Fatigue and Related Factors in People With Type 2 Diabetes

Rupali Singh, PT

Patricia M. Kluding, PT, PhD

From University of Kansas Medical Center, Kansas City, Kansas (Mrs Singh, Dr Kluding).

Correspondence to Dr Patricia M. Kluding, PT, PhD, Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, 3901 Rainbow Boulevard Mail Stop 3051, Kansas City, KS 66160 (PKLUDING@kumc.edu).

Acknowledgments: We would like to acknowledge the valuable assistance of Cray Diabetes Center at University of Kansas Medical Center, Erin Boidock, DPT, and Gurpreet Singh, PhD student, who assisted with data collection on this project. The authors have no financial conflict of interest to disclose.

DOI: 10.1177/0145721713479144

Purpose

The purpose of this study was to examine the presence and severity of fatigue in people with type 2 diabetes.

Methods

The Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), and Visual Analog Fatigue Scale (VAFS) were administered by anonymous survey of 37 individuals with and 33 individuals without diabetes to assess the presence of fatigue. Data on age, gender, weight, height, year of diagnosis, and number/type of complications were also collected. Nonparametric tests tested for differences in fatigue measures between the groups, and distribution characteristics of the FAS, FSS, and VAFS scores were examined. Spearman rank correlation coefficients examined the relationships between the variables.

Results

People with diabetes scored higher on all 3 fatigue assessment scales as compared to controls (FAS: 25.11 vs 19.94, $P = .001$; FSS: 4.30 vs 2.59, $P = .000$; VAFS: 4.64 vs 1.75, $P = .000$). Data were normally distributed for FSS in the group with diabetes and the group without diabetes, and scores of FAS, FSS, and VAFS showed no ceiling effects. A positive correlation was noted between fatigue measures and number of complications ($r = .482$; $P = .003$).

Conclusions

Higher levels of fatigue were noted in people with type 2 diabetes as compared to healthy age-matched control; however, the cause and impact of these changes remain unclear. FSS is a recommended tool for measuring fatigue in this population. Further studies are needed to explore the contributing factors to fatigue in those with diabetes.

Type 2 diabetes is a leading cause of adult disability and is a significant global health problem. In 2011, 25.8 million people were estimated to have diabetes in the United States and this figure is expected to rise to more than 40 million by 2050.[1] More specifically, type 2 diabetes contributes to 90% to 95% of this number. Fatigue is a persistent and distressing complaint among people with type 2 diabetes. While fatigue also occurs in other medical disorders, the importance of fatigue may be greater in individuals with type 2 diabetes due to the complex management strategies that must be continually maintained. Fatigue can take a considerable toll on individuals with diabetes, yet there is little empirical research describing the severity of the problem. Defining fatigue is a challenge because there is a great discrepancy among causes and indicators. In general, fatigue is recognized as a complex phenomenon including physiological, psychological, and situational components.[2-7] Since fatigue itself is difficult to define and is such a complex phenomenon, it becomes very challenging to transform fatigue into a quantifiable measure. To date, the most accurate or appropriate fatigue scales remain controversial. However, there are few a scales that appear to adequately identify and measure fatigue in individuals with diabetes; these scales include Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), and Visual Analog Fatigue Scale (VAFS),

Fatigue can result from various physiological factors associated with diabetes, such as hypoglycemia, hyperglycemia, and the wide swings between the two.[8,9] Polypharmacy, referring to the numerous medications this population has to take, can result in a number of complications and side effects including fatigue.[10-12] Numerous complications such as sleep disorders[13] or chronic neuropathic pain[14] can add to the burden of fatigue. The presence and number of diabetic complications have been shown to have a significant impact on quality of life in a number of studies.[15-18] Fatigue can also result from various lifestyle issues, such as lack of physical activity or high body mass index (BMI), which is commonly seen in people with type 2 diabetes.[19] Certain psychological factors like depression[20] or stress resulting from the diagnosis of diabetes or from the management of diabetes can also result in fatigue.[21-23] Therefore, it is very important to further explore this issue and identify the potential contributors of fatigue.

In an epidemiological study of 1137 subjects with type 2 diabetes, the prevalence of fatigue was found to reach 61%.[24] Despite this high frequency and the impact of fatigue on the persons' treatment efficacy, few studies have explored this symptom dimension in patients with diabetes, and most have been limited to nonspecific symptoms of fatigue.[25] Fatigue studies done in the past were either tested in subjects with additional comorbidities[26] or with additional challenges of maintaining employment status.[27] Therefore, future studies need to be done to find out how diabetes itself plays a role in fatigue levels of these individuals.

The primary purpose of this study was to investigate the presence and severity of fatigue in people with type 2 diabetes as compared to a group without diabetes and to identify the relationship between fatigue and certain variables of diabetes. An additional purpose was to compare three standardized measures of fatigue, the Fatigue Severity Scale, Fatigue Assessment Scale, and Visual Analog Fatigue Scale, to determine which would be the most appropriate tool to measure fatigue in this population.

Research Design and Methods

Research Design

This cross-sectional study utilized community-based surveys.

Data Collection Procedures

An invitation letter, fatigue surveys, and a brief medical history form were distributed by the researchers among the community, at health fairs, local clinics, and through a diabetes database that has a list of individuals with diabetes willing to be contacted for research purposes. The diabetes database is maintained at Georgia

Holland Research Lab where the study was conducted. The study was approved by University of Kansas Medical Center's Human Subjects Committee. The study utilized self-administered, anonymous surveys indicating that personal information, regarding the participants' name or date of birth, was not stated on the surveys.

Participants

Participants with and without type 2 diabetes were included if they were between the ages of 40 and 70 years.

Methods

Measures of fatigue. The Fatigue Assessment Scale (FAS) is a reliable scale for detecting the presence and severity of fatigue in terms of both physical and mental domains.[28] It focuses on the physical and mental domains of fatigue. FAS is a 10-item questionnaire that requires a subject to choose 1 out of 5 answer categories varying from never to always (1 = never, 2 = sometimes, 3 = regularly, 4 = often, and 5 = always). Responses for each question are summed to generate a score ranging from 10 to 50. Higher scores indicate more fatigue.

The FAS has previously been shown have good reliability, with a Cronbach's alpha of 0.90 for employed subjects (n = 351). The measure also demonstrates good validity, with factor analysis demonstrating strong construct validity[28] and concurrent validity with other fatigue scales, such as the Check List Individual Strength subjective experience of fatigue ($r = .76$, $P < .001$).[28]

The Fatigue Severity Scale (FSS) emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects, which appears suitable for detecting the presence and the severity of fatigue.[29,30] FSS is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. The FSS tests different domains, including motivation, exercise, and interference with work, family, or social life. It emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects, which appears to be suitable for detecting the presence of chronic fatigue. It has 9 item questionnaires, and scoring is done by adding up the responses (numbers) and dividing by 9. A score of less than 4 is considered as having no fatigue, scores of 4 to 4.9 are considered as having moderate fatigue, and scores of 5 or more are considered as having severe fatigue.[29]

The FSS has previously shown to have good reliability measures with a Cronbach's alpha = 0.89 for subjects with systemic lupus erythematosus (n = 28), 0.81 for subjects with multiple sclerosis (n = 25), 0.88 for normal healthy adults (n = 20), and 0.88 for total sample of 74 subjects.[29] The measure also demonstrates good validity. Results of factor analysis show strong construct validity when tested in cancer patients,[30] demonstrating strong construct validity. Additionally, FSS has strong concurrent validity with other scales, such as visual analog scale (n = 74) was $r = 0.68$; $P < .001$.[29]

The Visual Analog Fatigue Scale (VAFS) is a modified form of a visual analog scale that was designed to assess acute or transient fatigue in patients with stroke.[31,32] It consists of a 10 cm unmarked vertical line with written descriptions of "no fatigue" and "very severe fatigue" at each end. Subjects are asked to mark on the line the point where they feel their perception of fatigue is. Scores range from 0 to 100 and are measured in millimeters on the 10 cm vertical line. Scoring is done by measuring the line from no fatigue to the point indicated by the subjects. The higher the VAFS score, the higher the fatigue. VAFS has a major advantage among the other fatigue tests in that it avoids recollection among subjects. Rather, it requires subjects to base their answers on intuitive response at the moment, which helps avoid recollections of previous references.

The VAFS has been shown to have good reliability, with intraclass coefficient values for the VAFS = 0.851 (95% CI, 0.673-0.936, $P < .001$) for subjects post stroke.[32] The measure also demonstrates good validity, demonstrating strong concurrent validity, with significant co-relationships with heart rate and systolic blood pressure ($r = 0.632$, $P = .02$).[32]

Medical history form. Participants completed a medical history form, consisting of questions about age, gender, height, weight, year of diagnosis of diabetes, and a list of possible complications from diabetes that included: nerve problems, kidney disease, blindness or eye problems, heart attack or heart disease, stroke, amputation, high blood pressure, dental problems, problems with pregnancy, and problems with sexual function.

Data Analysis

Mann-Whitney *U* test and Wilcoxon signed rank test were used to test for differences in fatigue measures

Table 1

Participant Characteristics

	With Diabetes	Controls
n	37	33
Age (years)	57 ± 7	53 ± 9.11
Gender (female/male)	23/14 (62%)	26/7 (78%)
Body mass index	34.2 ± 8.21	26.20 ± 5.26
Years since diagnosis	14.62 ± 11.12	N/A
Neuropathy	26 (70.27%)	N/A
Nephropathy	0	N/A
Retinopathy	8	N/A
Cardiovascular disease	14 (37.83%)	N/A
Stroke	11	N/A
Amputation	0	N/A
High blood pressure	34 (91.8%)	N/A
Dental problems	11 (29.72%)	N/A
Problems with pregnancy	0	N/A
Problems with sexual function	8	N/A

between participants with diabetes and those without. The Kolmogorov-Smirnov test (K-S test) was used to compare the distribution of FSS, FAS, and VAFS scores in participants with diabetes and those without to a standard normal distribution curve. Potential floor and ceiling effects of the three measures were also analyzed. Spearman rank correlation coefficients were also calculated to explore the relationships between fatigue scores with age, gender, weight, height, year of diagnosis, and number of complications in participants with diabetes. Number of complications was calculated by adding up the number of yes answers in the list of complications. A significance level of .05 was utilized for all testing.

Results

Survey Responses

Surveys were received from 82 adult subjects (49 subjects with diabetes, 33 controls). Of the 49 surveys from people with diabetes, 42 had type 2 diabetes, 6 had type 1 diabetes, and 1 was unknown. In addition to excluding data from the 7 surveys without type 2 diabetes, surveys were also excluded from 5 people who did not fall between the 40 and 70 years of age range. A total of 70 surveys (37 with diabetes, 33 controls) were included in the study.

Table 2

Fatigue Scores

Fatigue Surveys	Diabetes	Control	*P* Value
FAS	25.10 ± 7.62	19.87 ± 4.3	.001**
FSS	4.28 ± 1.49	2.60 ± 1.13	.000**
VAFS	4.61 ± 3.17	1.60 ± 1.70	.000**

Abbreviations: FAS, Fatigue Assessment Scale; FSS, Fatigue Severity Scale; VAFS, Visual Analog Fatigue Scale.
**$p \leq .01$.

Participant characteristics are provided in Table 1. Participants in the group with diabetes had higher BMI (mean BMI 34.24 ± 8.21 kg/m^2) as compared to participants in the control group (mean BMI 34.24 ± 8.21 vs 30.45 ± 8.02 kg/m^2; $P < .001$). The mean number of years since diagnosis of diabetes was 14.62 ± 11.2 years.

Measures of Fatigue

Results of the FAS, FSS, and VAFS fatigue questionnaires are presented in Table 2. Subjects with diabetes scored significantly higher on all three fatigue assessment scales as compared to controls.

Distribution characteristics analysis. Results of the K-S test indicated that the FSS scores for the participants with diabetes and the FSS scores for participants without diabetes were normally distributed. The other scores were not normally distributed. None of the tests in either group (FSS, FAS, and VAFS) showed clustering of scores at the higher end or lower end, which indicated the absence of ceiling or floor effects.

Relationships Between Variables

Fatigue, as measured by both FAS and FSS, was significantly associated with number of complications (ρ = .483; P = .003 and .326; P = .049, respectively) in participants with diabetes. We also found that VAFS was negatively associated with age (ρ = –.420; P = .011) in the participants with diabetes. No significant relationships

were observed between fatigue scores and years since diagnosis, age, BMI, or gender in this small sample of individuals with diabetes.

Also of note, increasing years since diagnosis was significantly associated with number of complications (0.331; $P = .045$), while increasing age was associated with lower BMI (−0.380; $P = .020$), and increasing BMI was negatively associated with number of complications (−0.361; $P = .028$).

Discussion and Conclusions

Participants with diabetes in this study appeared to have higher fatigue levels when compared to controls without diabetes at a comparable age. Although fatigue is a common complaint among patients with type 2 diabetes, few studies have directly tested the presence and severity of fatigue in people with type 2 diabetes. Our results are in agreement with previous studies that have used FSS as a primary measure to assess fatigue.

For example, Ceullar et al[26] conducted a study evaluating fatigue, sleep, glycemic control, and depression in subjects with type 2 diabetes, both with and without restless leg syndrome (RLS). FSS was used to test fatigue and it was found that the mean FSS score for subjects with RLS and diabetes was 3.8. These results are in accordance with our pilot study, in which the mean FSS score in the diabetes group was 4.28 ± 1.49, representing a moderate level of fatigue.[29] This compared to a mean FSS score of 2.60 in the control group, which represents a low level of fatigue.[29] In another study examining subjects with immune mediated polyneuropathies, FSS was used as the primary tool to determine the prevalence and severity of fatigue.[33] Mean FSS score was 5.6 ± 1.4 in the patient group, which represents severe fatigue. These results may be relevant to our study because patients with diabetes often have similar symptoms resulting from neuropathy.

Merkies et al[33] defined severe fatigue as a FSS score above the 95th percentile of FSS in healthy controls, or a score of 5.0 or more. Following this criteria, severe fatigue was demonstrated in 13 of 37 (35%) individuals in our survey. Additionally, over 45% of the diabetic survey participants scored 5 or more on the 7-point scale for question 8 ("Fatigue is among my three most disabling symptoms") compared with only 12% (4/33) of the healthy controls.

Of the 3 fatigue measures used in this study, all 3 indicated that individuals with diabetes exhibited significantly greater levels of fatigue than control subjects. Since fatigue is such a complex phenomenon and is difficult to measure, 3 different tools were used to assess fatigue. All these tools have different conceptual definitions: FAS tests the presence and severity of fatigue in terms of both physical and mental domains, FSS emphasizes the impact of fatigue on daily life in terms of accumulation of functional fatigue effects, and VAFS assess acute or transient fatigue at the moment. Thus, although these tools have different conceptual definitions, all tools appear to be valid in measuring fatigue in people with diabetes.

Further, analysis of distribution curves revealed that FSS was normally distributed, even in this small sample, which may indicate that FSS is the most appropriate test to use in this population. None of the fatigue measures showed ceiling or floor effects, as the scores were widely spread over a broad range and not clustered at the either end of the scoring range.

Surprisingly, we were not able to identify any relationships between fatigue and the diabetic variables, such as BMI or years since diagnosis. Fatigue was only found to be significantly associated with number of complications. This finding supports previous studies that the number of complications can affect quality of life of individuals with diabetes.[15-17] The relationship between fatigue and the number of complications is understandable, as more complications can logically result in more tiredness or fatigue. Our survey participants reported high blood pressure and neuropathy as the most common comorbidities and/or complications resulting from diabetes. Both high blood pressure and neuropathy can cause general tiredness and fatigue. Neuropathy was the most common complication reported by our survey participants, and foot pain (resulting from neuropathy) has been previously found to be positively correlated with symptoms of general fatigue ($r = 0.63$, $P < .001$)[14] in adults with type 1 and type 2 diabetes.

Our study also showed a surprising negative direction in the relationship of fatigue (VAFS) with age. In contrast, we would expect a positive relationship between fatigue and age. This could be due to the small sample size of the study and the complexity of fatigue with potential causative factors.

Although this survey successfully identified the presence of fatigue in people with type 2 diabetes, there are

several limitations associated with this study. The first and most obvious limitation is the small sample size, which may have influenced the lack of significant relationships between fatigue and variables such as duration of diabetes. This relationship may also be complicated by the fact that there is often a period of unawareness prior to a diagnosis of diabetes being established.[34,35] Future studies should incorporate other variables, such as fasting blood glucose and glycosylated hemoglobin measures, and inclusion of other common comorbidities like depression, pain, and sleep problems. This may substantially clarify the relationships and contributing factors to fatigue in diabetes.

Another limitation of the study was the use of anonymous surveys, as we were unable to verify the data or follow up with the subjects. Further, fatigue is such a complex phenomenon that questionnaires alone will not capture the whole picture of fatigue. Therefore, there is a need to incorporate more rigorous methods to capture the whole phenomenon of fatigue in patients with diabetes.

As a part of diabetes management, individuals with diabetes are highly encouraged to engage in physical activities. However, due to the presence of fatigue, people with diabetes may have difficulty starting or continuing exercise programs. Exercise may actually reduce fatigue[36,37] as aerobic fitness improves, and this is an important area for future study.

In conclusion, people with type 2 diabetes appear to have greater levels of fatigue, and the number of the complications resulting from diabetes may be related to this tiredness. FSS is recommended for measuring fatigue in people with diabetes. Overall, these results appear to support previous research suggesting that individuals with diabetes suffer from general tiredness and fatigue, which may be linked to complications from diabetes. As this may be an important area for patient education and diabetes management, further investigation is warranted to examine fatigue and its contributing factors in people with type 2 diabetes.

References

1. Wu M, Hsu L, Zhang B, Shen N, Lu H, Li S. The experiences of cancer-related fatigue among Chinese children with leukaemia: a phenomenological study. *Int J Nurs Stud*. 2010;47(1):49-59.
2. Aaronson LS, Teel CS, Cassmeyer V, et al. Defining and measuring fatigue. *Image J Nurs Sch*. 1999;31(1):45-50.
3. Aistars J. Fatigue in the cancer patient: a conceptual approach to a clinical problem. *Oncol Nurs Forum*. 1987;14(6):25-30.
4. Magnusson K, Moller A, Ekman T, Wallgren A. A qualitative study to explore the experience of fatigue in cancer patients. *Eur J Cancer Care (Engl)*. 1999;8(4):224-232.
5. Ream E, Richardson A. Fatigue: a concept analysis. *Int J Nurs Stud*. 1996;33(5):519-529.
6. Rose L, Pugh LC, Lears K, Gordon DL. The fatigue experience: persons with HIV infection. *J Adv Nurs*. 1998;28(2):295-304.
7. Trendall J. Concept analysis: chronic fatigue. *J Adv Nurs*. 2000;32(5):1126-1131.
8. Morsch CM, Goncalves LF, Barros E. Health-related quality of life among haemodialysis patients—relationship with clinical indicators, morbidity and mortality. *J Clin Nurs*. 2006;15(4):498-504.
9. Weijman I, Kant I, Swaen GM, et al. Diabetes, employment and fatigue-related complaints: a comparison between diabetic employees, "healthy" employees, and employees with other chronic diseases. *J Occup Environ Med*. 2004;46(8):828-836.
10. Khurana R, Malik IS. Metformin: safety in cardiac patients. *Postgrad Med J*. 2010;86(1016):371-373.
11. McCormick M, Quinn L. Treatment of type 2 diabetes mellitus: pharmacologic intervention. *J Cardiovasc Nurs*. 2002;16(2):55-67.
12. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med*. 1999;131(4):281-303.
13. Resnick HE, Redline S, Shahar E, et al. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care*. 2003;26(3):702-709.
14. Rijken PM, Dekker J, Dekker E, et al. Clinical and functional correlates of foot pain in diabetic patients. *Disabil Rehabil*. 1998;20(9):330-336.
15. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L. Quality of life and associated characteristics in a large national sample of adults with diabetes. *Diabetes Care*. 1997;20(4):562-567.
16. Wandell PE, Brorsson B, Aberg H. Quality of life in diabetic patients registered with primary health care services in Sweden. *Scand J Prim Health Care*. 1997;15(2):97-102.
17. Anderson RM, Fitzgerald JT, Wisdom K, Davis WK, Hiss RG. A comparison of global versus disease-specific quality-of-life measures in patients with NIDDM. *Diabetes Care*. 1997;20(3):299-305.
18. Brown GC, Brown MM, Sharma S, Brown H, Gozum M, Denton P. Quality of life associated with diabetes mellitus in an adult population. *J Diabetes Complications*. 2000;14(1):18-24.
19. Telford RD. Low physical activity and obesity: causes of chronic disease or simply predictors? *Med Sci Sports Exerc*. 2007;39(8):1233-1240.
20. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24(6):1069-1078.
21. Katon W, von Korff M, Ciechanowski P, et al. Behavioral and clinical factors associated with depression among individuals with diabetes. *Diabetes Care*. 2004;27(4):914-920.
22. Egede LE, Zheng D. Independent factors associated with major depressive disorder in a national sample of individuals with diabetes. *Diabetes Care*. 2003;26(1):104-111.
23. Ryerson B, Tierney EF, Thompson TJ, et al. Excess physical limitations among adults with diabetes in the U.S. population, 1997-1999. *Diabetes Care*. 2003;26(1):206-210.
24. Drivsholm T, de Fine Olivarius N, Nielsen AB, Siersma V. Symptoms, signs and complications in newly diagnosed type 2 diabetic patients, and their relationship to glycaemia, blood pressure and weight. *Diabetologia*. 2005;48(2):210-214.

25. Fritschi C, Quinn L. Fatigue in patients with diabetes: a review. *J Psychosom Res*. 2010;69(1):33-41.
26. Cuellar NG, Ratcliffe SJ. A comparison of glycemic control, sleep, fatigue, and depression in type 2 diabetes with and without restless legs syndrome. *J Clin Sleep Med*. 2008;4(1):50-56.
27. Weijman I, Ros WJ, Rutten GE, Schaufeli WB, Schabracq MJ, Winnubst JA. Fatigue in employees with diabetes: its relation with work characteristics and diabetes related burden. *Occup Environ Med*. 2003;60(suppl 1):i93-i98.
28. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: the Fatigue Assessment Scale. *J Psychosom Res*. 2003;54(4):345-352.
29. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121-1123.
30. Winstead-Fry P. Psychometric assessment of four fatigue scales with a sample of rural cancer patients. *J Nurs Meas*. 1998;6(2):111-122.
31. Tseng BY, Billinger SA, Gajewski BJ, Kluding PM. Exertion fatigue and chronic fatigue are two distinct constructs in people post-stroke. *Stroke*. 2010;41(12):2908-2912.
32. Tseng BY, Gajewski BJ, Kluding PM. Reliability, responsiveness, and validity of the visual analog fatigue scale to measure exertion fatigue in people with chronic stroke: a preliminary study [Published online May 16, 2010]. *Stroke Res Treat*. doi:10.4061/2010/412964
33. Merkies IS, Schmitz PI, Samijn JP, van der Meche FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. *Neurology*. 1999;53(8):1648-1654.
34. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem*. 2011;57(6):e1-e47.
35. Troisi RJ, Cowie CC, Harris MI. Diurnal variation in fasting plasma glucose: implications for diagnosis of diabetes in patients examined in the afternoon. *JAMA*. 2000;284(24):3157-3159.
36. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ*. 1997;314(7095):1647-1652.
37. Gowans SE, deHueck A, Voss S, Richardson M. A randomized, controlled trial of exercise and education for individuals with fibromyalgia. *Arthritis Care Res*. 1999;12(2):120-128.