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Fatigue in Adolescents and Young Adults with Sickle Cell Disease: Biological and Behavioral Correlates and Health-Related Quality of Life

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Introduction

Sickle cell disease (SCD) is a genetic hemoglobin disorder that occurs in 1 in 500 African American live births in the United States annually (National Heart, Lung and Blood Institute, [NHLBI] 2009). Worldwide, more than 300,000 infants are born with the disease each year (World Health Organization, 2010). Complications of the disease can be severe and life-threatening, such as acute splenic sequestration, aplastic crisis, vaso-occlusive crisis, acute chest syndrome, and multiorgan failure. Several of the more common symptoms associated with SCD are fatigue, pain, shortness of breath, and dizziness. Despite fatigue being one of the more common symptoms, nearly nothing is known about its prevalence, frequency, or severity, or the interference it may cause. However, the chronic hemolytic anemia, inflammation, and pain that are characteristic of the disease suggest that individuals with SCD are at risk for experiencing substantial fatigue.

Increasing understanding of the nature of fatigue in SCD is important because evidence suggests fatigue may be a predictor of impending crisis (Jacob et al., 2005), may be chronic as well as acute, and may be related to poorer quality of life as it has in other chronic illnesses (Bakshi, 2003; Falk, Swedberg, Gastonjohansson, & Ekman, 2007; Kralik, Telford, Price, & Koch, 2005; Ream & Richardson, 1997). Adolescents and young adults (AYA) may be particularly vulnerable to the effects of fatigue as they seek independence and pursue life goals such as a higher education, a career, and beginning a family. Yet research on fatigue in this population is limited, inhibiting early recognition and treatment. The purpose of this study was to describe fatigue in AYA with SCD and to examine potential biological and behavioral correlates.

This research is guided by a biobehavioral model of fatigue which suggests illness-related fatigue is influenced by biological and behavioral factors, and that associated biomarkers may be subject to change in response to interventions (Payne, 2004). In this study fatigue was defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively

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and to function at one's usual level in family or social roles (Glaus, 1998; North America Nursing Diagnosis Association, 1996; Patient Reported Outcomes Measurement Information System [PROMIS] Cooperative Group, 2012; Stewart, Hayes & Ware, 1992). We focused on biological and behavioral factors that may contribute to SCD fatigue, as well as personal factors. In addition, we extended the model by adding quality of life, a health outcome known to be affected by fatigue (Ballas et al., 2006; McClish et al., 2005; Stone, Richards, A'Hern, & Hardy, 2000; Walco & Dampier, 1990).

Although systematic assessment is lacking, a hint of the degree and impact of SCD fatigue is evident in the literature. For example, in one qualitative study a majority of the AYA with SCD reported being tired and lacking energy (While & Mullen, 2004). Further, this fatigue often interfered with their ability to carry out daily activities. In two studies on quality of life, adolescents with SCD reported lower levels of general, sleep/rest, cognitive, and total fatigue compared to healthy peers (Dampier et al., 2010), and young adults with SCD had significantly lower levels of vitality (energy) than the general population (Dampier et al., 2011). Several studies found lower levels of vitality in adults with SCD compared to healthy adults and adults with other chronic illnesses such as hemochromatosis, asthma, cystic fibrosis, and in patients receiving dialysis (Anie, Steptoe, & Bevan, 2002; McClish et al., 2005).

There is support in the literature for certain biological and behavioral factors that may influence SCD fatigue, particularly inflammation, anemia, pain, sleep quality, anxiety, depression, and stress (Ameringer & Smith, 2011). Sickle cell disease has an inflammatory component that has only been appreciated more recently (Hebbel, Osarogiagbon, & Kaul, 2004). Inflammation is attributed to the stimulation and disruption of the vascular endothelium that occurs when deoxygenation conditions cause the red cell to sickle, becoming rigid, and deform. Inflammation is known to occur during and preceding a pain crisis and is suspected to be chronic in nature (Redding-Lallinger & Knoll, 2006). Several biomarkers of inflammation, specifically interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor- α (TNF) may be associated with fatigue because of their correlations with muscle fatigue and poor sleep quality (Carmichael et al., 2006; Spath-Schwalbe et al., 1998; Visser et al.. 2002; Yoshida, 2004).

Individuals with SCD are at risk for decreased oxygenation due to low hemoglobin from hemolytic anemia (premature destruction of sickled cells) yet there has been little research examining the association between anemia and fatigue in SCD. Anemia is a significant contributor to fatigue in diseases such as cancer (Cella, Lai, Chang, Peterman, & Slavin, 2002; Yeh et al., 2008) and chronic kidney disease (Lasch, Evans, & Schatell, 2009). However, in one study on anemia and fatigue in children and adolescents with SCD, hemoglobin levels did not contribute to fatigue when hemoglobinopathy was included (Dampier et al., 2010).

The key symptom that defines SCD is pain. Pain and fatigue have not been studied extensively in concert in SCD, yet these symptoms are known to have a marked influence on each other (Stone, Richards, A'Hern, & Hardy, 2000; Walco & Dampier, 1990). In SCD, more severe pain has been associated with decreased vitality in adults (Ballas et al., 2006; McClish et al., 2005), and with disruptions in sleep in children (Valrie, Gil, Redding-Lallinger, & Daeschner, 2007a). In one study on fatigue in children and adolescents with SCD, higher pain levels were found to be significantly associated with greater fatigue (Dampier et al., 2010).

Poor sleep quality, known to be a problem in SCD (Daniel, Grant, Kothare, Dampier, & Barakat, 2010; Kaleyias et al., 2008; Long, Krishnamurthy, & Palermo, 2008) is particularly

important because of its well-documented relationship with both pain and fatigue across illnesses (Devins et al., 1993; Lavidor, Weller, & Babkoff, 2003; Owen, Parker, & McGuire, 1999; Rasmussen, 1993). Anxiety and depression are strongly associated with fatigue, and, in fact, fatigue can be one of the symptoms of these disorders. As in other chronic illnesses, depression is more common in SCD compared to physically healthy individual (Cathebras, Robbins, Kirmayer, & Hayton, 1992; Hasan, Hashmi, Alhassen, Lawson, & Castro, 2003; Levenson et al., 2008). Stress, also a problem in SCD (Gil et al., 2004; Porter, Gill, Carson, Anthony, & Ready, 2000), has been significantly associated with fatigue across healthy and ill populations (Aaronson, Pallikkathayil, & Crighton, 2003; Kerr & Mattey, 2008). The relationships between these factors and fatigue need to be better understood in AYA with SCD.

Lastly, we added quality of life as an outcome that may be influenced by fatigue. The effects of fatigue on quality of life, including interference with daily activities, social isolation, and decreased well-being, have been demonstrated across various chronic illnesses (Bakshi, 2003; Falk et al., 2007; Kralik et al., 2005; Ream & Richardson, 1997), though these effects have not been examined in SCD. Because fatigue has been virtually excluded in much of the research on symptoms of sickle cell disease, prior to developing an intervention, a more in-depth understanding of fatigue is needed. The aims of this study were: 1) to describe fatigue; 2) to examine the relationships between fatigue and key biological and behavioral correlates, and personal and disease characteristics; and 3) to examine the relationships between fatigue and quality of life in AYA with SCD.

Method

This was a cross-sectional descriptive, correlational study. The institution's review board approved the study.

Participants

A convenience sample of 60 adolescents and young adults were recruited. Inclusion criteria were ages 15 to 30 years and diagnosed with SCD. Exclusion criteria were pregnancy and an individual's and/or minor's parent's inability to read and write in English.

Instruments

Fatigue—Three measures of fatigue were used to capture various dimensions of the symptom. The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) 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 (Stein, Jacobsen, Blanchard, & Thors, 2004; Stein, Martin, Hann, & Jacobsen, 1998; Wilkinson, Smeeton, Castle, & Watt, 2011). It 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. Internal consistency in this study was 0.89.

The *Brief Fatigue Inventory (BFI)* is 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 (von Baeyer et al., 2009).

The BFI has demonstrated excellent reliability, with an internal consistency reliability of 0.96, and validity (Mendoza et al., 1999). A mean total score of the 9 items was calculated, with higher scores indicating greater fatigue intensity. Internal consistency in this study was 0.88.

The *PROMIS Fatigue Short Form (PROMIS)* is a 7-item instrument that assesses the impact and experience of fatigue in the past week (PROMIS, 2012). The PROMIS uses a 5-point Likert-type format with response options ranging from “Never” to “Always.” A total score was calculated by summing scores across items. Internal consistency in this study was 0.83. For each of the 3 fatigue scales, higher scores indicate greater fatigue.

Biological and Behavioral Measures—*Brief Pain Inventory (BPI)* was used to assess pain (Cleeland & Syrjala, 1992; Daut, Cleeland, & Flanery, 1983). On a numeric rating scale, participants rated their worst and average pain during the past 24 hours, and pain now on an 11-point numeric rating scale. Higher scores indicate worse pain. Seven items assessed pain interference. The individual severity items and the mean of the interference items were used in the analysis. These items have been used extensively in research and have been shown to be reliable, valid, and sensitive to change (Cleeland & Syrjala, 1992).

Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-report measure that assesses seven dimensions of global sleep quality over a 1-month period: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication, and daytime function (Buysse, Reynolds, Monk, & Berman, 1989). A global sleep quality score is calculated, with a potential range of 0 to 21 points. Higher scores indicate poorer sleep quality. The PSQI has been used extensively and is a reliable and valid measure (Buysse et al., 1989).

State-Trait Anxiety Inventory (STAI) for adults was used to measure general anxiety. The adult form is on a 6th grade reading level and has been validated in adolescents 13 years and older (Spielberger, 1983). The State anxiety scale assesses the current emotional state and the Trait anxiety scale assesses anxiety proneness, asking how they feel in general. Response options are on a 4-point scale. Scores are totaled for each scale with a possible range of 20 to 80; higher scores indicate greater anxiety. The STAI has demonstrated adequate reliability with a test-retest in adolescents (Spielberger, 1983).

Center for Epidemiological Studies-Depression (CES-D): Depressive mood was assessed with the 20-item CES-D (Radloff, 1977). The CES-D measures the frequency at which individuals experience symptoms in the past week on a 4-point scale. A total score is calculated by simple summation of the scores for each item, for a possible range of 0 to 60. Higher scores indicate more depressive symptomatology. The CESD has been used extensively in research and is a valid and reliable measure with adolescents (Radloff, 1977; Radloff & Rae, 1979; Radloff, 1991).

Stress was assessed with the 10-item *Perceived Stress Scale (PSS)*, which measures the degree to which situations in an individual's life are appraised as stressful. Response options are on a 4-point scale and total scores can range from 0 to 40, with higher scores indicating greater perceived stress. The PSS is a widely used general measurement of perceived stress and it has accrued considerable reliability and validity data since inception (Cohen & Williamson, 1988).

Inflammation and Oxygenation: Blood samples were obtained for hemoglobin and cytokine levels. The inflammatory markers interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor- α (TNF) from plasma were examined. Plasma cytokine samples were

cryopreserved and batch processed to reduce inter-assay variability using the 17-plex kit with the BioPlex Pro 1(Bio-Rad; Hercules, CA).

Personal and Disease Characteristics: Age, gender, disease genotype, severity, and crisis status were obtained by survey or chart review. Disease severity was based upon clinical history as suggested by Panepinto, Pajewski, Foerster, and Hoffmann (2008). Participants were categorized a priori as having mild or severe disease. An individual who had a history of a sickle cell related stroke, acute chest syndrome, three or more hospitalizations in the past three years, or recurrent priapism was categorized as having severe disease.

Quality of Life—The *Medical Outcome 36-item Short Form (SF-36)* is a self-report measure of eight dimensions of quality of life: physical function, physical role functions, emotional role function, physical pain, vitality, general health, mental health, and social function. Scores are on a 100 point scale, with higher scores indicating better health-related quality of life. The SF-36 has been used extensively and is a reliable and valid instrument (Gandek et al., 1998; Ware & Sherbourne, 1992). In individuals with SCD, the SF-36 has correlated with SCD pain and SCD genotype (McClish et al., 2005).

Procedure

Recruitment took place from both the pediatric and adult hematology clinics and hospital units. Staff at the institution introduced the study to potential participants and parents of minors. Research personnel described the study in full to potential participants. Written informed consent was obtained from adult participants and from a parent of a minor participant, and written assent from the minor. Each participant received $25.00 after completing the study measures. During a routine clinic visit or hospitalization, participants were asked to complete a survey packet and provide blood samples.

Data Analysis

Descriptive statistics were used to describe the sample, fatigue, biological and behavioral variables, and quality of life, including means, standard deviations, and ranges for the continuous variables, and counts with frequencies for the categorical variables. Pearson's correlation coefficient was used to examine correlations. ANOVA was used to look for gender (male/female) and disease severity (mild/severe) differences in fatigue scores (BFI, MFSI-SF & PROMIS). The sample size was powered for the correlational analysis. For the correlation analysis an alpha = .05 two-sided Fisher's z test of the null hypothesis that the Pearson correlation coefficient equal zero, will have 80% power to detect a correlation as small as 0.39 with a sample size of 50 (per nQuery Advisor 6.0). Because the cytokine data were skewed positively, a log transformation was used to normalize the data and stabilize the variance. This was a pilot/descriptive study, therefore, no adjustment for multiplicity was used; the results from this trial should be regarded as exploratory and should be confirmed in a larger trial.

Results

Sample Characteristics

Sixty AYA, ages 15 to 30 years, participated in the study. Sample characteristics are reported in Table 1. More than half were females and most were single. A majority had HgbSS disease and most were categorized as having severe disease. Most were not receiving routine blood transfusions and upwards of one half were on hydroxyurea.

Descriptive results for the behavioral variables are in Table 2. Self-reported pain levels were of mild to moderate intensity. The mean PSQI Total score was 8.45; a score > 5 indicates

poor sleep quality. The mean STAI State score was 35.5 and Trait score was 39.6, which are comparable to normative samples of AYA of State scores which range from 35.2 to 40.5 and Trait scores which range from 34.8 to 41.0 (Spielberger, 1983). For the CES-D, the mean score was 16.1. For AYA, the CES-D cutoff score for depression is 22 (Cuijpers, Boluijt, & van Straten, 2008; Roberts, Lewinsohn, & Seeley, 1991) which is higher than the cutoff score of 16 for adults. The mean PSS score was 16.3, which is somewhat higher than normative samples of young adults and blacks, in which mean scores have range of 14.2 to 14.7 (Cohen & Williamson, 1988).

Fatigue

Our first aim was to describe fatigue. Most (69%) of the AYA reported feeling "unusually tired or fatigued" in the past week. Descriptive statistics of the fatigue measures are shown in Table 2. 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.

Fatigue and Potential Correlates

Our second aim was to examine the relationships between fatigue and the biological, behavioral, personal, and disease variables. Correlations between fatigue and the biological and behavioral variables are shown in Table 3. The correlations between the fatigue measures (BFI Total, MFSI-SF Total, PROMIS Total) and pain (BPI), sleep (PSQI), anxiety (STAI), depression (CESD), and stress (PSS) were all significant in the expected directions, such that as pain, sleep disruptions, anxiety, depression and stress scores worsened, so did fatigue. The strengths of these relationships were moderate to strong, with correlations ranging from 0.31 to 0.70. Fatigue scores were not significantly associated with any of the cytokines. Fatigue was correlated with hemoglobin on the PROMIS scale ($r = -0.30$, $p = 0.03$), but did not correlate with hemoglobin on the BFI or MFSI-SF (Figures 1-3).

Fatigue scores by sex, disease severity, and age were examined. Mean scores of fatigue differed significantly by sex on the PROMIS scale ($t = -2.90$, $p = 0.003$)—young women reported greater levels of fatigue ($M = 21.31$, $SE = 0.85$) than young men ($M = 17.58$, $SE = 0.97$)—but not on the BFI or MFSI-SF scales. Fatigue did not differ by disease severity or correlate with age on any of the fatigue scales.

Fatigue and Quality of Life

For the third aim, we examined the relationships between fatigue and quality of life. All of the fatigue measures (BFI Total, MFSI-SF Total, PROMIS Total) significantly and negatively correlated with all 8 subscales of the SF-36, indicating that greater fatigue was associated with lower quality of life (Table 4). The strengths of these relationships were also moderate to strong, with correlations ranging from $r = -0.34$ to -0.74.

Discussion

This study adds new information about the frequency, severity, and resulting interference of fatigue, as well as correlates of fatigue in AYA with SCD. Research in AYA with SCD is often combined with either adult or pediatric studies; therefore, findings from this study will be compared to studies in both these age groups. Fatigue was common and essentially moderate in severity in these AYA, whether it was assessed over the past day, week, or month. Based on scores on the BFI and PROMIS, fatigue moderately interfered with mood and daily activities such as school, work, and exercise. In other studies with adolescents with SCD, fatigue was widespread, and when compared to healthy adolescents, was more

frequent and severe (Barbarin, 1999; Dampier et al., 2010; While & Mullen, 2004). In adults with SCD, fatigue has not been systematically measured except as vitality. The mean score on the Vitality subscale of the SF-36 in our sample (47.4) was similar to other adults with SCD in the US (42.7) (McClish et al., 2005), and in the UK (47.7) (Anie et al., 2002).

We found fatigue to be a major problem in SCD compared to healthy populations but similar compared to others with chronic illnesses. In two studies, the mean MFSI-SF Total score in healthy individuals was much lower, −3.63 (Bardwell et al., 2006) and 3.65 (Pien et al., 2011), indicating less fatigue compared to our results, 14.82. Fatigue levels on the MFSI-SF were worse across all subscales compared to healthy young adults (Lim, Hong, Nelesen, & Dimsdale, 2005). Our mean score on the PROMIS was similar to Noonan et al.'s (2011) findings in multiple sclerosis (19.8 and 20.5 respectively). Compared to other diseases, including cancer, chronic pain, and HIV infection, fatigue levels are comparable, but most similar to those with chronic pain (Mendoza et al., 2010; Radbruch et al., 2003; Simmonds, Novy, & Sandoval, 2005).

Most of the biological and behavioral variables were significantly correlated with fatigue. Pain, the hallmark symptom of SCD, was significantly correlated with all fatigue measures. Similarly, sickle cell pain in children was found to be a significant predictor of fatigue (Dampier et al., 2010). Mechanisms between pain and fatigue remain unclear although sleep may be a critical factor. In children with SCD, Valrie, Gil, Redding-Lallinger, and Daeschner (2007b) found poor sleep was associated with greater levels of pain, with stress amplifying the relationship, but fatigue was not assessed. Our scores on the PSQI indicate average sleep quality was poor. Further, sleep quality was significantly correlated with fatigue across all three fatigue measures. Poor sleep quality in AYA with SCD may be due to sleep hygiene and sleep disordered breathing. Sleep hygiene was a robust predictor of sleep quality in a large study of healthy adolescents (LeBourgeois, 2005), and the prevalence of sleep-disordered breathing is higher in children with SCD (Kaleyias et al., 2008; Samuels, Stebbens, Davies, Picton-Jones, & Southall, 1992). In summary, whether aiming to improve fatigue and/or pain, there is empirical support that sleep quality should be addressed. Sleep hygiene may be particularly important and may be amenable to interventions, as would sleep disordered breathing.

In general, anxiety in SCD occurs at rates comparable to or slightly greater than healthy populations (Levenson et al., 2008; Simon, Barakat, Patterson, & Dampier, 2009). However, we were most interested in the relationship between anxiety and fatigue. The correlations between both state and trait anxiety and all fatigue measures were significant. Anxiety may be severe for certain sub-populations of AYA with SCD, and given its correlation with fatigue, should be routinely assessed, particularly if fatigue is present.

There is substantial evidence of a significant association between depression and fatigue in chronic illnesses (Kopp, Falger, Appels, & Szedmak 1998; Millikin, Rourke, Halman, & Power, 2003; Mohr, Hart, & Goldberg, 2003; Tench, McCurdie, White, & D'Cruz, 2000). We found moderate to strong correlations between the CESD and each of the measures of fatigue in these AYA. In the only study found on depression and fatigue in SCD, scores on the vitality subscale of the SF-36 were significantly lower for those who were depressed compared to those who were not (Levenson et al., 2008).

Acute and chronic stressors have been identified as key causes of fatigue among healthy adults (Brown & Thorsteinsson, 2009). We found moderate to strong correlations between perceived stress and fatigue. Although the relationship between stress and fatigue in SCD has not been studied, there are reports of decreased activity with stress. Adolescents with SCD have reported lower levels of activities, such as engagement in school and

extracurricular activities, with higher levels of stress (Gil et al., 2003). Adults with SCD have reported a reduction in housework, social activities (Porter et al., 1998), and general activities (Gil et al., 2004) when stress levels were higher.

Inflammatory markers have inconsistently been associated with muscle fatigue and poor sleep quality in previous studies (Bower et al., 2009; Davis et al., 2008; Kwak et al., 2012; Lim et al., 2005). We found no significant relationships found between the inflammatory markers, IL-1, IL-6, IL-10, and TNF, and fatigue in this study. These findings do not unlink bodily symptoms such as pain and fatigue from the vasculopathy and hemolysis of SCD, but suggest that more chronic indicators, like hemoglobin, correlate with fatigue than more acute ones, like peripheral cytokines. One-time collection, small sample size, and the complex nature of the inflammatory processes in SCD may all make it challenging to investigate the association between cytokines and fatigue.

Fatigue is universally considered a key symptom of anemia, for example, in cancer (Cella et al., 2002; Hinds et al., 2007; Smith, Glaspy, Tchekmedyian, Austin, & Kallich, 2003; Yeh et al,. 2008). Yet findings in SCD are intriguing. Dampier et al. (2010) found hemoglobin was not a significant contributor to fatigue when hemoglobinopathy was considered. In a study on hydroxyurea (HU), Ballas et al. (2006) found that scores on vigor and fatigue in high responders to HU (i.e., >50% change in hemoglobin F from baseline over a 2-year period) did not differ significantly from low responders. In the current study, lower levels of hemoglobin were significantly correlated with higher levels of fatigue on only one of the measures, the PROMIS, and the correlation was relatively weak. The PROMIS measures fatigue over the past week, the BFI over the past 24 hours, and MFSI-SF over the past month. So why has hemoglobin been inconsistently associated with fatigue in SCD? There may be a response shift or a degree of accommodation within the individual to low hemoglobin levels over time. Alternatively, certain measures of fatigue may be more sensitive based on the time frame (e.g., fatigue measured over a week or month) or on the dimensions assessed (e.g., impact or experience).

There was no association between age and fatigue in this sample but the age span was not broad. Similarly, in a study in healthy younger adults, there was no association between age and any of the MFSI-SF subscales (Lim et al., 2005). Fatigue differed significantly by gender on the PROMIS scale, with women reporting higher levels of fatigue, but not on either the BFI or MFSI-SF scales. These findings are consistent with a study that used a longer version of the PROMIS in which women of all ages reported higher levels of fatigue (Junghaenel, Christodoulou, Lai, & Stone, 2011). Studies on gender differences in fatigue among adolescents have varied (Mears, Taylor, Jordan, & Binns, 2004; ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2006). Fatigue may be affected by age and gender, but results across populations are mixed. However, other factors including pain, sleep, anxiety, depressive mood, and stress have stronger and more consistent correlations, and therefore may be more important to address in research and practice.

Fatigue did not differ by disease severity; there were no significant differences in fatigue levels between those with mild disease versus those with severe disease. Disease severity has been difficult to determine in SCD. Panepinto et al.'s (2008) categorization of disease severity is one of the few that exist and is as good as any other that we found. Again, small sample size, lack of true association, as well as the difficulty with measurement of SCD severity could explain our results.

Fatigue was significantly correlated with quality of life across all fatigue measures. Although other factors are correlated with quality of life in SCD, such as pain (Anie et al., 2002; McClish et al., 2005), age (Dampier et al., 2011; McClish et al., 2005) and disease

complications (Dampier et al., 2011), this study highlights the need for fatigue to be further examined to understand the degree and direction of influence on daily functioning and quality of life. The NHLBI has a collaborative project with PROMIS to develop a quality of life measurement information system specifically for SCD: the Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) (Czajkowski & Riley, 2012). This tool is designed to be used with the PROMIS and may provide a uniform, systematic approach to measuring quality of life in SCD.

There are several limitations of this study. The cross-sectional design limited the ability to examine fatigue over time. Findings are from one institution and a convenience sample which limits generalizability. A healthy group of AYA for comparison of fatigue levels was not included. However, we were able to use findings from other studies with similar age groups for comparison.

Conclusion

Adolescents and young adults reported mild to moderate levels of fatigue that were associated with higher levels of depressed mood and lower levels of activities of daily living. Across all measures of fatigue, SCD scores were worse compared to healthy individuals and were similar to those reported by individuals with other chronic illnesses. The fatigue measures assessed different periods of time: past day, past week, and past month. For the most part, all measures yielded similar results except for gender and hemoglobin, in which the PROMIS was the only measure that showed differences. Because fatigue is more than just being tired, a measure that assesses fatigue over the past week or month may more appropriately reflect the symptom.

The numerous factors that were significantly associated with fatigue suggest that common etiologies or mechanisms may be involved. For example, fatigue is recognized as a symptom of anxiety, depression, and stress; yet, fatigue is also a symptom of the disease itself. Distinguishing the etiologies of fatigue in SCD will be challenging. Clinically, fatigue could be used to gauge health. If fatigue is present, it is important to screen for these conditions. However, if one of these conditions is present, it most likely will not explain all of the fatigue. Correctly identifying the cause/s of fatigue is critical in determining appropriate interventions. Longitudinal studies to understand the trajectory of fatigue and influencing factors are needed.

More importantly, what can be done to reduce fatigue in SCD? While general management of the disease is provided to patients, specific management of fatigue is not usually addressed (Hassell et al., 2009; Kavanagh, Sprinz, Vinci, Bauchner, & Wang, 2011; Pack-Mabien & Haynes, 2009; Redding-Lallinger & Knoll, 2006). In fact, in the literature on fatigue in those with chronic illnesses, SCD is rarely included (Harris, 2008; Kralik et al., 2005; Neill, Belan, & Ried, 2006). There are no known reports of interventions to reduce or manage fatigue in the SCD literature. It has been proposed that perhaps this is because there is a perception that little can be done to reduce SCD fatigue and it is an expected consequence of the disease (While & Mullen, 2004). Life expectancy with SCD is increasing; ignoring this symptom is no longer acceptable. For cancer-related fatigue, the National Comprehensive Cancer Network (NCCN®) has an extensive guideline for screening for and managing fatigue (NCCN, 2009). Interventions for SCD may differ but this guideline can be used as a preliminary model. For AYA with SCD, routine assessment and improved management of fatigue is critically needed, as are effective interventions to reduce fatigue.

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Table 1

Sample Characteristics (N = 60)

Variable	***n* (%)**
Age (*M* ± *SD*)	22.5 ± 4.1
Hemoglobin (*M* ± *SD*) (range 6 – 14.9 g/dL)	9.6 ± 2.2
Sex	
Male	24 (40.0)
Female	36 (60.0)
Marital Status	
Single, never married	56 (93.3)
Married/Partner	1 (1.7)
Other[a]	3 (5.0)
Work Status	
Disabled	12 (20.3)
Full-time	7 (11.9)
Part-time	6 (10.2)
Student	20 (33.9)
Unemployed	11 (18.6)
Other[b]	3 (5.1)
Exercise: days per week (*M* ± *SD*)	1.8 ± 1.69
Genotype	
SS	39 (65.0)
SB_0 Thalasemia	2 (3.3)
SC	11 (18.4)
Sb+ Thalasemia	6 (10.0)
Unknown	2 (3.3)
Disease Severity	
Mild	15 (25.0)
Severe	45 (75.0)
Routine Blood Transfusions	
No	48 (80.0)
Yes	12 (20.0)
On hydroxyurea	
No	27 (45)
Yes	33 (55)
Crisis Status	
Not in crisis	53 (88.3)
In crisis	7 (11.7)
History of:	
Stroke	10 (16.7)
Acute Chest Syndrome	31 (51.7)

Variable	*n* (%)
Recurrent priapism	5 (20.8)[c]

Note.

[a] Other responses for marital status included girlfriend.

[b] Other responses for work status included homemaker, babysitter, pending disability.

[c] Percent of males.

Table 2

Means and Standard Deviations of Study Variables

Variable (Potential Range)	*M* (*SD*)
BFI subscales (0–10)	
Now	3.83 (2.52)
Usual	4.10 (2.63)
Worst	5.32 (2.97)
Interference	3.96 (2.38)
BFI Total (0–10)	4.30 (2.16)
MFSI-SF subscales (0–24)	
General	9.13 (5.7)
Emotional	6.83 (5.6)
Physical	4.75 (4.8)
Mental	5.52 (4.9)
Vigor	11.35 (5.4)
MFSI-SF Total (−24–86)	14.89 (20.3)
PROMIS Fatigue Short Form (7–35)	19.82 (5.3)
BPI	
Now (0–10)	2.75 (2.8)
Average (0–10)	4.0 (2.5)
Worst (0–10)	4.1 (3.1)
Interference (0–10)	3.8 (2.9)
PSQI (0–21)	8.45 (4.0)
STAI	
State (20–80)	35.5 (10.5)
Trait (20–80)	39.6 (10.1)
CES-D (0–60)	16.1 (9.3)
PSS (0–40)	16.3 (6.7)
SF-36 (0 – 100)	
Physical Function	61.2 (24.7)
Physical Role Functions	42.9 (41.2)
Emotional Role Function	62.2 (40.9)
Physical Pain	53.4 (26.4)
Vitality	47.4 (19.6)
General Health	41.1 (20.44)
Mental Health	71.3 (18.3)
Social Function	67.7 (24.1)

Note. *n* = 60. For the PROMIS, BFI, and MFSI–SF, higher scores indicate greater fatigue. BFI = Brief Fatigue Inventory; MFSI-SF = Multidimensional Fatigue Symptom Inventory-Short Form; PROMIS = Patient Reported Outcomes Measurement Information System; BPI = Brief Pain Inventory; PSQI = Pittsburgh Sleep Quality Index; STAI = State Trait Anxiety Inventory; PSS=Perceived Stress Scale; CESD = Center for Epidemiology Studies-Depression. SF-36 = Medical Outcome Short Form.

Table 3

Correlations between Fatigue and Biological and Behavioral Variables

Variable	BFI Total	MFSI-SF Total	PROMIS
BPI worst	0.65***	0.40**	0.41***
BPI average	0.51***	0.48***	0.31*
BPI interference	0.55***	0.45***	0.42***
PSQI	0.53***	0.51***	0.47***
STAI – State	0.44***	0.70***	0.45***
STAI – Trait	0.38**	0.55***	0.35**
CESD	0.42***	0.45***	0.45***
PSS	0.41***	0.69***	0.37**
Hemoglobin	−0.18	−0.03	−0.30*
log IL-1b	−0.10	−0.18	−0.13
log IL-6	0.20	0.06	0.17
log IL-10	−0.19	0.01	0.09
log TNF-α	−0.11	−0.18	0.03
Age	0.24	0.14	0.07

Note. For the PROMIS, BFI, and MFSI–SF: higher scores indicate greater fatigue. BFI = Brief Fatigue Inventory; MFSI-SF I = Multidimensional Fatigue Symptom Inventory-Short Form; BPI = Brief Pain Inventory; PSQI = Pittsburgh Sleep Quality Index; STAI = State Trait Anxiety Inventory; CESD = Center for Epidemiology Studies-Depression; PSS = Perceived Stress Scale; IL 1b = Interleukin-1b; TNF-α = Tumor necrosis factor-alpha.

* $p < 0.05$.

** $p < 0.01$.

*** $p \leq 0.001$.

Table 4

Correlations between Fatigue Scores and Quality of Life

SF-36 Subscales	BFI Total	MFSI-SF Total	PROMIS
Physical	−0.45**	−0.48**	−0.56**
Role-Physical	−0.53**	−0.57**	−0.57**
Bodily Pain	−0.60**	−0.58**	−0.49**
General Health	−0.44**	−0.53**	−0.36*
Vitality	−0.58**	−0.74**	−0.65**
Social Function	−0.53**	−0.70**	−0.57**
Role-Emotional	−0.38*	−0.45**	−0.34*
Mental Health	−0.49**	−0.67**	−0.51**

Note. SF-36 = Medical Outcome 36-Item Short Form; BFI = Brief Fatigue Inventory; MFSI-SF = Multidimensional Fatigue Symptom Inventory-Short form, PROMIS = Patient Reported Outcomes Measurement Information System.

* $p < 0.01$.

** $p \leq 0.001$