

Original Article

## The Measurement of Fatigue in Hemoglobinopathies: A Systematic Review of Fatigue Measures

**Eleni Aslani, RN MSc PhDc**

Department of Nursing, Faculty of Human Movement and Quality of Life Sciences, University of the Peloponnese, Sparti, Greece. Registered Nurse Thalassaemia Transfusion Unit, General Hospital of Nikaia, "Agios Panteleimon", Nikaia, Greece

**Lyrakos Georgios, MSc Mph PhD Post Doc**

Health Psychologist, Psychiatric Department, General Hospital of Nikaia, "Agios Panteleimon", Nikaia, Greece and Post Doc, Department of Nursing, Faculty of Human Movement and Quality of Life Sciences, University of the Peloponnese, Sparti, Greece

**Tsironi Maria, PhD**

Professor, Department of Nursing, Faculty of Human Movement and Quality of Life Sciences, University of the Peloponnese, Sparti, Greece

**Correspondence:** Georgios Lyrakos, Ofryniou 46, Nikaia, 18454, Greece e-mail: geolyr@hotmail.com

### Abstract

**Background:** Fatigue is a common characteristic of physical or neurological disease as well as psychiatric disorders, often reported amongst patients' with hemoglobinopathies, as one of the most severe and distressing symptoms. A large number of scales have been developed attempting to measure the nature, severity and impact of fatigue in a range of clinical populations but only few have been used in hemoglobinopathies.

**Aim:** The aim of the present review is to explore the existing methods of fatigue evaluation in this population providing guidelines for the evaluation of fatigue for clinicians and nurses.

**Methods:** Database searches of Medline, PsycINFO, Cochrane and Google scholar were undertaken to find articles evaluating fatigue in patients with hemoglobinopathies.

**Results:** Out of the 72 initially identified papers, 7 fulfilled completely the eligibility criteria and were, thus, included in this review. To measure fatigue most studies used the 18-item PedsQL™ Multidimensional Fatigue Scale and the PROMIS Short form fatigue scale (7 items) in young children and adolescents, mainly with sickle cell disease.

**Conclusions:** Valid measurements concerning the measurement of fatigue have been used in patients with sickle cell disease but a lack of research was found in patients with thalassaemia major, emphasizing on the importance of studying and conducting more research targeting fatigue evaluation in beta thalassaemia patients.

**Key Words:** Fatigue, measurement, hemoglobinopathies, thalassaemia major, sickle cell disease

### Introduction

Fatigue is a condition that is used in our everyday life with subjective importance and great effect. Alternatively terms like tiredness, drowsiness, lack of energy, and exhaustion are used while in the literature, the definitions of fatigue vary greatly, making the identification of

the condition more difficult, as there are only few differentiating factors between causes, assessment indicators and the results that fatigue causes on human beings (Bartley 1976; Winningham et al. 1994). To a large extent, fatigue is defined either as a subjective symptom or as an objective reduction in the individual's performance (Wessely 1998), but it has also been

described as an independent syndrome (chronic fatigue syndrome). Through the existing research up to now, it is recognized that fatigue is generally complex and / or multifactorial (Aistars 1987; Ream & Richardson 1996), as it includes both physiological and psychological parameters, but also occupational and life events (Lewis & Wessely 1992; Ream & Richardson 1996; Aaronson et al, 1999; Magnusson et al. 1999).

Up to now, there are only few studies, regarding fatigue as a syndrome in patients with hemoglobinopathies and Thalassemia Major in particular. Specifically due to the fact that Thalassemia Major is a disease that put limits in the patient, as it requires continuous transfusions as well as specific activities that keep the level of hemoglobin stable to reduce the symptoms, the reduced hemoglobin value has been associated with increased fatigue (Shan et al. 2010). Chronic anemia has also been associated with fatigue as the transfusion itself seems to lead to fatigue in accordance with thalassemia guidelines (Gilron et al. 2010) And while fatigue is a widespread symptom in recent years and its incidence varies between 7% and 45% (Cathébras et al. 1992) in the working population, (Nijrolder, van der Windt, & van der Horst 2008) it is also a common symptom in patients with chronic conditions (Aistars 1987; Lewis & Wessely 1992; Smets et al. 1995; Bartsch, Weis, & Moser 2003), especially when there is a comorbidity with another disease (Franssen et al. 2003; Farren, Goodacre, & Stigant, 2013). Still, there is only one published interventional study dealing with fatigue in patients with Thalassemia Major, exploring the effect of carnitine and folic acid in reducing fatigue and muscle weakness in patients with homozygous beta thalassemia minor anemia, with positive results in the reduction of muscle weakness (Tabei et al. 2013). Also, in two case studies, that were published a few years ago, it is reported that paroxysmal nocturnal hemoglobinuria, which is also one of the hemoglobinopathies, may be accompanied by fatigue (Yin et al. 2011) and the same may happen in the case of other hemoglobinopathies (Kanavakis et al. 2004). Finally, there is a study that describes the existence of fatigue in sickle cell anemia as one of the major symptoms along with pain (White & Mullen 2004).

Although anemia is not a disease, it can be characterized as a condition which results from impaired erythrocyte production, inadequate

hemoglobin production, blood loss or abnormal erythrocyte maturation which is the case in hemoglobinopathies. The severity of clinical symptoms of anemia varies according to how effective the compensatory activity that is mobilized to increase oxygen delivery to vital tissues will be. As a result, when the anemic condition persists over time, like the case which happens in hemoglobinopathies, those compensatory mechanisms become exhausted and the patient suffers from dyspnea, tachycardia and palpitations, vertigo and fatigue, even when he or she is resting (Johansen et al. 2011). Like other conditions that impairs tissue oxygenation, fatigue when coexists with anemia, reduces patients ability to engage in the everyday normal activities and depression and stress may occur which makes this fatigue an intolerable physiologic and emotional burden (Curt 2000; Gillespie 2002).

According to the previous information, one can realize that it is important to discover whether this fatigue is a symptom of anemia (Beatrice 2003a) or psychologically related since this can differentiate the treatment which can be used (Beatrice 2003b) in order to allow patients with hemoglobinopathies to live a life with a better quality of life. However, there are no systematic reviews exploring the effect and severity of fatigue, studying the different ways of measuring fatigue in thalassemia and other hemoglobinopathies.

It can be concluded that even though fatigue is both prevalent and potentially debilitating, yet, it remains relatively unexplored, since it is difficult to define it, as it is a subjective experience (Dittner, Wessely, & Brown 2004) and hence, difficult to measure (Ream & Richardson 1996). However, it is important that research into fatigue is not restrained by the use of measures that lack reliability and validity and perpetuate the inability to cross-tabulate results across studies. Symptom assessment and management, both to detect the existence of symptoms and to manage symptoms through disease course, is vital both for treatment decisions as well as outcomes while symptom assessment measures should be comprehensive, accurate, and reliable.

Thus the aim of this systematic review was to identify the currently available measurements for fatigue used in hemoglobinopathies and thalassemia major in particular and make a

review on the effect of fatigue based on robust studies measuring the symptom.

### Methodology

To conduct this review, an electronic search on Scopus, Science Direct, PubMed and Google Scholar databases was used, through the keywords: "fatigue" OR "fatigue" AND "haemoglobinopathies" OR "hemoglobinopathies" OR "hemoglobinopathies" and augmented with follow-up references from article reference lists, which revealed 486 articles. After the exclusion of duplicate papers, and papers concerning other health conditions, 72 papers were identified.

The SPIDER (sample, phenomenon of interest, design, evaluation, and research type) approach, was used in order to help us choose the right articles for the systematic review, using hemoglobinopathies as the sample, fatigue as the phenomenon of interest, survey as the design of the selected studies, different factors of fatigue as the evaluation and quantitative as the research type.

Study selection was made by two independent reviewers (EA) and (GL) who selected the studies using the inclusion and exclusion criteria. Any disagreements during this process was resolved by discussion or by a third reviewer (MT).

Studies fulfilled the eligibility criteria of this review if they: (i) focused on patients diagnosed with hemoglobinopathies (Thalassemia major or minor, Sickle cell disease), (ii) outlined fatigue as one of major targeted symptoms, in order to measure fatigue as a unique symptom and not as a comorbid condition, (iii) were only cohort, and cross-sectional studies, but not reviews in order to avoid bias to the results of the study, and, (iv) studies where the full-text was available, so that the evaluation of the quality of the measurements would be possible. No exclusion criteria were used regarding the age of patients with hemoglobinopathies. However, scales that were cited only in abstracts or in reports of meetings were excluded. Studies were also excluded if not written in the Greek or English language.

Following the case of clinical trials where both editors and researchers share the context of a reporting standard (CONSORT and its amendments (Barbour 2013)), as a requirement for potential, public registration of those clinical trials, a combination that keeps transparency in

the design, conduct, and reporting of clinical trials, and has been recognized as sufficiently flexible in order to let editors to define appropriate omissions, the same happens with systematic reviews and meta-analyses, which often extant a basis for clinical decisions, and are also subject to firm reporting guidelines (PRISMA 2015). On the other hand, case-control, cohort, and cross-sectional studies, which are observational studies and are the ones used in the present report, even when given ethics review, they are not subject to all of the principles that assist standardized reporting of clinical trials. However, when those studies provide the best evidence available, they impact clinical practice. Careful presentation of analyses or non-publication of results can hence misinform patient care. As the authors of the STROBE guidelines for reporting observational studies have noted, "Research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn" (Vandenbroucke et al. 2007).

This is the reason why the quality criteria, based on which the included papers were evaluated, were derived from the STROBE checklist for observational studies cohort, case-control or cross-sectional studies (STROBE 2007) regarding study design, setting, participants, data sources/ measurement, results, methodology, demographics, unadjusted estimates, limitations and external validity of the study results. The aforementioned criteria were used so as to evaluate the reliability and validity of the papers examined in this review. Studies were scored with a 'Y' ('Yes') if they fulfilled a criterion, and, a 'N' ('No') if they did not fulfil a criterion. Scoring ranged from 0-10.

### Results

#### Eligible Studies

Once the duplicate papers were removed, there were 72 studies resulting from the search on the electronic databases. Out of the total number of studies, the authors excluded 56 papers on the basis of being irrelevant to this research, 2 on the basis of not measuring fatigue as a main symptom, 2 due to the full-text not being available, 2 on the basis of being literature reviews and, finally, 1 was excluded due to not using at least two groups of patients for the observation. The final included studies were 7, as shown in the Figure 1 'Flow Diagram' below.

### **The scales used for measuring fatigue in patients with hemoglobinopathies**

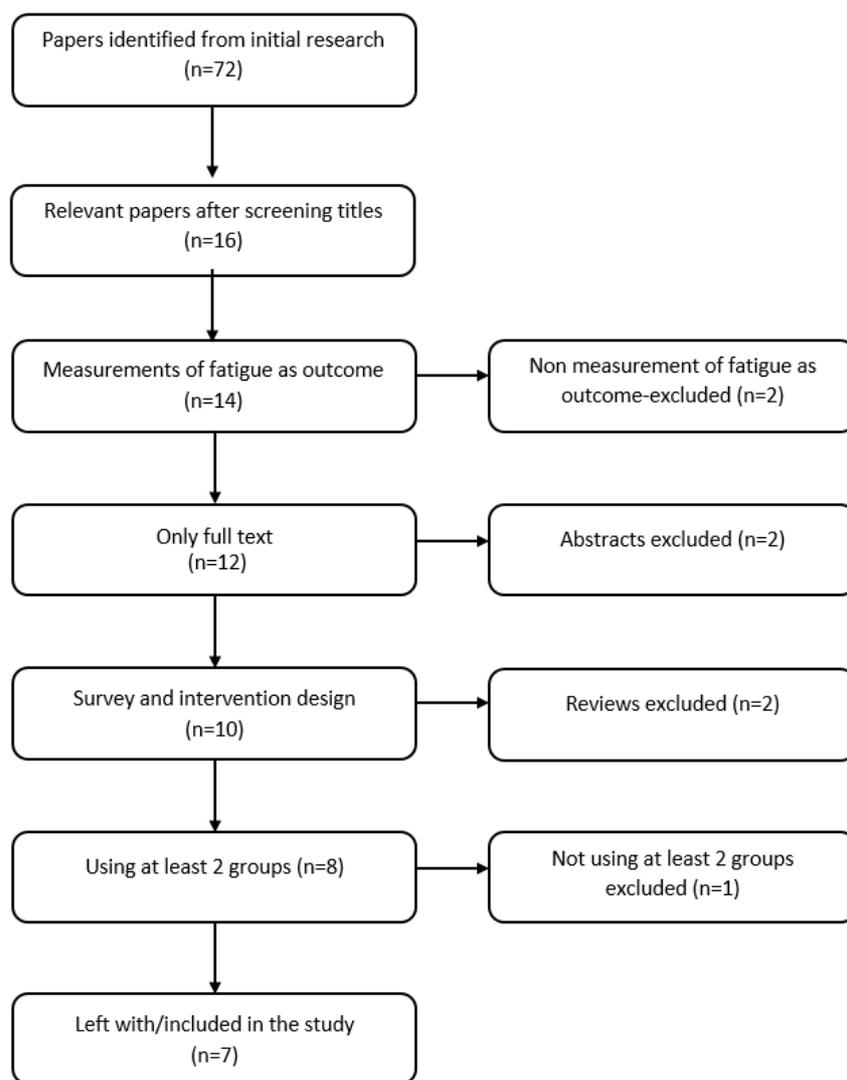
The 18-item PedsQL™ Multidimensional Fatigue Scale was used in two studies (Dampier et al. 2010; Panepinto et al. 2014), while a battery of three fatigue questionnaires (the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), the Brief Fatigue Inventory (BFI), and PROMIS Fatigue Short Form (7 items)) were used in one study (Ameringer, Elswick & Smith 2014). Three studies used the PROMIS Fatigue Short Form (7 items) in combination with blood tests (Lyon et al. 2014) or other questionnaires (Dampier et al. 2016; Keller et al. 2017) and finally, an alternative form of PROMIS Fatigue Short Form with 10 items was used in the last study (DeWalt et al. 2015).

Both the 18-item PedsQL™ Multidimensional Fatigue Scale, as well as the PROMIS Fatigue Short Form (7 items), were found to have robust psychometric properties, since the majority of the studied concerned the validation of these questionnaires (Dampier et al. 2010; Panepinto et al. 2014; Dampier et al. 2016; DeWalt et al. 2015; Keller et al. 2017) for young children and adolescents, as well as for adults with SCD (Keller et al. 2017). Also, both questionnaires are part of the Patient Reported Outcomes Measurement Information System (PROMIS®), which is a National Institutes of Health (NIH) initiative, that were created to advance the assessment of patient-reported outcomes (PRO) in patients with chronic diseases. Over the past ten years, PROMIS has developed several pediatric self-report item banks for ages 8-17 years across five general health domains (physical function, pain, fatigue, emotional health, and social health) consistent with the larger PROMIS network and were developed using qualitative and quantitative methods, including focus groups, expert item review,

cognitive interviewing, and item administration to a large population of children and adolescents to create banks of items specific to selected domains (Irwin et al. 2008; Walsh et al. 2008; Irwin et al. 2010). Higher scores indicate more of the measured symptom being experienced, which signifies worse health for the experienced symptom which in this research is fatigue. The fatigue scale has also a short form of 10 items and all items have a 7-day recall period and use standardized 5-point response options (e.g., never, almost never, sometimes, often, almost always; or, with no trouble, with a little trouble, with some trouble, with a lot of trouble, not able to do). The PROMIS Pediatrics T score of 50 was anchored as the mean of the calibration population, which was mixed with healthy children and chronically ill children. As such, the score of 50 does not represent any one group, but the same scoring metric is used for all applications, which allows for comparability across populations.

The 18-item PedsQL™ Multidimensional Fatigue Scale covers three domains, including General Fatigue (6 items), Sleep/Rest Fatigue (6 items) and Cognitive Fatigue (6 items) (Varni et al. 2002; Varni, Burwinkle, & Szer 2004), and has been validated among samples of children with numerous chronic health conditions (Varni et al. 2002; Varni, Burwinkle, & Szer 2004; Varni et al. 2009; Varni et al. 2010), including SCD (Ameringer, Elswick & Smith 2014). This scale has parallel child self-report and parent proxy-report formats identical to those of the Generic Core Scales. The format, instructions, and scoring method are also identical to the Generic Core Scales. The scales are scored similarly to the SCD Module scales, with higher scores indicating better HRQOL (lower fatigue). There is also a short form with 10 items available (Lai et al. 2013).

**Figure 1: Flow diagram of the studies included in the systematic review**



**Table 2: Summary results for final articles entering the review**

Authors	Population	Intervention	Comparison	Outcome
Dampier et al. 2010	825 girls (47%) and 947 boys (53%) from the Comprehensive Sickle Cell Centers Clinical Trial Consortium (N:1772)	18-item PedsQL™ Multidimensional Fatigue Scale	(SS/Sβ0 thalassemia versus SC/Sβ+ thalassemia	Moderate ceiling effects (15– 30%) were observed in cognitive fatigue (parent and child report) and general and sleep/rest fatigue scales (parent report).
Panepinto et al. 2014	240 paediatric patients with SCD and 303 parents from five clinical centers across the United States and 256 healthy adults N:799)	18-item PedsQL™ Multidimensional Fatigue Scale.	patients with SCD in 2 groups according disease severity Versus a sample of healthy children	For all scores, patients and their parents reported statistically significant greater fatigue than healthy children
Ameringer et al. 2014	60 adolescents and young adults were recruited with HgbSS disease (N:60)	Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), Brief Fatigue Inventory (BFI), PROMIS Fatigue Short Form (7 items)	Patients with mild versus severe disease No control group	Fatigue scores were moderate in severity in the past 24 hours as measured on the BFI and PROMIS scales. Fatigue scores on the MFSI-SF were mild to moderate in severity. On the MFSI-SF, scores were higher on the vigor and general fatigue subscales and lowest on the physical fatigue subscale
Lyon et al. 2014	295 participants, 60 of which with SCA from the Center of Excellence for Biobehavioral Approaches to Symptom Management (N:295)	PROMIS Short form fatigue scale (7 items)	Experience of fatigue and the impact of fatigue different patients groups VS cytokines	The means of individuals diagnosed with SCD (19.8) were lower than the total sample mean (21.1). There were no statistically significant relationships between any cytokine and fatigue.
De Walt et al, 2015	4 chronic health conditions (N = 1136), with pediatric patients from sickle cell disease programs at Emory University and	PROMIS®) and PROMIS Short form fatigue scale (10 items)	Patients with SCD who had received home treatment for pain in the past week VS those who had not	Patients who had been treated for pain reported lower mobility and upper extremity functioning and higher depressive symptoms, anxiety, pain interference, and fatigue than patients who had not. Also patients for all groups who had been hospitalized

	Duke University (N=235)			in the past 6 months showed significantly worse functioning in all areas, Fatigue was highly correlated with many other scales, over 0.55 (in absolute value) with all of the other scales except peer relationships
Dampier et al. 2016	A convenience sample of SCD children, aged 8–17 years, from two sickle cell programs (N:235)	PROMIS questionnaire paediatric items and PROMIS Short form fatigue scale (7 items)	SC/SB+ thalassemia vs. SS/SB <sup>0</sup> thalassemia	Female participants reported significantly higher fatigue. The number of pain episodes managed at home, number of ED visits for pain, and number of hospitalizations in the past 6 months were all significantly and positively associated with an increase in fatigue
Keller et al. 2017	490 adults with SCD from seven geographically-disbursed clinics within the US	PROMIS Fatigue Short Form (7 items) and ASCQ-Me	SCD patients in Low, Medium and High level of severity based on medical history characterized by prescription pain medication, blood transfusions and a number of these diagnoses (retinopathy, avascular necrosis, leg ulcers, kidney disease, stroke, and pulmonary hypertension)	Fatigue scores for the total sample were between 54.41 and 58.24. There was a statistical significant difference between 3 levels of severity in fatigue scores with one-way analysis of variance. aF-statistic=9.34 p < 0.0001. The PROMIS Fatigue SF was highly, significantly related to SCD severity

The PROMIS Fatigue Short Form (PROMIS), is a 7-item instrument that assesses the impact (4 items) and experience (3 items) of fatigue in the past week. In the PROMIS® initiative, fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue (upon physical, mental, and social activities). The PROMIS uses a 5-point Likert-type format with response options ranging from “Never” to “Always.” and are summed for a Total score and transformed to a T-score metric, which has a mean of 50 and a SD of 10. Higher scores indicate more fatigue. The PROMIS Fatigue

Short-Form has demonstrated robust reliability and validity across multiple samples (Cook et al. 2012)

Another scale which was used for measuring fatigue in a smaller sample of patients, was the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), which is a 30-item survey that assesses fatigue over the past month and has evidence of being a reliable and valid measure, including young adults (Wilkinson et al. 2011). The scale consists of 5 subscales: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor that have been

validated with confirmatory factor analysis (Stein et al. 2004). Using a 5-point Likert-type format with response options ranging from 0 (Not at all) to 4 (Extremely), responses are summed to obtain subscale scores. A total fatigue score is obtained by summing the four fatigue subscales (general, physical, emotional, mental) and subtracting the vigor subscale.

Finally, the last scale used was the Brief Fatigue Inventory (BFI), a 10-item self-report measure that assesses the severity of fatigue and interference in daily functioning over past the 24 hours (Mendoza et al. 1999). The first item asks if the individual felt “unusually tired or fatigued” in the past week. Three items address fatigue severity (worst and usual fatigue during the past 24 hours, and current fatigue) and 6 items address interference on an 11-point numeric rating scale. Numeric rating scales have been validated for use in adolescents (vonBaeyer et al. 2009). A mean total score of the 9 items was calculated, with higher scores indicating greater fatigue intensity.

### **Results about fatigue severity in hemoglobinopathies**

Since different populations and questionnaires were used for each study, it is not possible to draw total results from the studies but individually from each one. Though articles as a hole can be found for authors, population, intervention and outcome in table 2.

Individually for each study, first, Dampier et al. (2010), carried out a retrospective study in 1772 subjects (53% boys) with an average age of 9.6 years (SD 4.7). The sample consisted of patients with SS or S $\beta$ 0 thalassemia in 68% and SC or S $\beta$  + thalassemia at 32%. This study, which was one of the first to investigate fatigue in a hemoglobinopathic population, showed a progressive decline in all parent reported PedsQL™ scale scores except for cognitive fatigue across younger to older age groups (5–7, 8–12, 13–18), reflecting a declining health-related quality of life. Overall tests of mean difference across age groups were statistically significant for parent-reported total ( $p < 0.001$ ), physical ( $p = 0.002$ ), emotional ( $p = 0.027$ ), school functioning ( $p < 0.001$ ), total, general, sleep/rest fatigue scales (all  $p < 0.001$ ), and cognitive fatigue scale ( $p = 0.01$ ), as well as for child-reported physical ( $p = 0.023$ ), emotional ( $p = 0.002$ ), social ( $p < 0.001$ ), school functioning ( $p = 0.007$ ), and sleep/rest ( $p = 0.014$ ) and cognitive fatigue

( $p = 0.002$ ) scales. Finally, it should be noted that hemoglobin was not correlated with fatigue in this study.

A few years later, Panepinto et al. (2014), conducted a study with a larger sample aiming to report on the feasibility, reliability, and validity of the PedsQL™ Multidimensional Fatigue Scale in SCD for pediatric patient self-report ages 5–18 years and parent proxy-report for ages 2–18 years. This study included 240 pediatric SCD patients and 303 parents from five clinical centers in the United States and 256 healthy adults ( $N = 799$ ). PedsQL™ Multidimensional Fatigue Scale Scores were significantly worse with large effects sizes ( $\geq 0.80$ ) for patients with SCD than for a comparison sample of healthy children. Also, greater fatigue was significantly correlated with lower generic HRQOL. The correlations were mostly in the large effect size range. There were no significant differences between mild and severe SCD for self-report. Parent proxy-report demonstrated statistically significant greater fatigue in patients with severe disease than patients with mild disease. Though, the most important result of this study was the fact that patients with SCD and their parents demonstrated poor to fair and moderate agreement, result that is consistent with the extant literature that information provided by proxy-respondents is not equivalent to that reported by the patient, particularly for domains that are less observable and more internal such as fatigue.

In the same year, a study was conducted by Ameringer et al. (2014), to investigate the effect of fatigue in patients with sickle cell anemia. This study consisted of a smaller convenient sample of 60 adolescents and young adults aged 15 to 30 years. Results revealed that fatigue was moderate in severity over the last 24 hours, as measured with the BFI and PROMIS scales. The results of fatigue in the MFSI-SF questionnaire were mild to moderate. In MFSI-SF, results were higher in the stress and general fatigue sub-scales and lower in the physical fatigue sub-scale. The correlations between BFI Total (MFSI-SF Total, PROMIS Total) and pain (BPI), Sleep (PSQI), Stress (STAI) and Depression (CESD) were all statistically significant and had the expected direction, such that as pain, sleep disruptions, anxiety, depression and stress scores worsened, so did fatigue. In contrast, scores on fatigue scales were not significantly correlated with any of the cytokines, whereas there was moderate

correlation of fatigue with hemoglobin in the PROMIS scale, but not in BFI or MFSI-SF. Finally, all the measurements of fatigue (BFI Total, MFSI-SF Total, PROMIS Total) had a significant and negative correlation with the 8 SF-36 subscales, indicating that higher fatigue is associated with a lower quality of life.

In another study conducted by Lyon et al. (2014), fatigue was measured in different chronic conditions. Data were analyzed from 295 participants with fibromyalgia (N=72), second trimester pregnancy (N=73), sickle cell anemia (N=60), and cardiometabolic risk (N=91). The mean age of participants was 35.4 years and most participants were female. Symptoms were generally elevated between the samples: the fatigue level ranged from 18.9 to 24.7. The means of individuals diagnosed with SCD (19.8) were lower than the total sample mean (21.1). Also, the T-scores of individuals diagnosed with SCD (55.9) were lower than the total sample T-score (57.9). Finally, there were no statistically significant relationships between any cytokine and fatigue. The results of this analysis demonstrated a difference in cytokine patterns across the psychobehavioral variables that does not fully support the premise that fatigue, perceived stress, and depressive symptoms share a common biological mechanism as measured by peripheral cytokine levels. The positive correlation between several cytokines and level of depressive symptoms warrants further investigation.

A year later, De Walt et al. (2015) compared patients with 4 chronic health conditions (N = 1136), with pediatric patients from sickle cell disease programs at Emory University and Duke University (N=235). The hemoglobin genotypes for the SCD patients were SS (76.5%), SC (16.7%), Sickle B+ thalassemia (4.7%), and Sickle B0 thalassemia (1.3%). PROMIS® and PROMIS Short form fatigue scale were administered to the sample and patients with SCD were categorized in two groups based on the severity of the disease in those who had received home treatment for pain in the past week versus those who had not. Analysis indicated that patients who had been treated for pain reported lower mobility and upper extremity functioning and higher depressive symptoms, anxiety, pain interference, and fatigue than patients who had not. Also patients for all groups who had been hospitalized in the past 6 months showed significantly worse functioning in all

areas. Finally, fatigue was highly correlated with many other scales, over 0.55 (in absolute value) with all of the other scales except peer relationships.

Another study by Dampier et al. (2016), used a convenience sample of SCD patients (N:235) aged 8–17 years followed at two large Sickle Cell programs (Children's Healthcare of Atlanta and Duke University) which was recruited over an 8-month period at the time of routine clinic visits. In this study, each participant was administered between 97 and 107 PROMIS items from both the full bank (all PROMIS items that measure a single HRQOL domain) and short form measures (a small set of representative PROMIS items from each bank).

The mean scores for fatigue were 46.7 (SD:13.0) which are lower from the general population score but results showed that female participants reported significantly higher fatigue. The number of pain episodes managed at home, number of ED visits for pain, and number of hospitalizations in the past 6 months were all significantly and positively associated with an increase in fatigue. Also, pain, either from recent acute vaso-occlusive pain or from persistent bone/joint disease, equally impacted pain interference and fatigue scores.

Finally, last year, Keller et al. (2017) examined 490 adults with SCD from seven geographically-dispersed clinics within the US in order to validate two scales for use in adults with SCD. The scales used, were PROMIS Fatigue Short Form (7 items) and ASCQ-Me measuring disease severity. The sample was categorized in Low, Medium and High level of severity based on medical history characterized by prescription pain medication, blood transfusions and a number of these diagnoses (retinopathy, avascular necrosis, leg ulcers, kidney disease, stroke, and pulmonary hypertension).

Beyond the robust psychometric properties that the measurements had, the results that were revealed from this study concerning fatigue, indicated a statistical significant difference between the 3 levels of severity in fatigue scores with one-way analysis of variance. The PROMIS Fatigue SF was highly, significantly related to SCD severity, while fatigue scores for the total sample ranged from 54.41 to 58.24, scores that are significantly higher than those of the general population.

## Conclusions

Summarizing the findings, most of the studies found, were about measuring fatigue as a contributing factor in quality of life, or about measuring the psychometric properties of fatigue measurements. All studies targeted mostly children and young adults while regarding diagnosis most of them were about SCD patients. As highlighted by this review's findings, valid measurements regarding the measurement of fatigue already exist about SCD children and adolescents but there is a lack of papers exploring the consequences of fatigue in beta thalassemia major patients. These results are emphasizing on the importance of studying and conducting more research targeting fatigue evaluation in beta thalassemia patients.

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