmill tests are not possible. MHGS measurement may be useful to evaluate the maximal physical performance of patients with fatigue. However, it is important to remember the sole MHGS measurement cannot replace the information provided by a maximal exercise test that can increase in exercise-induced oxidative stress [35,36].

The American Thoracic Society introduced the 6-Minute Walk Test (6MWT) in 2002 to measure both aerobic capacity and endurance in walking over 6 minutes [37]. It is a simple and inexpensive test that is sensitive to fatigue-related changes when the patient walks in a 100-foot hallway space for 6 minutes [38,39]. Since its inauguration, the 6MWT has been utilized to evaluate fatigue and dyspnea in patients with various medical conditions [40,41]. At the beginning of the test, the patient stands and rates their baseline overall symptoms of fatigue and dyspnea using the Borg scale [42]. Immediately after the 6 minutes of walking or when the patient stops due to exhaustion and sits in the chair, the patient is asked to rate their symptoms of fatigue and dyspnea again using the same Borg scale [43]. The 6MWT is a useful measure of functional capacity and is helpful in measuring the patient's symptom of fatigue particularly when examining the effect of a therapeutic intervention [44,45].

Role of mitochondrial bioenergetics and ATP biomarkers for fatigue

The next step of NIH-SSM after identifying the phenotypes of fatigue is identifying a biomarker to measure fatigue. Since fatigue is related to the reduction of mitochondrial ATP production, it is important to begin with understanding mitochondrial dysfunction and biomarkers to measure oxidation phosphorylation. Mitochondria are the powerhouse of cells and play a key role in maintaining cellular functions and survival by producing ATP. Dysfunction in mitochondria can cause impaired mitochondrial bioenergetics that may be due to: (1) an inadequate number of mitochondria; (2) an inability

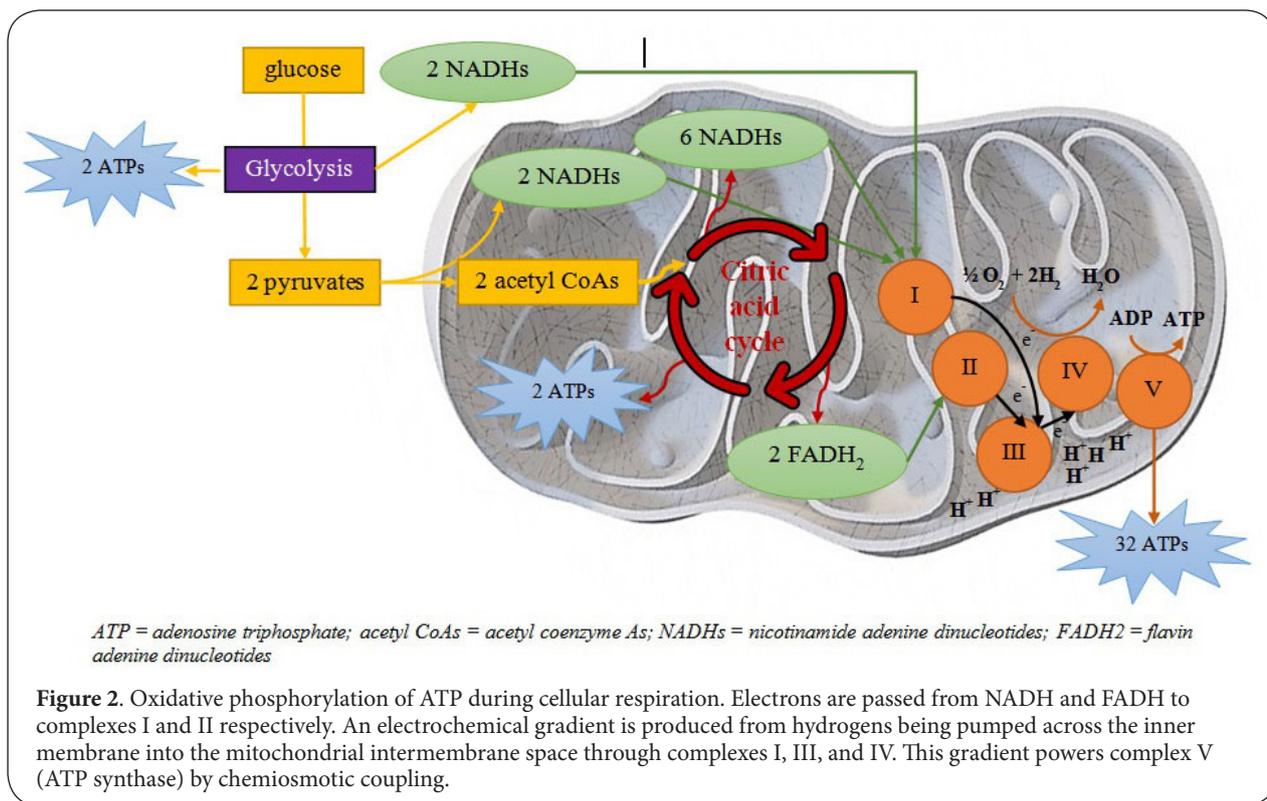
to produce the needed substrates to mitochondria; and/or (3) a problem within the mitochondrial electron transport chain and ATP machinery [12].

Adenosine triphosphate production in the cell

The ATP molecule produced within the mitochondria serves as the primary source for cellular energy. Production of ATP is required for the preservation of normal cellular function [12], and higher quantities of mitochondria can be found in cardiac muscle, brain cells, and skeletal muscles that require more ATP to function [46]. The majority of ATP is produced in the mitochondria by a process called cellular respiration (**Figure 2**). Cellular respiration involves several biochemical reactions to yield 36 molecules of ATP [47]. In the cell cytoplasm, glucose is metabolized by the process of glycolysis to yield 2 molecules of pyruvate, which are then shuttled into the mitochondria. The 2 molecules of pyruvate undergo oxidization to form 2 molecules of acetyl coenzyme A (acetyl CoA) to participate in the citric acid cycle. In this process, often referred as the Krebs cycle, a series of chemical reactions occur to release stored energy from proteins, carbohydrates, and fats into carbon dioxide and ATP. Glycolysis, pyruvate oxidation, and the citric acid cycle all contributes electrons through carrier molecules to the main component of ATP production, the electron transport chain (ETC). The ETC is composed of five complexes that generate approximately 32 molecules of ATP [10,48,49]. In the process of chemiosmosis, electrons in complexes I to IV produce an electrochemical gradient in which hydrogen ions leave the mitochondrial matrix. The electrons are then used in complex V (ATP synthase) to produce ATP by oxidative phosphorylation [49,50].

Impaired mitochondrial bioenergetics

Dysfunction in cellular respiration can lead to impaired bioenergetics and a severe reduction in ATP production [51,52]. Within the complexes, ubiquinone is reduced to ubiquinol that is essential for oxidative phosphorylation. However, this process is significantly decreased with aging and in chronic diseases such heart failure. Subsequently, there is a reduction in the generation of ATP because there is less ubiquinol produced [48,53,54]. Impaired mitochondrial bioenergetics significantly affects cellular and organ functions, contributing to various signs and symptoms including the fatigue that patients experience. Many investigators have hypothesized that fatigue is correlated with mitochondrial dysfunction, for example, among patients with heart failure [10,55,56]. Reduced myocardium oxidative metabolism can lead to the inability to generate and transfer energy. This is the primary mechanism linking mitochondrial dysfunction and contractile failure. In patients with heart failure, the mitochondria cardiac myocytes have structural and energetic abnormalities leading to free radical damage that reduces ATP production. Impaired ATP production in cardiomyocytes negatively impacts the cardiac cycles, resulting in reduced cardiac output to meet the body's



metabolic requirements. Thus, researchers are investigating whether supplemental oral ubiquinol could stimulate production of additional ATP to assist older patients with heart failure. More ATP will perhaps improve myocardial function, and the patient will experience less fatigue [57].

Measuring ATP as a biomarker

Impaired mitochondrial bioenergetics is considered one of the key underlying biological mechanisms associated with the symptom of fatigue [58]. ATP is often used by scientists as an indicator of cellular energy and is a useful biomarker to assess mitochondrial bioenergetics. The most common method for ATP measurement is using bioluminescence that relies on the enzyme luciferase's consumption of ATP. Luciferase is the substance produced in the tail of the firefly, and the oxidation of the luciferin requires ATP [59,60]. When luciferin and luciferase are added to a sample, an amount of light is generated that is proportional to the amount of ATP production [61]. A new and novel method to measure ATP uses atomic force microscopy (AFM) [62,63] that can measure ATP at the single molecule level. AFM uses a real-time 3D-observation technique to visualize the ATP molecule in order to quantify and compare ATP molecular images. This technique still uses the firefly luciferin-luciferase method with a luminometer. There are now hand-held devices to monitor clean surfaces in hospitals based on ATP luminescence [64,65]. Recently, a point-of-contact luminometer has been adapted to measure

ATP in blood samples of patients with heart failure who are experiencing extreme fatigue [66]. There are also fluorometric and colorimetric dual-mode assays to detect ATP that uses specific fluorescent labeled aptamer to target ATP [67,68]. This technique allows for a very accurate quantification of ATP as well as visual colorimetric detection [67,69].

Measuring Electron Transport Chain (ETC) and Oxidative Phosphorylation (OXPHOS)

Within the mitochondrial oxidative phosphorylation (OXPHOS) system, there are 5 complexes embedded in the mitochondrial inner membrane. These complexes assist with the aerobic synthesis of ATP. Thus, many investigators measure OXPHOS system enzymes in cells and tissues. Most commonly polarographic and spectrophotometric assays are used and can be completed in one day of work. These biomarkers often require isolation of mitochondria quickly and are very dependent of the quality of the sample. The reagents used in the biomarker must be freshly prepared and can be technically limited in resolution of direct assessment of O₂ consumption and ATP production [70-72]. However, in the future more advanced development and application of these techniques may clarify the role of mitochondria on the symptom of fatigue.

Clinical Application and Implications

Fatigue is a common symptom experienced by many patients with chronic medical conditions. The severity of fatigue can

range from mild to serious and it can have a significant impact on the patient's health as well as their cognitive, work, and safety performance. Recognizing the symptom of fatigue early by using appropriate tools and instruments such as PROMIS-F could prompt clinicians to gather additional information to facilitate an appropriate treatment plan. Careful selection of the correct psychometric fatigue tool would be an important first step when the patient reports fatigue. In addition, searching for the underlying biological mechanisms that lead to the symptom of fatigue is equally important in order to personalize therapeutic interventions. The symptom of fatigue is commonly associated with impaired ATP synthesis and an indication of mitochondrial dysfunction. Levels of ATP and/or OXPHOS ETC enzymatic activity can be used as biomarkers for mitochondrial function and as a way to evaluate the effectiveness of interventions to treat fatigue. Researchers have developed methods to measure ATP both in the laboratory and in the clinic. These techniques are being adapted for rapid measurement of ATP using a point-of-contact luminometer. This presents an exciting opportunity for clinicians to not only assess the patient's self-reported symptom of fatigue, but also have a physiologic biomarker for fatigue.

The NIH-SSM is useful in guiding the development and implementation of studies on symptom science. For example, researchers are examining the effectiveness of dietary supplements (ubiquinol and D-ribose) in patients with heart failure with preserved ejection fraction (HFpEF) [73-76] who present with fatigue and decreased vigor [57]. In a randomized clinical trial, fatigue is measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and vigor is measured using the Profile of Moods State (POMS) Vigor subscale. The behavioral data are combined with an additional clinical measure using a 6-minute walk test to characterize cardiac dysfunction-related fatigue. Decreased energy and physical fatigue may occur when ATP production is impaired due to mitochondrial dysfunction. ATP is measured and is used as a biomarker to assess the patient's fatigue and to evaluate the efficacy of therapeutic agents ubiquinol and D-ribose in reducing the symptom of fatigue [77].

Using the NIH-SSM to examine the symptom of fatigue has significant implications to nursing research, practice, and education. Nurse scientists are measuring mitochondrial function in relation to fatigue in a number of diseases such as heart failure and cancer [14,57,66]. They are using new instrumentation and technology to measure mitochondrial bioenergetics and how it relates to the symptom of fatigue in different disease processes. Findings from these studies will then be able to provide nurses in practice the evidence-based data needed to measure fatigue in the clinic or provide a treatment to reduce the symptom burden of fatigue. Finally, the NIH-SSM and mitochondrial bioenergetics as it relates to fatigue needs to be in both undergraduate and graduate nursing educational programs. Providing the pathophysiologic mechanisms for a disease is essential for nurses to understand

that the symptom of fatigue has a physiologic basis.

Conclusion

The symptom of fatigue is closely related to impaired mitochondrial bioenergetics. Future research that aims to reduce the symptom burden of fatigue should focus on investigation of factors that impact this biological mechanism and on exploration of interventions that decrease fatigue and restore mitochondrial bioenergetics. Direct and indirect biomarkers for mitochondrial function are essential to evaluate the effectiveness of this type of research. Measurements of these biomarkers are often completed in laboratory and are time-consuming and labor-intensive. Research is now focusing on the development of mitochondrial biomarkers that are simple, rapid, and easy for the clinicians to use at the bedside.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	QS	DM	JP	FR	KJK	JBH	JDP
Research concept and design	✓	--	--	✓	--	✓	✓
Collection and/or assembly of data	✓	--	--	--	--	--	✓
Data analysis and interpretation	✓	✓	✓	✓	✓	✓	✓
Writing the article	✓	✓	✓	✓	✓	✓	✓
Critical revision of the article	✓	✓	✓	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓	✓	✓	✓

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