SELF-REPORTED FATIGUE IN INDIVIDUALS WITH KNEE OSTEOARTHRITIS

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PURPOSE: The purposes of this study were to: 1) describe the magnitude and dimensions of self-reported fatigue in individuals with knee OA and 2) determine the influence of quadriceps fatigue and cardiorespiratory endurance on self-reported fatigue in individuals with knee OA, after accounting for potential confounders such as age, sex, pain, depression, and anxiety. **SUBJECTS:** The sample consisted of 44 adults (75% female) with radiographically confirmed knee OA. **METHODS:** All subjects participated in two testing sessions using a dynamometer with a software program developed specifically for this study. During the first session, subjects completed the Multidimensional Assessment of Fatigue Scale (MAF), the WOMAC Osteoarthritis Index, the Center for Epidemiologic Studies Depression Scale (CES-D), and the Beck Anxiety Inventory Scale (BAI). A burst superimposition maximum isometric quadriceps torque test was performed to determine maximum voluntary isometric contraction (MVIC) torque that was used in the quadriceps fatigue test. In the first testing session, subjects also performed a submaximal cycle ergometer test to estimate VO_2 max as a measure of cardiorespiratory endurance. Within 1 week of the first session, subjects returned for the quadriceps fatigue test in which they performed repeated submaximal contractions equal to 50% of their MVIC isometric torque output for 6 seconds followed by a 4-second rest period (duty cycle 60%). The contractions were continued until the subject could no longer generate the torque target for 3 successive contractions. During the sixth contraction and every minute

thereafter, subjects were instructed to push with a maximum effort and the train of electrical stimuli was superimposed upon the maximal effort quadriceps contraction. Quadriceps fatigue was measured as the rate of decline of the MVIC torque output over the course of the test. **ANALYSIS:** Descriptive statistics were used to describe the magnitude and dimensions of fatigue. An independent samples t-test was used to compare fatigue in individuals with knee OA to the levels of fatigue reported by normal controls and individuals with rheumatoid arthritis. Hierarchical regression analysis was used to determine the influence of quadriceps fatigue and cardiorespiratory endurance self-reported fatigue. **RESULTS:** The mean global fatigue index score was 23.6 (SD = 10.4, range 1-40)**.** Individuals with knee OA reported significantly higher fatigue than controls and significantly lower fatigue than RA patients ($p < 0.05$). Fatigue was reported to occur every day by 25% of the sample. Fatigue most often affected walking, doing household chores, shopping, and exercise. Fatigue was significantly associated with sex (r = .52, greater fatigue in females), pain (r = .62), depression (r = .47), anxiety (r = .54), and cardiorespiratory endurance (r = -.55) but not to quadriceps fatigue (r= .01). Hierarchical regression analyses revealed that adding quadriceps fatigue or cardiorespiratory endurance to the model after controlling for age, sex, pain, depression, and anxiety did not explain any additional variance in fatigue, (ΔR^2 =.00). **CONCLUSION:** Fatigue is common in individuals with knee OA. Quadriceps fatigue is not related to self-reported fatigue. Cardiorespiratory endurance is related to self-reported fatigue, but not after controlling for age, sex, pain, depression, and anxiety. **CLINICAL RELEVANCE:** Management of fatigue in individuals with knee OA may require interventions to address psychosocial issues and/or cardiorespiratory endurance.

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1 INTRODUCTION

1.1 Overview

Everyone experiences fatigue occasionally. It is the body's way of signaling its need for rest and sleep. But when fatigue becomes a persistent feeling of tiredness or exhaustion that goes beyond normal sleepiness, it is usually a sign that something more serious is amiss. In healthy individuals, fatigue may result from strenuous physical exercise, a busy day at work, or emotional tension. Fortunately, rest brings relief from fatigue. Both fatigue and recovery from fatigue are normal daily experiences. Healthy people rarely considered fatigue as a serious problem because of the duration of the condition is temporary and the relief measures are effective. In contrast, for those with chronic illness, the cause of fatigue may not be obvious, a good night of sleep alone may not completely relieve the fatigue, and fatigue may not be a transient condition.

Chronic illness is a primary health concern. Individuals with chronic illness face changes in lifestyle, and self-esteem, as well as many other physical, psychological, and economic issues. Living with chronic illness requires the individuals to manage symptoms and treatments on day-to-day basis, as well as cope with the demands of daily life.[18] Chronic illness is known to affect many people. However, it is especially prevalent in individuals aged 65 years and older.[61] In view of the relationship of chronic illness to aging, it is important to recognize that in the United Sates, the number of individuals aged 65 years and older has increased by about 4.5 million (12%) in each decade since the World War II, more than twice the rate for the remainder of the population.[41] In 2000, 35.0 million people 65 years of age and older were counted in the United States.[56] This represents a 12% increase since 1990, when 31.2 million people 65 years of age and older were counted.[56] The continued aging of the population will result in a geometric

increase in the number of elderly people at risk for disabling chronic illness. This escalation in the elderly population creates an increase in concern for health, wellness, and quality of life among the elderly.

One important and pervasive health concern among the elderly is arthritis. Arthritis is one of the predominant chronic illnesses that affected an estimated 15% of the US population in 1995 (almost 40 million Americans). By the year 2020, this number is expected to increase to 18.2% or nearly 59.4 million Americans.[79] Arthritis is the leading cause of disability among adults in the United States.[27]

Osteoarthritis (OA) is the most prevalent form of arthritis. In 1990, an estimated 20.7 million Americans had physician-diagnosed OA and current projections suggest that approximately 30 million people in the United States will have OA in the year 2020.[79] The prevalence of OA is highly correlated with advancing age. More than 80% of all people over the age of 65 years have radiographic evidence of OA.[82] Although not all individuals with radiographic evidence of OA are symptomatic, 16 million Americans have significant joint pain as a result of OA.[21,106]

One of the most significant threats to an older person's ability to live and function independently is loss of mobility. Physical disability is an important public health outcome for older adults. OA was shown to have a formidable effect on physical activities and it was deemed the second most common cause of disability.[54] Given the substantial prevalence of OA in an aging population, OA may account for greater loss of independence in activities of daily living than any other chronic illness. Osteoarthritis of the knee is the most prevalent type of OA and contributes significantly to functional limitations in performance of weight bearing tasks.[54,79] Osteoarthritis of the knee is particularly disabling because it limits basic, but important to

independent living and quality of life, activities of daily living such as, walking, using stairs, getting in and out of chairs and vehicles, housekeeping, and carrying bundles.[54] At the extreme, OA can result in complete debility, with rising from a chair or taking but a few steps becoming an agonizingly painful activity.

Individuals with arthritis are challenged with managing pain, preserving joint mobility and function, adhering to exercise programs, pacing activities to conserve energy, and obtaining emotional and physical rest. Fatigue may be a major limiting factor and one of the challenges to cope with arthritis because of its interfering with activities of daily living which negatively impact the quality of life of individuals with arthritis. Tasks taken for granted by healthy people require special attention for suffers of arthritis. Individuals with arthritis, as compared to healthy people, may require extra effort to perform routine activities of daily living (e.g., prolonged standing, walking, climbing stairs, and rising from a seated position). This extra effort may induce fatigue more quickly in individuals with arthritis than it does in healthy people. As a result of these constant challenges, fatigue in arthritis has received an increasing research interest during the past two decades.

1.2 Statement of the Problem

Fatigue has a special place in rheumatic diseases. It is one of the most common symptoms reported by patients with Systemic Lupus Erythematosus (SLE)[24,74,88,115,118,124], Fibromyalgia (FM)[75,76,93,123] and Rheumatoid Arthritis (RA).[12,13,64,101,113,114,123] Fatigue and factors contributing to fatigue have been extensively investigated in rheumatic diseases[12,13,24,74-76,93,113-115,118,123,124] except OA.[123] The reason for that might be the assumption that the

relationship between fatigue and autoimmune disease was thought to be due to the systemic nature of the disease. However, current research has demonstrated that fatigue was not related to disease activity.[12,12,24,64,118,123]

Out of all rheumatic diseases, RA and OA are the most common joint diseases affecting the elderly.[79] Both diseases are sharing relatively common clinical manifestations such as pain, morning stiffness, joint radiographic changes and psychosocial distress due to functional limitations.[102] It is estimated that 88-100% of individuals with RA experience fatigue.[12,13,123] Moreover, it was well documented that fatigue in autoimmune diseases such as RA has a strong association with disease-related factors such as joint pain and psychosocial variables.[12,13,123] However, these factors are also related to knee OA.

Given that OA and RA share common disease-related factors (e.g., pain and psychosocial distress), this raises a question of whether debilitating fatigue exists in individuals with in knee OA and if it does exist, what is the nature of the relationship between fatigue and other factors associated with knee OA such as age, sex, pain, depression, anxiety, quadriceps fatigue and cardiorespiratory endurance.

After an extensive and careful review of the literature, it appears that only one study has been conducted to address fatigue in individuals with OA.[123] This study was limited due to the use of a simple unidimensional measure of fatigue (i.e., a Visual Analog Scale (VAS)). The magnitude of fatigue in individuals with knee OA has not been thoroughly described and its relationship to physiological and psychosocial factors has not been clearly delineated. Because fatigue is a subjective experience, self-report is the most common approach used to measure fatigue. However, self-report measure of fatigue reflects the individual's perception of his or her ability to perform enduring-type tasks, whereas, performance-based measure of fatigue (e.g.,

muscle fatigue and cardiorespiratory endurance) examine the individual's ability to complete an enduring-type task.[100] Therefore, it is imperative to describe the relationship between self-reported fatigue and a performance-based measure of fatigue to see if the information obtained by both measures is complimentary.

The multidimensionality of fatigue makes it a difficult phenomenon to investigate. The complexity of psychosomatic and somatic factors no doubt account for the dearth of relevant studies on the experience of fatigue in OA. Therefore, it is not surprising to find a paucity of information about fatigue in non-systemic diseases such as OA, which have local signs and symptoms confined to the affected joint compared to the wealth of information about fatigue in autoimmune systemic diseases such as RA.

1.3 Purpose of the Study

The purposes of this study were to; 1) describe the magnitude and dimensions of self-reported fatigue in individuals with knee OA, 2) determine the influence of the quadriceps fatigue on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety and 3) determine the influence of the cardiorespiratory endurance on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety.

1.4 Significance of the Study

Completion of this study will provide a clearer description of the magnitude and dimensions of fatigue in individuals with knee OA and the nature of its relationship with other factors such as demographic variables, pain, psychosocial distress, quadriceps fatigue, and cardiorespiratory endurance. If it can be demonstrated that debilitating fatigue is high in individuals with knee OA and it is related to the quadriceps fatigue and cardiorespiratory endurance, then strategies to manage fatigue in individuals with knee OA and specific interventions tailored to reduce the quadriceps fatigue and increase cardiorespiratory endurance need to be developed.

This study contributes significantly to rehabilitation science by describing the magnitude and correlates of fatigue in individuals with knee OA. Because fatigue is a common harbinger of the presence of illness and disease progression, the identification of fatigue severity and impact is important in clinical monitoring. Furthermore, these data may draw the attention of clinicians and researchers toward this debilitating symptom and provide direction for more effective management of patients with knee OA.

2 REVIEW OF THE LITERATURE

2.1 Introduction

The review of literature will include the following; 1) definition of fatigue, 2) magnitude of fatigue, 3) measurement of fatigue, 4) review of previous studies on the magnitude and dimensions of fatigue and variables contributing to fatigue in RA, 5) review of previous research addressing fatigue in OA to provide clarity and focus to the research hypotheses, 6) identification of variables that may contribute to fatigue in OA, 7) research questions and hypotheses.

2.2 Definition of Fatigue

Not surprisingly, defining fatigue, given its complexity, and its multicausal and multidimensional nature, has challenged researchers for many years to agree on a universal definition.[1] Currently, no such definition exists**.** Investigators have difficulties in differentiating between its causes (e.g., anemia, or depression); its signs and symptoms (e.g., reduction in force, legs or whole body); and its outcomes (e.g., decreased activity, functional disability).[120]

Fatigue is defined as the enduring, subjective sensation of generalized tiredness or exhaustion. The term “enduring” connotes that the sensation of fatigue has persisted over a period of time. The term "subjective" implies fatigue is a self-recognized phenomenon embedded in the individual's own evaluation of his or her current state. "Generalized" connotes that the sensation encompasses the person as a whole and is not restricted to specific anatomical structures, regions, or functions.[114]

2.3 Magnitude of Fatigue

Fatigue is a universal symptom not only associated with most acute and chronic illnesses, but also with normal, healthy functioning and everyday life. The US Health and Nutrition Survey (NHANES-1) reported fatigue in 20.4% of women and 14.3% of the men in the general population.[28] Fatigue has been accepted as an almost universal symptom of aging. Approximately 70% of all elderly people report that fatigue bothers them, and of that number, 59% experience it very often.[23] It is also a universal human experience that is often overlooked as a potentially important symptom of disease. Indeed, clinical experience suggests that fatigue is often the first indication of abnormality but individuals do not mention fatigue unless it is a prominent symptom, it is impeding an important aspect of their lives, or they are asked.[45] Therefore, fatigue can be a principal limiting factor for ill, as well as healthy individuals.

In clinical settings, fatigue is the most prevalent symptom and often the first indicator of physical or mental illness, but unless asked, less than 79% of elderly people will mention it.[23] In surveys of patients in primary care setting, fatigue was reported by as many as 25% of the patients with the mean duration of 3.3 years.[57] A British survey of those attending general practice found that 18.3% of 15,283 respondents had had substantial fatigue lasting six months or longer.[95] Fatigue and psychological morbidity were moderately correlated ($r = 0.62$). Women were more likely to complain of fatigue than men. Of those reporting fatigue, 56.8% attributed their fatigue to psychosocial causes.[95]

2.4 Measurement of Fatigue

Because fatigue is primarily a subjective experience, self-report is the most common approach used to measure fatigue. Numerous self-report instruments have been developed to measure fatigue. Unfortunately, each of these measures was tailored to the situation in which fatigue is studied. Therefore, each has advantages and disadvantages largely tied to the purpose for which it was developed.

Krupp, et al[73], recognizing the complexity and difficulty of defining and studying fatigue as a distinct entity developed the Fatigue Severity Scale (FSS). The FSS was originally used to assess disabling fatigue across two different clinical disorders, Multiple Sclerosis (MS) and SLE, both chronic illnesses in which fatigue is a common presenting symptom or a chronic and disabling problem. These researchers' use of this scale helped elucidate the relationship of fatigue and depressive symptoms and identified features of fatigue that might be characteristic of specific diseases.[73]

The FSS contains nine statements (e.g., "My motivation is lower when I am fatigued", "I am easily fatigued", "Fatigue causes frequent problems for me." etc.). Subjects choose a number from 1 (strongly disagree) to 7 (strongly agree) to indicate agreement/disagreement with each statement. Krupp et al[73] reported high internal consistency reliability (Cronbach's alpha =.88) for the FSS and high concurrent validity as estimated by the correlation of the FSS with a visual analogue scale of fatigue ($r = .68$, $p < .001$).

Given the multidimensionality nature of fatigue, a more comprehensive measure of fatigue is needed to address all possible dimensions of fatigue. Piper et al[98] conceptualizes the sensation of fatigue as having four dimensions: temporal, intensity/severity, affective, and sensory. The Piper Fatigue Scale (PFS), a self-report scale that measures multiple dimensions of

subjective fatigue has been developed for research with cancer patients receiving radiation therapy.[98] The PFS uses 41 different 100-mm VASs to measure subjectively reported fatigue across the four primary dimensions: 1) temporal (i.e., timing, frequency, and duration of fatigue, 2) intensity/severity (i.e., severity and degree of disruption in activities of daily living), 3) affective (i.e., emotional meaning attributed to fatigue) and 4) sensory (i.e., physical, emotional, and mental symptoms of fatigue).

The PFS reliability and validity estimates have been calculated in a sample of cancer patients receiving radiation therapy. High internal consistency reliability (Cronbach's alpha = .95) was reported for the total fatigue score. Pearson correlations indicated that the PFS demonstrates convergent validity with the Fatigue Symptom Checklist (r =.47, p<.01) and divergent validity with the Profile of Mood States (POMS) vigor subscale (r = -.57, p<.001).[98]

The multiple dimensions of subjective fatigue also can be measured by the Multidimensional Assessment of Fatigue (MAF) that has been developed for research involving patients with rheumatoid arthritis.[12] The scale has 16 items that measures five dimensions of fatigue: degree (item 1), severity (item 2), distress (item 3), degree of interference with activities of daily living (items 4-14), and timing (items 15-16). Fourteen items contain 10-point numerical rating scales (items 1-14) and two items have multiple-choice responses (items 15-16). The 10-point numerical rating scale ranges from 1(not at all) to 10 (a great deal). Respondents are asked to reflect on fatigue patterns for the past week. Scoring the MAF results in the Global Fatigue Index (GFI), which ranges from 1 (no fatigue) to 50 (extreme fatigue). The Cronbach's alpha was 0.93 when this measure was tested on group of 51 individuals with RA and 26 age and sex matched controls.[12] Belza[12] reported convergent validity of the MAF with the POMS fatigue

subscale (r=0.84, $p<0.01$) and divergent validity with the POMS vigor subscale (r=-0.62, $p<0.01$).

The MAF scale is a good choice when selecting an instrument to measure fatigue in chronic illness as it is: easy to administer and score, relatively short in length (it takes less than five minutes to complete) and assesses the subjective aspects of fatigue including degree, severity, distress, impact, and timing. The questionnaire allows patients to omit activity items that do not apply, thus making it a more accurate assessment of the impact of fatigue on activities of daily living (ADLs). To yield reliable and valid responses, instructions are included on page one of the three-page instrument. The instructions read: "These questions are about fatigue and the effect of fatigue on your activities during the past week". If no fatigue is reported (i.e., respondents answer (item 1) by indicating they have not had any fatigue in the past week) then they are instructed to stop. The reason to stop is because items 2-16 are only applicable if the respondent had fatigue in the past week. So as to assure variability in the outcome variable of fatigue, respondents who report no fatigue are assigned a zero score for items 2-16 and kept in the analysis. This scale was used in this study as it assesses the multiple dimensions of fatigue and was tested on patients with RA that have functional limitations and complaints of fatigue, similar to patients with OA. A complete description of how to score the MAF results into the GFI is found in chapter III.

2.5 Fatigue in Rheumatoid Arthritis

Although the primary symptoms of RA are in the joints, the systemic nature of the disease produces extraarticular symptoms, such as fatigue. Existing in all gradations of RA,

fatigue is increased during flares and minimally present during remissions. In fact, the presence of fatigue is considered a prodromal symptom of RA and the absence of fatigue is a criterion for disease remission.[97] In rheumatic disorders, fatigue may be prominent even when the patient has not been active physically. Indeed, fatigue in RA patients may be sensed when they are resting, and it is experienced as an aversion to activity.[92]

In a study of fatigue in 20 outpatients with RA, 19 patients reported having experienced fatigue and 57% of these subjects reported fatigue to be the most problematic aspect of having RA.[113] Respondents reported that their fatigue may have a sudden or gradual onset, may be predictable or unpredictable, may be dull or intense in severity, and may have a short or long duration. They felt that the frequency and duration of their fatigue varied based on several factors including physical factors (e.g., arthritis disease activity), psychological factors (e.g., emotional stress), environmental factors (e.g., work setting), and treatment (e.g., dose of steroids). Indeed, Tack (1990)[113] found that fatigue, pain, and depression are significantly and positively correlated, suggesting that an increase in pain, depression, or fatigue is associated with an increase in the other variables.

Because of the relatively small sample size and the use of basic descriptive statistics and very lengthy and difficult to administer measure of fatigue (i.e., POMS; consists of 65 items) the generalizibilty of that study was limited. Belza et al[13], subsequently developed the MAF and used it in a study of fatigue in 133 individuals with RA. Ninety-three percent of the sample reported experiencing fatigue during the past week. Forty percent of the sample reported that fatigue occurred every day. About half the sample (48%) reported fatigue was unchanged during the course of week, and most often fatigue affected walking, doing household chores, and shopping.

In another study of fatigue, Belza et al[12], compared fatigue in 51 patients with RA (age ranged 21-55) with 46 age-and sex-matched controls without RA. All patients with RA reported some degree of fatigue in the week before completing the questionnaire. Thirty-five of the 46 (76%) of the controls reported fatigue within the past week. The difference in proportion was significant (p<.001). Patients with RA reported statistically significant higher fatigue scores on the MAF scale than age-and sex-matched controls. The mean GFI scores for patients with RA was 27.8 ± 10.5, whereas for the controls it was 16.4 ± 11.5 (p <.001). On a 10-point numerical rating scale (1=not at all and 10=a great deal), patients with RA reported a moderate to high degree of fatigue (mean =6.3, SD=1.7), moderate fatigue severity (mean= 5.4, SD=1.8) and moderate distress from fatigue (mean=4.9, SD=2.3). For half of the patients, fatigue occurred most or every day of the week before completing the questionnaire. The average impact of fatigue on ADL was 4.2±2.1. Fatigue most often affected exercise (mean= 5.3, SD=2.7), leisure (mean= 4.8, SD=2.8) and shopping (mean=4.6, SD=2.3).

Recently, Wolfe et al[123], conducted a study on 1488 patients with 3 rheumatic diseases (RA, OA and FM) to determine the prevalence of fatigue in these disorders. Fatigue in this study was measured by a double anchored VAS labeled at one end "Fatigue is no problem," and at the other end, "Fatigue is a major problem." The question read, "How much of a problem has fatigue or tiredness been for you in the past week?". The scale for the response categories range from 0 to 3. Clinically important levels of fatigue were considered to be greater than or equal to 2 on VAS scale. The findings showed that fatigue was present in 88.4% of the RA patients (n = 628), but substantial fatigue (≥ 2 on VAS) was present in only 41% of the RA patients. Fatigue was also present in 90.1% and 98.2% of the OA (n =535) and FM (n =325) patients, respectively.

However, substantial fatigue was present in only 41% of the OA patients and 76% of the FM patients.

What causes fatigue in RA?. It would seem reasonable to assume, given the prevalence of fatigue in RA that fatigue is related to inflammation. This leads to the hypothesis that fatigue will diminish as inflammation decreases. If this hypothesis is correct, then patients with noninflammatory disorders, such as OA should have less fatigue, but this has not been extensively investigated. Several reports dispelled this hypothesis and demonstrated that the inflammatory process was not associated with fatigue in RA.[12,13,64,123] In fact, they showed that disease-related factors such as pain, depression, sleep disturbance and functional disability were highly associated with fatigue and independently predicted fatigue.[13,64,123] Belza and associates[13] in their study of fatigue in RA used a hierarchical regression to study this question. They found that 61% of the variance in fatigue could be explained by pain (19%), sex (13%), sleep (8%), activity level (4%), cormorbid conditions (4%), and functional status (4%). Pain, sex, and sleep quality were found to be the best predictors of fatigue. Other studies[64,123] also found pain, depression, sleep disturbance, functional disability and sex were the best predictors of fatigue in RA and they developed the best model that explained 53%[64] and 49%[123] of the variance in fatigue. In the study by Wolfe et al[123], 90% of the 49% of the variance accounted for by the model was explained by pain, sleep disturbance, and depression.

2.6 Fatigue in Knee Osteoarthritis

Knee OA may be seen as a different case, where the cause of almost universal fatigue is not known, but in which factors such as pain, psychosocial distress, reduced muscle function, and reduced aerobic capacity may play important roles. After a careful review of the literature, it

appears that only one study has been conducted to address fatigue in individuals with OA.[123] Despite the limitation of using a simple unidimensional measure of fatigue (i.e., VAS), Wolfe et al[123], reported that more than 41% of patients with OA had substantial, clinically important fatigue and 90% of the variance in fatigue in OA was explained by pain, sleep disturbance, and depression.

In our clinic, patients with knee OA often report fatigue when they attempt to perform activities of daily living that require them to stand for a long period of time or to perform simple activities such as walking. Stair climbing was ranked by individuals with knee OA as the most common cause of pain and fatigue. While this can be partially explained by the relationship of fatigue to pain, muscular dysfunction and reduced aerobic capacity ascribed to inactivity may also play important roles. In preliminary work, we found that individuals with knee OA had lower scores on the vitality subscale of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) than age-and sex-matched controls (57.4 ± 21.70 vs. 71.8 ± 22.86, respectively, $p = .013$). The vitality subscale of the SF-36 is a four-item measure of energy level and fatigue. Scores for the vitality subscale range from 0 to 100, where 0 indicates feeling tired and worn out all of the time and 100 indicates feeling full of pep and energy all of the time.

To compare the vitality scores of our sample with the US population normative data, standardized scores were created for the 25 randomly selected individuals with knee OA and the age-and sex-matched controls using the age-and sex-matched US population means and standard deviations (SF-36 Survey Manual). The average standardized vitality score for the controls was on the order of .54 and the average standardized score for the age-and sex-matched subjects with knee OA was on the order of -.11. This means that the OA group in our sample felt relatively more fatigue than the age-and sex-matched US population, whereas the controls were less

fatigued. A paired t-test revealed a significant difference between the two groups after normalization to the US population (p = .015).

Moreover, the vitality subscale scores for individuals with knee OA (n=84) in our sample were found to be negatively correlated with pain measured by the pain subscale of WOMAC (r = -.46, p<.001), depression measured by the Center of Epidemiological Studies Depression Scale (CES-D) (r = -.57, p<.001) and anxiety measured by the Beck Anxiety Inventory (BAI) (r = -.49, p<.001). These findings suggested potential relationships between pain, depression, anxiety, and fatigue in people with knee OA, but this was not substantiated with another study that was specifically designed to investigate fatigue in OA.

2.7 Variables Contributing to Fatigue

The subsequent section focuses on identification of disease-related factors such as; pain, depression, anxiety, muscle dysfunction and decreased cardiorespiratory endurance that may contribute to fatigue in OA.

2.7.1 Pain

Pain is the most important symptom of OA and is the principal reason why individuals seek medical care, which may include major interventions such as joint replacement. Patients with knee OA and their care providers discuss pain at 98% of all visits.[60] McKenna & Wright surveyed a heterogeneous sample of individuals with arthritis and found that 75% of those with OA ranked pain as the most important symptom to be treated.[86] The origin of pain in knee OA is

unclear since cartilage, the target of the disease, lacks innervation. Effects of the OA to the adjacent structures are thought to contribute to the pain. These include; synovitis; distension of the joint capsule (which is innervated) due to joint deformity; periosteal elevation from bony proliferation; ischemia and pressure in subchondral bone (also innervated); muscle spasm; and damage to periarticular structures, such as ligaments, tendons, and fascia.[30] Early in the course of the disease, individuals may report poorly localized, asymmetric, and episodic pain that is nagging and aching. As the disease progresses, reports of severity and frequency of pain increase. Pain is typically worse with activity and relieved by rest. In advanced disease, however, the individual may be kept awake at night by the pain.[16]

2.7.1.1 Pain and Functional Limitation

Pain can be the principal cause for functional limitation in individuals with knee OA. The severity of pain will cause people to be reluctant to move the joint. A vicious cycle may be initiated in which pain leads to decreased movement that in turn leads to stiffness and immobility of the joint. The associated inactivity can lead to muscle weakness, and muscle fatigue which in turn lead to less joint protection and a greater tendency to injure the joint during weight-bearing activities. Injury increases pain and the cycle starts again.[44]

Pain is also a risk factor for disability both in cross-sectional and longitudinal studies. Most show that with increasing severity of knee pain in individuals with knee OA, there is an increase in the self-reported physical disability.[62,67,78] Using data from the Johnston County Osteoarthritis Project, a community based sample of African-Americans and Caucasians aged 45 years and older in rural North Carolina, Jordan et al[67], reported that knee pain severity was strongly associated with overall self-reported disability measured by mean Health Assessment

Questionnaire (HAQ) score. In addition, they noted that the difference in mean HAQ scores between those with and without radiographic knee OA was not independent of knee pain, sociodemographic factors, and obesity. Based on these observations, they concluded that knee pain severity was more important than radiographic knee OA severity in determining disability.

In another community-based study, results showed that physical disability measured by the Sickness Impact Profile (SIP), a more general health questionnaire than the HAQ, in patients with knee OA age 55-74 years old was significantly associated with the chronicity and severity of knee pain. The mean of physical disability in the group with chronic and severe knee pain was 5.4 times higher than in an age-and sex-matched control group.[62] Data from the first National Health and Nutrition Examination Survey (NHANES-1) Epidemiologic Follow-up Study (1971-1975), showed that baseline knee pain in individuals with knee OA was associated with increased risk of difficulties with functional activity 7-13 years later, irrespective of baseline radiographic changes.[78]

2.7.1.2 Pain and Fatigue

There is a consensus in the literature that fatigue is significantly correlated with pain.[12,32,64,122,123] Huyser et al[64] reported a moderate correlation (r = .49) between fatigue measured by the PFS and pain measured by the McGill Pain Questionnaire (MPQ) in 73 patients with RA. Wolfe et al[123], found fatigue as measured by a VAS was associated with pain as measured by a VAS (r = .57) in 1488 patients with rheumatic diseases (RA, OA, and FM). Belza et al[12], reported an association between fatigue measured by the MAF and pain measured by a VAS (r = .48) in 51 patients with RA. Wolf[122], found that fatigue measured by a 15 cm VAS was correlated with pain measured by the WOMAC (r =0.60) in 2115 patients with RA, OA and

FM. Creamer et al[32], studying a group of hospital outpatients with knee OA, found that fatigue measured by the MPQ was significantly related to pain (r = 0.34) measured by the FSS.

Pain may contribute to fatigue through several mechanisms. First, dealing with severe or unusual amounts of pain requires additional physical and emotional energy. Second, extra steps (requiring more energy) may be needed to complete a task in manner causing the least pain. Third, pain may interfere with a restful night of sleep, thereby resulting in daytime fatigue.[85]

The precedent review provided a brief description of the effect of knee joint pain on individuals with knee OA. Pain is the most important symptom of OA and is the major reason why individuals seek medical attention, which may include major interventions such as joint replacement. Pain is also a major determinant of loss of function in individuals with OA. Individuals with OA may limit their functional activities to avoid movements that exacerbate pain. Pain is typically worse with activity, relieved by rest, and results from compression or shearing stresses on exposed subchondral bone. Inactivity may lead to more deconditioning and muscle dysfunction which may contribute to fatigue during ADL. Given the lack of disease-modifying drugs for OA, the goal of treatment is to minimize pain associated with OA and its impact on patient function and quality of life. Fatigue is strongly related to pain.

2.7.2 Depression and Anxiety

The expression of psychological reactions, notably depression and anxiety, in patients with knee OA is not surprising, given the amount and persistence of pain and disability they experience, and the uncertainty about what the future might hold for them. Depression or anxiety are frequently expressed when a person fails to cope with the pain and disability

resulting from OA.[20] As the disease progresses, knee pain persists and becomes chronic which may trigger anxiety and avoidance of movement as a normal response to protect the knee and the individual may become worried about the loss of function he or she will encounter in the future. Sleep-interrupting pain increases fatigue, and individuals may feel helpless about what is perceived as an additional burden to the normal demands of daily living. Most individuals with knee OA are elderly and are likely to have some age-related comorbidity; knee pain provides an additional health problem.

Depression and anxiety have been shown to be higher in patients with knee OA compared to age-and sex-matched controls.[22,83] Individuals with knee OA were found to be over three times as likely as age-and sex-matched controls who do not have OA to have a depressed mood.[83] In a longitudinal study[22], patients with knee OA reported higher depression scores measured by the CES-D than age-and sex-matched controls at both baseline and average 31 months follow-up. Recently, we investigated depression (measured by the CES-D) and anxiety (measured by the BAI) in elderly subjects (mean age 60 years) (Irrgang et al, unpublished data). The subjects included 84 individuals diagnosed with knee OA, and 25 subjects without OA who were matched on age and sex with a randomly selected subset of subjects from the OA group. Individuals with knee OA scored higher than age-and sex-matched controls for both the mean depression score (7.64 ± 6.29 and 5.12 ± 6.16, p=.148) and the mean anxiety score (3.80 ± 4.30 and 2.6 ± 3.41, p=.329). Although the difference in the mean depression score was not significant between the OA group and age-and sex-matched controls, 14% of OA group compared to 3% of age-and sex-matched controls scored 16 or above on CES-D that qualified them to be possibly depressed as defined by Radloff in 1977.[99] However, the difference in proportions was not significant (p=.375). The insignificant differences in the mean depression

and anxiety scores and the proportions of depressed or anxious individuals found between the OA group and age-and sex-matched controls may be attributed to the small sample used for matching.

2.7.2.1 Depression, Anxiety and Pain

A number of studies have linked psychological factors and the presence or absence of pain[22,31,35,59], and pain severity[62,105,112] in individuals with knee OA. Brandt et al[22], attempted to determine if depression scores (measured by the CES-D) in subjects with knee pain but not radiographic evidence of OA are different from those of subjects with symptomatic knee OA. They found that, in contrast to those with symptomatic knee OA, women who had knee pain but no radiographic evidence of OA had CES-D scores high enough to qualify for a diagnosis of clinical depression. The mean CES-D score for women with knee pain but no radiographic evidence of OA was significantly greater than that for women with symptomatic knee OA. However, this relationship did not exist for men.

In a community study, Creamer et al[31] investigated the relationship of depression and anxiety with reported knee pain in individuals with knee OA who participated in the Baltimore Longitudinal Study of Aging. Knee pain was defined by the NHANES-1 question "have you ever had pain in or around your knee on most days for at least one month?". Depression and anxiety were measured by the relevant subscales of Arthritis Impact Measurement Scales (AIMS) questionnaire. After adjustment for age, they found that among women who reported "ever" having knee pain without radiographic evidence of OA, anxiety scores were higher than those of women that reported "never" having pain. In this study, depression was not significantly related to knee pain.

Hochberg et al[59] reporting data from the NHANES-1 cohort, found that 49% of white women with knee pain reported feeling “low or very low in spirits" compared with 33% of those without knee pain. Further reports from the same cohort, using the General Well-Being Index, found that psychological status was positively associated with knee pain independent of radiographic changes.[35] Of the 6 General Well-Being subscales, the "energy level" and "freedom from health worry" subscales were most consistently related to knee pain, but "cheerful versus depressed mood" and "relaxed versus anxious" were also associated. They suggested that General Well-Being was related to pain in subjects both with and without radiographic changes of knee OA.

Other studies have examined the relationship between psychological factors and pain severity, rather than the presence or absence of knee pain. In a community survey of 306 elderly (mean age 65.5 years) the relationship of chronicity and severity of pain to psychosocial disability (as measured by the subscales of the SIP,) was explored.[62] The chronicity and severity of pain were associated with higher psychosocial disability when compared with age and sex matched pain free controls from the same community. The mean of psychosocial disability in the group with chronic and severe knee pain was 3.6 times higher than age and sex matched control group.

In a study of 61 patients with knee OA (mean age 63.5 years) Salaffi et al[105], found significant correlations between pain measured by the MPQ and Zung Anxiety and Depression Inventory scores. The strongest correlations were between affective pain and anxiety ($r = 0.56$) and depression ($r = 0.62$). Summers et al[112] reporting on 65 patients with hip or knee OA (mean age 71 year), found that depression (as measured by the Beck Depression Inventory) and anxiety (measured by the State-Trait Anxiety Index (STAI)) correlated with pain measured by the MPQ.

In our preliminary work, we found significant correlations between knee pain severity (as measured by the pain subscale of WOMAC) and depression (measured by the CES-D) and anxiety (measured by the BAI). In OA group (N=84), knee pain was significantly correlated with depression (r = .26, *p*= .008) and anxiety (r = .34, *p* =.001).

2.7.2.2 Depression, Anxiety and Fatigue

Fatigue was first described clinically, in the early 1900s, as a "generalized neurasthenia" or weakness of the body. If reviewed today, many of those early cases would be described as psychological disorders.[53] In fact, fatigue is often a significant component in affective and anxiety disorders. Fatigue or loss of energy nearly every day is a hallmark diagnostic criterion for a major depressive episode.[110] Furthermore, fatigue may be magnified by poor psychological status, particularly in a patient who feels worthless when he or she has no strength. In addition to experiencing hopelessness, the depressed patient may have a sensation that great effort is necessary to initiate action. In general, fatigue may be deemed as a manifestation of psychological problems.

Several reports found psychological problems to be strongly associated with fatigue in collections of rheumatic disorders.[12,13,64,123] Fatigue (measured by the PFS) was found to be strongly correlated with depression (measured by the CES-D) and anxiety (measured by the STAI) (r = .51, r = .41, respectively) in a group of patients with RA.[64] In another group of RA patients, Belza[12] reported a high correlation between fatigue (measured by the MAF) and depression (measured by the depression subscale of POMS) (r = .47). Wolfe et al[123], found fatigue assessed by a VAS was strongly associated with the AIMS depression (r = .50) and AIMS anxiety scales (r =.52) in 1488 patients with rheumatic diseases (RA, OA, and FM).

The mechanisms by which these psychosocial factors contribute to fatigue are not clear. However, it has been hypothesized that patients with knee OA tend to avoid physical activity because increased levels of physical activity are associated with pain.[36] This in turn contributes to progressive muscle weakness and fatigue and disability. As a result, patients may feel frustrated and hopeless of this vicious cycle and be at risk of developing psychological distress. Depression and anxiety may serve to amplify this loop by increasing the degree of avoidance. Prolonged depression and anxiety may, by resulting in persistent attempts to avoid knee pain, lead to further muscle wasting, cardiovascular deconditioning and a sensation of generalized fatigue during normal activities of daily living.

In summary, depression and anxiety are frequently expressed when a person fails to cope with the pain and disability resulting from OA. Depression and anxiety have been shown to be higher in patients with knee OA compared to age-and sex-matched controls. Depression and anxiety were found to be strongly associated with fatigue in collections of rheumatic disorders. These psychosocial variables contribute to fatigue by causing the individual with knee OA to be reluctant to move due to pain which leads to muscle dysfunction and decreased aerobic capacity which eventually lead to a sensation fatigue of generalized fatigue.

2.7.3 Quadriceps Fatigue

2.7.3.1 Definition

A conclusive definition of muscle fatigue does not exist because it is dependent upon the type of task performed (i.e., high or submaximal intensity, intermittent or sustained).[40] However,

muscle fatigue can be operationally defined as a progressive decline in maximal muscle force generating capacity during physical activity.[15] The development of this progressive decline in force is a complex process and results from multiple factors. Bigland-Ritchie and Woods[15] classified the mechanisms of muscle fatigue as failure of: 1) excitatory input to higher motor centers; 2) excitatory drive to lower motor neurons; 3) motor neuron excitability; 4) neuromuscular transmission; 5) sarcolemmal excitability; 6) excitation - contraction coupling; 7) contractile mechanisms, and 8) metabolic energy supply and metabolite accumulation.

Muscle fatigue has frequently been classified as central or peripheral fatigue.[42] Central fatigue involves failure of motor drive from the central nervous system that results in a reduction of the number of functioning motor units and/or a reduction in motor unit firing rate.[42] Peripheral fatigue, on the other hand, occurs within the muscle itself and involves failure of force generating capacity of the whole muscle due to failure of the muscle action potential, impaired excitation-contraction coupling, depletion of active muscle metabolic energy supply or metabolite accumulation.[15,42,116]

2.7.3.2 Quadriceps Fatigue in Knee Osteoarthritis

Quadriceps fatigue is another symptom often reported by patients with knee OA.[46-50,94] Since quadriceps fatigue may limit the time a person can stand, the distance a person can ambulate, or the number of stairs a person can ascend or descend, it may play a major role in the reduced functional performance and disability experienced by individuals with knee OA. Previous studies have shown that improvements in quadriceps muscle function (i.e., strength and endurance) resulted in significant improvements in functional performance in knee OA patients.[47,49] In spite of the profound clinical implications of quadriceps fatigue in individuals

with knee OA, there is a paucity of published data on the effects of knee OA on quadriceps muscle endurance.

Few studies have investigated the effect of knee OA on quadriceps fatigue.[48,94] In these investigations, quadriceps fatigue was assessed by determining an individual's ability to sustain a maximal isometric contraction for 90 seconds[48] or 120 seconds.[94] Fisher and Pendergrast[48] measured fatigue as the area under the fatigue curve or the tension-time index. Nordesjo et al[94] measured fatigue as the steepness of the torque curve or the difference in maximal isometric torque between 0 and 120 seconds.

The relationship between knee OA and quadriceps fatigue is unclear. Fisher and Pendergrast[48] found that individuals with knee OA exhibited 203% greater quadriceps fatigue than did individuals without knee OA. Nordesjo et al[94] found the endurance curve to be steeper on the non-involved side in individuals with unilateral knee OA, indicating less quadriceps fatigue on the side with OA.

The functional significance of quadriceps fatigue is also unclear. Quadriceps fatigue has been found to be related to the time required to walk 50 ft, but not to the degree of dependence, difficulty, or pain experienced during a variety of daily activities.[48] The failure to demonstrate the functional significance of quadriceps fatigue, measured as the ability to maintain a maximal isometric contraction for 90 to 120 seconds, may be due to the fact that most daily activities do not require a single maximal isometric contraction of the quadriceps. The ability to sustain a single maximal isometric contraction may be influenced by many other factors including pain tolerance, ischemia, and motivation. A single maximal isometric contraction may also create an unsafe increase in heart rate and blood pressure. The demands of normal daily functional activities on muscles are more closely reproduced by repetitive, submaximal exercise.

To measure quadriceps fatigue in individuals with knee OA, we developed a fatigue test that consisted of repeated submaximal quadriceps contractions at 50% of maximal effort (unpublished data). Fatigue was operationally defined as the number of contractions an individual could perform before they were no longer able to generate 50% of the maximum isometric quadriceps torque. Using this procedure, we tested 84 subjects diagnosed with knee OA, and 25 subjects without OA who were matched on age and sex with a randomly selected subset of subjects from the OA group. The findings from this study demonstrated that individuals with knee OA performed significantly more repetitions indicating less quadriceps fatigue than control subjects (72.96 $\pm$ 60.03 and 42.20 $\pm$ 42.64 respectively, p=.014). In addition, the number of repetitions was not correlated with concurrent self-reported or performance-based measures of physical function. Concurrent self-reported measures of physical function included the WOMAC physical function and total scores, the Activities of Daily Living Scale (ADLS) of the Knee Outcome Survey, and the physical components summary scores of the SF-36. The "get-up and go" test was used as the performance-based measure of physical function. With this fatigue test, we were unable to demonstrate that individuals with knee OA had greater quadriceps fatigue than age-and sex-matched controls. It is unknown if subjects with knee OA truly have less quadriceps fatigue than age and sex matched controls or if the measure of fatigue in this study was not a valid measure of quadriceps fatigue. With the technique that we used to measure quadriceps fatigue, we were unable to determine the mechanisms of fatigue, if any. The conflicting findings of the studies that investigated the effect of knee OA on quadriceps fatigue may be due to the way quadriceps fatigue was operationally defined and measured in each of these studies. Alternative methods are needed to measure quadriceps fatigue.

2.7.3.3 Quadriceps Fatigue Measurement

To obtain more insight into the causes of muscle fatigue, it is important to determine the mechanisms of muscle fatigue. Based on the definition of muscle fatigue, it is possible to quantify muscle fatigue by having the subject performing brief maximum voluntary contractions at regular intervals during repeated, submaximal, intermittent, isometric contractions. The progressive decline of the maximum voluntary contractions over the course of time will be defined as muscle fatigue. Direct electrical stimulation of the muscle will elicit involuntary force output. Comparison of the rate of decline in maximal voluntary contractions with the rate of decline in electrically elicited force output allow one to distinguish between muscle fatigue caused by reduced motor drive from central nervous system (i.e., central fatigue) and muscle fatigue caused by the inability of the muscle itself to generate force (peripheral fatigue).[14,39,65,69,87,90,117] If a parallel decline in the maximal voluntary contraction and electrically elicited force output is observed, it would indicate that the central nervous system is still capable of fully activating the muscle and any observed muscle fatigue would likely be due to failure of contractile properties within the muscle (i.e., peripheral fatigue). On the other hand, if slopes declined at different rates, than the observed fatigue would be likely due to failure of neural drive of the muscle from the central nervous system (i.e., central fatigue).

Several studies have investigated quadriceps fatigue using the aforementioned technique [14, 39,65,90,117] Bigland-Ritchie et al[14] and Vollestad et al[117], have used the technique to assess quadriceps fatigue evoked by intermittent submaximal voluntary isometric contractions in young healthy subjects. Subjects were asked to hold a targeted force level for 6 seconds (e.g., 50% of maximal voluntary contraction), then to rest for 4 seconds. The subjects repeated this 10-second cycle until they could no longer generate and maintain the targeted force level. Every minute

during the test, the subject performed a maximal voluntary isometric contraction, upon which a supra-maximal electrical stimulus was applied. This was then followed by an electrical stimulus delivered to the resting quadriceps muscle. Over a course of time, the rate of decline of the maximal voluntary contraction force output was compared to the electrically elicited force output from a relaxed quadriceps muscle. The results indicated that the slope of both force outputs declined at a similar rate, suggesting that the source of the fatigue was peripheral. Other investigators used the same technique to assess quadriceps fatigue in subjects with FM[90] and Addison's disease.[65] To the best of our knowledge, no published data on using the above technique to quantify quadriceps fatigue in individuals with knee OA.

2.7.3.4 Quadriceps Fatigue and Self-Reported Fatigue

The association between quadriceps fatigue and sensation of generalized fatigue has not been reported. However, it can be assumed by looking at the effect of quadriceps fatigue on the neuromuscular control of the lower limb. It has been demonstrated in young healthy subjects that neuromuscular control of the lower limb is compromised in the fatigued state.[66,121] Johnston et al[66] investigated the effect of lower limb fatigue on lower extremity balance as a mean of quantifying neuromuscular control of the knee in 20 healthy subjects. They found that after fatiguing exercise on a lower limb dynamometer to less than 50% of original strength values, subjects had a significantly decreased ability to maintain balance on one or both legs. Wojtys et al[121] investigated the effect of quadriceps and hamstring muscle fatigue on anterior tibial translation and muscle reaction time in 10 healthy subjects. They defined muscle reaction time as the time between onset of passive anterior tibial translation and onset of muscle firing. They found an average increase of 32.5% in anterior tibial translation, a delay in muscle reaction

times, decreased firing rates of the quadriceps and hamstring, and delayed spinal reflexes after a fatiguing protocol that led to a 50% decrease in work performed on the dynamometer.

The precise physiologic mechanisms behind the fatigue-mediated alterations in neuromuscular control of the knee have yet to be determined. It has been hypothesized that quadriceps fatigue decreases neuromuscular control of the knee joint by altering knee joint proprioception.[58] Several studies have demonstrated that knee proprioception is less accurate in patients with knee OA versus control subjects.[51,55,63,72,107] These studies have provided strong evidence that arthritic changes within the joint reduce the activity of the mechanoreceptors and subsequently diminish the joint proprioception. Furthermore, several reports have demonstrated that muscle spindle and Golgi tendon organ activity may decrease with muscle fatigue, which in turn leads to decreased proprioception.[77,84] The combined effects of knee OA and quadriceps fatigue on knee proprioception could potentially affect neuromuscular control of the knee and significantly decrease postural stability and lead to a staggering gait. As a consequence this will impair mobility and performance of ADL in individuals with knee OA, leading to decreased patient's confidence and increased anxiety of falling. Manipulating the difficulty of the postural control and keeping a smooth gait may significantly contribute to sensation of generalized fatigue. By failing to sustain the required muscle force, the quadriceps fatigue may limit the time a person can stand, the distance a person can ambulate, or the number of stairs a person can ascend or descend. Therefore, it may play a major role in the reduced functional performance and fatigue experienced by individuals with knee OA.

Thus, quadriceps fatigue is another important finding in individuals with knee OA. Individuals with knee OA exhibited greater quadriceps fatigue than individuals without knee OA. Quadriceps fatigue may decrease the neuromuscular control of the knee joint, which in turn

impairs the postural stability. It is postulated that individuals with knee OA exhibit increased muscle fatigue which decreases their postural stability and put them at a risk of falling. Managing postural stability during performance of ADL could be an energy draining task for an elderly individual with knee OA.

2.7.4 Cardiorespiratory Endurance

2.7.4.1 Definition

Cardiorespiratory endurance is defined as the ability to perform moderate to high intensity exercise using large muscle groups for an extended time period.[4] Performance of such exercise depends on the functional state of the respiratory and cardiovascular systems. The single best measure of cardiorespiratory endurance is maximal oxygen uptake (VO_2 max) or aerobic capacity, which is the ability of these systems to supply oxygen to the working muscles in a manner that permits continuous exercise, or physical activities.

2.7.4.2 Cardiorespiratory Endurance in Knee Osteoarthritis

Knee OA restricts physical activity both directly and indirectly. Pain, stiffness, fear of doing harm, and complying with incorrect beliefs to avoid strenuous and weight-bearing activities, encourage a sedentary lifestyle. It has been reported that the presence of knee OA contributes substantially to functional limitations in performance of functional weight bearing tasks such as walking, stairclimbing, housekeeping, and carrying bundles.[54]. Inactivity and subsequent decreased cardiorespiratory endurance, superimposed on the numerous impairments

associated with knee OA play a significant role in patient's overall functional status and quality of life. Decreased cardiorespiratory endurance in this population can be great burden and could obviously accelerate functional decline.[96] Previous studies have demonstrated that individuals with knee OA have low aerobic capacity[44,91] and significantly lower than age-and sex-matched controls.[96] In the study by Minor et al[91], 80 volunteers with symptomatic OA in weight-bearing joints were assessed using a maximal symptom-limited graded exercise tolerance test as per the Naughton treadmill protocol. They found that VO_2 max scores of patients with OA (mean age 64 yrs) to be 15.3 ml/kg/min. This value is approximately 20% lower than values in healthy older adults.[8]

In further support of the findings, Philbin et al[96] assessed VO_2 max in 19 patients with knee OA (mean age 68 yrs) using a maximal symptom-limited graded exercise tolerance test utilizing a bicycle ergometer. They found that patients with knee OA had significantly lower VO_2 max mean scores compared to age-and sex-matched controls (knee OA 12.8 ± 3.7 versus controls 17.6 ± 5.2 ml/kg/min, $p < 0.0005$).

VO_2 max can be also expressed as the metabolic equivalent (MET) which is ratio of the metabolic rate of the average person while seated and resting, to the metabolic rate of a particular person while performing some task. Resting metabolic rate (1 MET) requires 3.5 milliliters of oxygen per kilogram of body weight per minute.[2] In a study by Ettinger et al[44] it was reported that a high proportion of older people with knee OA have a VO_2 max of 3-4 METS as measured by a symptom limited treadmill test. It is equivalent to energy expenditure at moderate walking or doing multiple households tasks all at once with a moderate effort.[2] Thus, the anaerobic

threshold may be reached in course of daily activities, causing fatigue and limited physical activities.

2.7.4.3 Cardiorespiratory Endurance and Self-Reported Fatigue

The relationship between cardiorespiratory endurance and fatigue in individuals with knee OA has not been reported. This may be due to the paucity of information about fatigue in individuals with knee OA. In our clinic, patients with knee OA often report fatigue when they attempt to perform activities of daily living that require them to stand for a long period of time or to perform simple activities such as walking. Stairs climbing was ranked by individuals with knee OA as the most common cause of pain and fatigue. While this can be partially explained by the relationship of fatigue to pain, muscular dysfunction and decreased aerobic capacity ascribed to inactivity may also play important roles. Aerobic capacity is an important component of overall health status, since it indicates the capacity to perform routine activities of daily living, required occupational tasks, and recreational endeavors, thus quality of life. It is expected that decrease aerobic capacity and muscular dysfunction will preclude individuals with knee OA from continuing their activities of daily living and it will be manifested as subjective sensation of fatigue.

2.7.4.4 Estimation of VO_2 max (Aerobic Capacity)

One of the most widely used submaximal exercise tests is the Astrand-Ryhming submaximal cycle ergometer test.[7] This test was designed to predict VO_2 max based upon the steady-state heart rate of a person exercising at one submaximal workload for 6 minutes. A nomogram is used to estimate VO_2 max based on the linear relationship between the heart rate and the VO_2 max. Because maximal heart rate decreases with age, and the data were collected

on young subjects ages 18-30 yrs, Astrand[5] established age correction factors to multiply the estimated VO_2 max values taken from the nomogram in order to correct for the lower maximal heart rate. Astrand and Rodahl[6] reported that the VO_2 max estimated from the nomogram after correction for age underestimate the directly measured VO2 max when the value was low, but overestimate the value for well-trained athletes who have a high VO_2 max.

Siconolfi et al[108] developed a modification of the Astrand-Ryhming protocol which accurately estimates VO_2 max and is safe and suitable for assessing the cardiorespiratory endurance status of inactive people 20 to 70 years of age. This protocol was adapted in this study for two reasons; 1) the procedure was validated on men and women of ages 20 to 70 years and 2) put the subjects under less stress by requiring that a heart rate of only 70% of age-predicted maximal heart rate be achieved as described in chapter III. It is deemed appropriate for the knee OA population because of the aforementioned reasons.

The precedent section highlighted the relationship between knee OA and decreased aerobic capacity. Inactivity and subsequent decreased aerobic capacity, superimposed on the numerous impairments associated with knee OA play a significant role in patient's overall functional status and quality of life. Decreased aerobic capacity in this population can be a great burden and could obviously accelerate functional decline. An association between decreased aerobic capacity and self-reported fatigue in individuals with knee OA was presumed. It is hypothesized that decreased aerobic capacity will preclude individuals with knee OA from continuing their activities of daily living and it will be manifested as subjective sensation of fatigue. Thus, the anaerobic threshold may be reached in course of daily activities, causing fatigue and limited physical activities.

2.8 Summary

In summary, fatigue is a complex phenomenon that may be affected by other frequently occurring problems in knee OA. It appears that little is known about the degree of fatigue severity in knee OA. It also appears that nothing is known about how well relevant muscle dysfunction, such as quadriceps fatigue and cardiorespiratory endurance are related to the subjective experience of fatigue in individuals with knee OA, above and beyond important demographic, physiological and psychosocial variables. As a result of the limited research to date, which focuses primarily on the degree of fatigue severity and its relationships to other frequently occurring problems in knee OA, there was a need for a well designed study to explicate these complex interrelationships.

2.9 Assumptions

There are several assumptions in this study. One assumption is that individuals with knee OA experience fatigue indirectly as a result of the disease process. Another assumption is that individuals with knee OA are able to quantify and qualify their fatigue. Demographic, physiological, and psychosocial variables are assumed to influence the experience of fatigue.

2.10 Research Questions

The following research questions were addressed in this study:

1. What is the magnitude and dimensions of self-reported fatigue in individuals with knee OA compared to others without knee OA?
2. What is the influence of the quadriceps fatigue on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as

age, sex, pain, depression, and anxiety?

3. What is the influence of the cardiorespiratory endurance on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety?

2.11 Hypotheses

Hypotheses for this study included the following:

1. Individuals with knee OA would report significantly higher fatigue scores than those individuals who do not have knee OA and similar levels of fatigue as individuals with rheumatoid arthritis.
2. When controlling for age, sex, pain, depression, and anxiety, individuals who have less quadriceps fatigue would report significantly lower fatigue scores than individuals who have more quadriceps fatigue. In other words, quadriceps fatigue is a significant predictor of self-reported fatigue after controlling for age, sex, pain, depression, and anxiety.
3. When controlling for age, sex, pain, depression, and anxiety, individuals who have better cardiorespiratory endurance would report significantly lower fatigue scores than individuals who have poor cardiorespiratory endurance. In other words, cardiorespiratory endurance quadriceps fatigue is a significant predictor of self-reported fatigue after controlling for age, sex, pain, depression, and anxiety.

3 METHODOLOGY

3.1 Introduction

This chapter focuses on the methodology used in this study of fatigue in older adults with knee OA. The outline for this chapter includes a description of the research design, subjects, measurement procedures, including psychometric properties of each procedure and procedures for statistical analysis.

3.2 Research Design

This descriptive study used a one group cross-sectional, correlational design to describe the prevalence and impact of fatigue and the role of factors that contribute to fatigue in knee OA. Descriptive and multiple regression analyses were conducted on data gathered from self-reported measures of pain and health-related quality of life and performance-based measures of function on a sample of patients with knee OA. Self-reported measures collected in this study included demographic information, fatigue severity, pain intensity, depression, and anxiety. Performance-based measures collected in this study included quadriceps maximum voluntary isometric contraction (MVIC) torque output, cardiorespiratory endurance, and quadriceps fatigue.

3.3 Study Sample

3.3.1 Recruitment

Subjects were recruited from physician's offices of the University of Pittsburgh Medical Center (UPMC) Arthritis Network, the UPMC Arthritis Network Registry and from the physical therapy clinic at the UPMC Health System's Center for Sports Medicine. Potential subjects were informed of the study by their care providers (i.e., the physician for those subjects identified

through the UPMC Arthritis Network or the physical therapist for those patients identified through physical therapy clinic). Permission to contact the subjects was obtained prior to making contact with the subjects. Once potential subjects had granted permission to be contacted, the purpose of the study and the procedures that were to be utilized were described to them. Additionally, subjects who participated in previously approved IRB studies related to knee OA conducted by our investigative team who verbally indicated to us that they would be willing to participate in future studies were also notified of the present study by letter and were asked to return a postcard (or telephone call) if they would like to participate in this study (Appendix A).

When an individual agreed to participate in the study, the individual's physician was contacted to ensure that there were no contra-indications to the individual's participation in this study. To accomplish this, a form was mailed or transmitted by fax to the physician. The form included the subject's name and explained the purpose of the study and the type of activities that the subject would be required to perform to participate in the study. The subject's physician was asked to indicate his/her approval for the subject to participate in this study, sign the form, and mail it back to the principal investigator. Once permission from the individual's physician had been granted, the individual was scheduled for the testing procedures (Appendix B). All subjects signed an informed consent form approved by the University of Pittsburgh Institutional Review Board prior to participation in the study.

3.3.2 Inclusion Criteria

Subjects included 44 individuals (33 females and 11 males) who had been diagnosed by their physician with knee OA involving the tibiofemoral and/or patellofemoral compartments. Subjects were included in the study if they were 45 years of age or older, met the 1986 American College of Rheumatology (ACR) clinical and radiographic criteria for knee osteoarthritis[3], and had grade II or greater Kellgren and Lawrence radiographic changes.[68] The 1986 ACR criteria for diagnosis of knee osteoarthritis includes knee pain with osteophytes and **at least one** of the following: age greater than or equal to 50 years, morning stiffness less than 30 minutes, or crepitus with active motion of the knee, such as when squatting while weightbearing.

3.3.3 Exclusion Criteria

Subjects were excluded from the study if they: 1) had limitations in knee motion that prevented them from comfortably positioning their knee for the quadriceps strength and fatigue tests (i.e. they have less than 70° of flexion); 2) had undergone total knee arthroplasty; 3) exhibited uncontrolled hypertension (i.e., systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg); 4) had a history of cardiovascular disease; 5) had a history of patellar or quadriceps tendon rupture; 6) had a history of patellar fracture; 7) had any surgical procedures involving the patella, quadriceps tendon or patellar tendon or 8) had a steroid injection of the patellar or quadriceps tendons (Appendix C).

Subject demographic information is provided in Table 1.

3.4 Data Collection Methods

All subjects participated in two testing sessions. During the first session, individuals completed a demographic information questionnaire and self-reported measures of fatigue, pain,

depression, and anxiety. A burst superimposition maximum isometric quadriceps torque test was performed to determine the quadriceps MVIC torque output that was used in the quadriceps fatigue test during the second session. Individuals also performed a series of 10 submaximal isometric contractions of the quadriceps at 50% of MVIC torque to become familiar with the effort that will be required during the quadriceps fatigue test. During the first testing session, subjects also performed a submaximal cycle ergometer test to estimate VO_2 max as a measure of cardiorespiratory endurance. Within one week after completing the first testing session, individuals were scheduled to come back again for a second testing session. During the second testing session, the quadriceps fatigue test was performed on the same leg that was tested during the burst superimposition test.

3.4.1 Self-Reported Measures

3.4.1.1 Demographic Information

Demographic data collected in this study included age, sex, height, weight, ethnicity, marital status, education level, employment status, past medical history and disease duration (Appendix D).

3.4.1.2 Multidimensional Assessment of Fatigue

The Multidimensional Assessment of Fatigue (MAF) scale is a self-administered measure that contains 16 items and measures five dimensions of fatigue: degree (item 1), severity (item 2), distress (item 3), degree of interference with activities of daily living (items 4-14), and timing (items 15-16)[12] (Appendix E). The MAF was scored according to the instructions from the MAF home page and through personal communication with the author of the instrument.[12] Fourteen

items contain 10-point numerical rating scales (items 1-14) and two items have multiple-choice responses (items 15-16). The 10-point numerical rating scale ranges from 1(not at all) to 10 (a great deal). Respondents are asked to reflect on fatigue patterns for the past week. Scoring the MAF results in the Global Fatigue Index (GFI), a composite score of five dimensions of fatigue (degree, severity, distress, impact, and timing). If the respondent reported no fatigue (item 1), a zero was assigned to all remaining items (2-16). Respondents, who do not do certain activities for reasons other than fatigue, are instructed to check a box to the left of each activity item and no score was assigned to this item. For all respondents, item 15 which ask about frequency of fatigue was converted from 1-4 to 2.5-10 by multiplying responses by 2.5 for this item. This conversion then allowed the items measuring degree of fatigue (item 1), severity of fatigue (item 2), distress of fatigue (item 3), the average of impact on ADL items (items 4-14), and the newly scored frequency of fatigue item (item 15) to be summed to create the GFI. The index score can range from 1 to 50 with 1 representing no fatigue and 50 representing extreme fatigue.

Psychometric properties of the MAF were tested with 51 respondents with RA and 26 age-and sex-matched controls.[12] Cronbach's alpha was computed for the MAF to determine internal consistency and was found to be .93. In this study, Cronbach's alpha of the MAF was .92 for respondents with knee OA. Evidence for validity was provided by a relatively high positive correlation with a concurrent measure of fatigue (POMS fatigue subscale, $r=.84$, $p<.01$) and a relatively strong negative correlation with a concurrent measure of vigor (POMS vigor subscale, $r=-.62$, $p<.01$).[12]

The MAF scale is a good choice when selecting an instrument to measure fatigue in chronic illness as it is: easy to administer and score, relatively short in length (it takes less than five minutes to complete) and assesses the subjective aspects of fatigue including degree,

severity, distress, impact, and timing. The questionnaire allows patients to omit activity items that do not apply, thus making it a more accurate assessment of the impact of fatigue on ADL. To yield reliable and valid responses, instructions are included on page one of the three-page instrument. The instructions read: "These questions are about fatigue and the effect of fatigue on your activities during the past week". If no fatigue is reported (i.e., respondents answer item 1 by indicating they have not had any fatigue in the past week) then they are instructed to stop. The reason to stop is because items 2-16 are only applicable if the respondent had fatigue in the past week. So as to assure variability in the outcome variable of fatigue, respondents who report no fatigue are assigned a zero score for items 2-16 and kept in the analysis.

3.4.1.3 Pain

Pain was assessed using the pain subscale of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index[11] The WOMAC is a widely used disease-specific, self-report measure of pain, stiffness, and physical function in individuals with OA of the hip or the knee. The WOMAC consists of 5 questions about pain, 2 about stiffness and 17 about degree of difficulty in accomplishing daily living activities. The responses to the items are in the form of a 5-point Likert scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extreme. The subscales are summed to maximum scores of 20, 8, and 68, respectively. There is also an overall osteoarthritis index score, which is calculated by summing the scores of the 3 subscales. The psychometric properties of the WOMAC score have been established. [11] Internal consistency (Cronbach's alpha) of the WOMAC was found to be 0.86, .90 and .95 for the pain, stiffness and physical function subscales respectively. Based on comparison with Lequesne Index scores, evidence for convergent construct validity of the WOMAC subscales was demonstrated by

Pearson correlation coefficients of 0.57, .35, and .55 for the WOMAC pain, stiffness, and physical function subscales respectively. Evidence for divergent construct validity, based on comparison of WOMAC subscales with Bradburn Index of Well Being scores, was demonstrated by non-significant Pearson correlation coefficients of .15, -.09, and .24 for the WOMAC pain, stiffness, physical function subscales respectively. The questionnaire is self-administered and takes 5 minutes to complete.

3.4.1.4 Depression

Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)[99]. The CES-D is a 20-item self-report measure that includes questions that pertain to a wide range of depressive symptoms. Respondents are asked to rate the frequency of occurrence of each symptom in the past week on a 4-point Likert scale, which ranges from, 0 = rarely or none of the time (less than 1 day) to 3 = most or all of the time (5-7 days). After reverse-scoring of items that are indicative of positive mood status (items 4, 8, 12, and 16), responses to the 20 items are summed to obtain a total scale score. The potential range of scores is from 0-60; higher scores indicate greater depression. A score of 16 or greater typically is employed as a cut-off that indicates clinical depression.[19]

The CES-D has been used in numerous studies involving the psychiatric populations[119] as well as older adult general populations[80] and arthritis populations[17] and has generally been found to have excellent psychometric properties. Cronbach's alpha coefficient of 0.91 has been reported in the arthritis populations. Convergent construct validity is evidenced by a positive correlation of 0.81 with AIMS depression subscale and divergent validity is evidenced by negative correlations of -0.59 to -0.80 with Rosenberg Self-Esteem Scale, Satisfaction With Life

scale, and General Positive Affect subscale from the 18-item Mental Health Inventory.[17] Some arthritis researchers are concerned that four items on this scale might be measuring disease symptoms rather than depression, and thus depression scores might be inflated among people with arthritis. These items include; "I felt that everything I did was an effort," "I felt hopeful about the future," "My sleep was restless," and "I could not get going." However, study has found that results are the same when scores were analyzed with or without these four items in a sample of arthritis patients.[17] The CES-D is an easy to complete self-administered questionnaire that has demonstrated its usefulness as a screening tool for detecting depressive symptoms among community-residing elderly adults and arthritic patients[17,80]

3.4.1.5 Anxiety

Anxiety was assessed using the Beck Anxiety Inventory Scale (BAI). The BAI is a 21-item self-report questionnaire measuring common symptoms of clinical anxiety, such as nervousness and fear of losing control[10]. Respondents indicate the degree to which they were bothered by each symptom during the past week. Each symptom is rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (severely, I could barely stand it), and the total score ranges from 0 to 63, with higher scores corresponding to higher levels of anxiety. The BAI has excellent internal consistency with psychiatric outpatients.[10] Beck, et al[10] reported a Cronbach's alpha of 0.92. The BAI discriminated anxious from non-anxious diagnostic groups. In addition, the BAI was moderately correlated with the clinician-administered Hamilton Rating Scale for Anxiety (r =.56), and mildly correlated with Hamilton Rating Scale for Anxiety (r = .25)[10]

3.4.2 Performance-Based Measures

3.4.2.1 Burst Superimposition Maximum Isometric Quadriceps Torque Test:

To perform this test, subjects were seated on an isokinetic dynamometer (Biodex System 3 Pro, Shirley, NY) and secured to the seat by torso, pelvic and thigh straps to minimize movements of these segments. The knee that the subject reported as being the most symptomatic knee with regard to pain and functional limitation was selected for testing. The center of rotation of the dynamometer was aligned with the lateral femoral epicondyle. The knee being tested was positioned at 60° of flexion with the force arm-pad attached just above the ankle by means of a Velcro strap. A Grass Model S8800 electrical stimulator with a Grass Model SIU8T stimulus isolation unit (Grass Instrument Company, Braintree, MA) was used to deliver the electrical stimulation. The skin in the area of electrode placement sites over the anterior thigh was cleansed with rubbing alcohol, then two 6.9 cm by 12.7 cm self-adhesive electrodes (Dura-Stick, Chattanooga Group, Hixson, TN) were placed on the quadriceps muscle so that an electrical stimulus could be applied during the testing procedure. The cathode was placed proximally over the muscle belly of the vastus lateralis and the anode was placed distally over the muscle belly of the vastus medialis.

Once the patient was prepared for testing, we employed a process of potentiating the quadriceps muscle to maximize the subject's ability to produce maximum torque output.[109] In addition, this process familiarized the subjects with the maximum voluntary isometric torque test procedure as well as the electrical stimulus to be used during testing which also minimized the potential for learning effects on the test results. The first step in this process was to instruct the subjects to practice producing voluntary isometric quadriceps contractions against the arm of the dynamometer at 50%, 75% and 100% of their maximum voluntary effort. Following the practice

trials, three successive trains of electrical stimulus (pulse duration= 0.6 msec, pulse interval=10 msec, train duration=100 msec), separated by 30 seconds, were applied to the subject's resting quadriceps muscle at amplitudes of 40 volts, 60 volts, and 100 volts respectively.

Following the potentiating process, the burst superimposition maximum isometric quadriceps torque test was performed. Subjects were instructed to exert as much force as possible while extending the knee against the force-sensing arm of the dynamometer. During the contraction, a train of electrical stimuli (amplitude = 100 volts, pulse duration=0.6 msec, pulse interval=10 msec, train duration=100 msec) was applied to determine the extent of QAF. A torque target line was displayed on the computer monitor to provide subjects with visual feedback in an effort to maximize their ability to produce maximum torque during the test. The torque target was placed at a force level slightly greater than the peak torque produced during the practice MVIC. If subjects exceeded this torque target during a given trial, the target was reset at a higher level on the next trial. The test was repeated 4 times. The MVIC and superimposed electrical stimulation (SES) torque outputs were recorded (Appendix F). The highest MVIC achieved during the 4 trials was used for the analyses described below. Experience over the last three years has indicated that individuals ranging in age from 18 to 82 have been able to tolerate this test without difficulty. This procedure has been shown to yield reliable quadriceps muscle torque measurements. Test-retest reliability of the procedure on healthy subjects (no knee impairments) demonstrated an ICC of 0.98.[111]

3.4.2.2 Submaximal Cycle Ergometer Test

A modified Astrand-Ryhming submaximal cycle ergometer test was used to estimate VO_2 max.[108] To eliminate any potential factors that might affect the performance of the test

subjects were requested not to eat, smoke, or exercise for 2 hours prior testing. To perform this test subjects rode a stationary ergometer (Monarch, Ergomedic 818E). The bike seat was adjusted so that the subject's knees were almost completely extended when the foot was at the bottom of the pedaling cycle. The subject started pedaling at a rate of 50 revolutions per minute (rpm) against an initial workload of 25 W. The pedaling rate was kept constant during the course of the test using the bike's built-in electronic meter. During the test, the heart rate was monitored every minute using a chest strap heart rate monitor (Polar Electro, Inc Woodbury, NY). The workload was increased by 25 W every two minutes until the subject achieved a target heart rate (i.e., 70% of age-predicted maximal heart rate). After attaining this threshold, the subject continued exercising at the same workload for at least two more minutes until a steady-state heart rate was achieved. Steady-state heart was concluded to be present when consecutive (1 min apart) heart rates differed by ≤ 5 bpm. Figure 1 shows a schematic representation of the protocol.

To ensure the subject's safety during this submaximal cycle ergometer test, blood pressure was monitored every 3 minutes during the test. The normal blood pressure response during exercise includes a progressive increase in systolic blood pressure with no change or a slight decrease in diastolic blood pressure. An abnormal blood pressure response is one in which systolic blood pressure fails to increase with increased exercise intensity or an excessive increase in either systolic or diastolic blood pressure. The test was terminated if an abnormal blood pressure response to exercise occurred. The submaximal exercise test was terminated if systolic blood pressure failed to increase with increased exercise intensity or if systolic blood pressure exceeded 170 mm Hg or diastolic blood pressure exceeded 110 mm Hg or if the heart rate exceeded 85% of the subject's age-predicted maximum value.

The VO_2 max was estimated from the table of VO_2 max values derived from the Astrand-Ryhming nomogram[6,7] using the mean steady-state heart rate and the final workload. The mean steady-state heart rate is the average of the last two heart rate readings (Appendix G) The estimated VO_2 max obtained from the table was corrected for age with sex-specific regression equations derived by Siconolfi et al[108]. The age-corrected estimated VO_2 max value was then compared to norms of VO_2 max relative to age and sex to determine the fitness level for each subject.[52]

The original Astrand-Ryhming submaximal cycle ergometer test was designed to estimate VO_2 max based on the steady-state heart rate of a person exercising at a constant submaximal workload for 6 minutes and was validated on young subjects ages 18-30 years.[7] However, the modified Astrand-Ryhming cycle ergometer test was selected as a submaximal measure of VO_2 max because the procedure has been validated on men and women 20 to 70 years of age and it only requires subjects to reach 70% of their age-predicted maximum heart rate value.[108]

Concurrent validity of the test was established by comparing the estimated VO_2 max score using the regression equations to the VO_2 max score measured directly using a pneumotachograph and gas analyzers during a maximal cycle ergometer test.[108] No significant difference was found between the measured and estimated VO_2 max and they were highly correlated to each other ($r = .94$). The standard error in predicting the directly measured VO_2 max was ± .248 L/min.

3.4.2.3 Quadriceps Fatigue Test

To perform the quadriceps fatigue test, subjects were seated on the dynamometer with the dynamometer position settings identical to those used during the burst superimposition maximum isometric quadriceps torque test. Before initiating the quadriceps fatigue test in the second session, the quadriceps was potentiated in the same manner as the first session as described earlier. Because the SES isometric torque output determined by the burst superimposition test is the best estimate of peak isometric quadriceps torque output, it was used to establish the target torque level that was displayed on the computer monitor during the quadriceps fatigue test. The torque target value was equal to 50% of the SES isometric torque output. During the fatigue test, subjects performed repeated submaximal contractions equal to 50% of their SES isometric torque output for 6 seconds followed by a 4-second rest period (duty cycle 60%). The contractions were continued until the subject could no longer generate that torque target for 3 successive contractions (i.e., exhaustion). During the sixth contraction and every minute thereafter, subjects were instructed to push with a maximum effort and the train of electrical stimuli (amplitude = 100 volts, pulse duration=0.6 msec, pulse interval=10 msec, train duration=100 msec) was superimposed upon the maximal effort quadriceps contraction (Figure 2)

Standardized instructions were provided during the testing procedure (i.e. start pushing, stop pushing) to avoid undue influence of the tester on the individual's effort. Individuals were free to stop the test at any point. Blood pressure and heart rate were monitored every three minutes during the test. The quadriceps fatigue test was terminated if systolic blood pressure exceeded 170 mm Hg, or if diastolic blood pressure exceeded 110 mm Hg or if heart rate exceeded 85% of age predicted maximum heart rate. The MVIC and SES torques were recorded

(Appendix H). Quadriceps fatigue was measured as the rate of decline of the MVIC torque output over the course of the test. Good test-retest reliability for the quadriceps fatigue test was determined in healthy individuals (ICC = 0.89, 95% CI = 0.75 to 0.95). The SEM value for the test was 0.77 percent of the maximum electrically elicited isometric force output per minute. The minimum detectable change (MDC) based on the SEM for repeated measurements was 2.13 percent of the maximum electrically elicited isometric force output per minute.

3.5 Data Analysis

The Statistical Package for the Social Sciences (SPSS for Windows, version 11.01, Chicago, IL) was used to calculate descriptive statistics for the sample and to perform the inferential statistical analyses used in this study.

Descriptive statistics, including frequency counts for categorical variables and measures of central tendency and dispersion for continuous variables were first calculated to summarize the data. Means, standard deviations, and ranges were used to describe the total score on GFI and the score on the five dimensions of fatigue: degree, severity, distress, impact on activities of daily living, and timing. To measure quadriceps fatigue, simple linear regression was performed to determine the rates of decline (i.e. the slope parameters) for the MVIC, and SES torque outputs. To determine the mechanisms of quadriceps fatigue, paired samples t-tests were performed to detect difference among the rates of decline in MVIC and SES torques. If the rates of decline were not statistically different, then we concluded that fatigue was peripheral. In contrast, if the rates of decline were statistically different (i.e., the MVIC torque declined quicker than the SES torque) then we concluded that fatigue was central. Pearson correlation coefficients were calculated to describe the relationships between age, sex, pain, depression,

anxiety, quadriceps fatigue, cardiorespiratory endurance, and fatigue. Statistical significance for all tests was set at $p < 0.05$. All data were screened to ensure they met the assumptions for the inferential statistical analyses described below.

3.5.1 Research Question 1

What is the magnitude and dimensions of self-reported fatigue in individuals with knee OA compared to healthy control subjects and individuals with rheumatoid arthritis?

3.5.1.1 Hypothesis 1

It was hypothesized that individuals with knee OA would report significantly higher fatigue scores than those individuals who do not have knee OA and similar levels of fatigue as individuals with rheumatoid arthritis.

3.5.1.2 Analysis Hypothesis 1

These hypotheses were tested with independent samples t-test. The magnitude and dimensions of self-reported fatigue in this study were compared to those of controls and patients with RA obtained from a previous study that used the same fatigue scale (i.e., MAF) that was used in this study to measure fatigue.[12]

3.5.2 Research Question 2

What is the influence of the quadriceps fatigue on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety?

3.5.2.1 Hypothesis 2

It was hypothesized that when controlling for age, sex, pain, depression, and anxiety, individuals who have less quadriceps fatigue would report significantly lower fatigue scores than individuals who have more quadriceps fatigue. In other words, quadriceps fatigue is a significant predictor of self-reported fatigue after controlling for age, sex, pain, depression, and anxiety.

3.5.2.2 Analysis Hypothesis 2

To examine this hypothesis, a hierarchical multiple regression analysis was performed to determine the influence of quadriceps fatigue on the subject's perception of fatigue in individuals with knee OA. The dependent variable for this analysis was the GFI total score. In this analysis, the variables that were hypothesized to influence fatigue including age, sex, pain, depression, and anxiety were accounted for first. This was accomplished by first entering these variables into the model in one block followed by quadriceps fatigue in the second block to determine how much additional variance (R^2) in GFI was accounted for by quadriceps fatigue after controlling for age, sex, pain, depression, and anxiety.

3.5.3 Research Question 3

What is the influence of the cardiorespiratory endurance on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety?

3.5.3.1 Hypothesis 3

It was hypothesized that when controlling for age, sex, pain, depression, and anxiety, individuals who have better cardiorespiratory endurance would report significantly lower fatigue scores than individuals who have poor cardiorespiratory endurance. In other words, cardiorespiratory endurance is a significant predictor of self-reported fatigue after controlling for age, sex, pain, depression, and anxiety.

3.5.3.2 Hypothesis Analysis 3

To examine this hypothesis, a hierarchical multiple regression analysis was performed to determine the influence of cardiorespiratory endurance on the subject's perception of fatigue in individuals with knee OA. The dependent variable for this analysis was the GFI total score. In this analysis, the variables that were hypothesized to influence fatigue including age, sex, pain, depression, and anxiety were accounted for first. This was accomplished by first entering these variables into the model in one block followed by cardiorespiratory endurance in the second block to determine how much additional variance (R^2) in GFI was accounted for by cardiorespiratory endurance after controlling for age, sex, pain, depression, and anxiety.

3.5.4 Sample Size Estimation

The general multiple regression option in SamplePower, Release 1.20 (SPSS Inc., Chicago, IL) was used to estimate the sample size needed to achieve statistical power of at least 80%. Refer to Table 2 for parameters used to estimate this study sample size. Based on the proposed analytical design to study age, sex, pain, depression, anxiety, cardiorespiratory endurance, and quadriceps fatigue variables as determinants of fatigue, the following

calculations were used to estimate the necessary sample size. The six covariates used in this multiple regression analysis were age, sex, pain, depression, and anxiety. In a previous study that investigated fatigue in RA patients, sex, pain, depression, and anxiety accounted for 49% of the variability in fatigue.[64] A 10% increase in explained variability with the addition of either quadriceps fatigue or cardiorespiratory endurance was believed to be a clinically meaningful increase in explained variability of self-reported fatigue. Given these assumptions, at least 40 subjects were necessary to obtain 80% power for this study.

4 RESULTS

4.1 Introduction

This chapter presents the results of a study of fatigue in 44 older adults with knee OA. The outline for this chapter includes a description of the: 1) demographic characteristics of the sample; 2) magnitude of fatigue; 3) factors associated with fatigue; 4) relationships of age, sex, pain, depression, anxiety, quadriceps fatigue, and cardiorespiratory endurance with self-reported fatigue; and 5) the results of the hypothesis tests described above.

4.2 Demographic Characteristics

Demographic characteristics of the sample are presented in Table 1. The mean age of the sample was 65 years (SD=8.9, range 50-86). There were 33 females (75%) and 11 males (25%). Slightly less than half of the sample (43.2%) had the symptoms of knee OA for 5 to 10 years. Over half of the sample (68.2%) was married and 18.2% was widowed. The educational level of the sample was high. All subjects had completed high school and 19 (43%) completed college. Twenty-five percent of the sample had post-graduate degree. Less than half of the sample (38.6%) was retired, 29.5% were working full time regular duty, and only few (6.8%) were unable to work or were retired due to health status. Almost half (47.7%) of the sample was involved in a walking program and performing muscle stretching to help lessen their pain and stiffness from knee OA.

4.3 Magnitude of Fatigue

The magnitude of fatigue in this sample of individuals with knee OA is described in Table 3. In this sample, 41 (93.2%) respondents reported some degree of fatigue during the week before participation in this study. The mean score on the GFI was 23.6 (SD = 10.4, range 1-40). Respondents reported a mean score of 5.3 ± 2.1 for the degree of fatigue, 4.6 ± 2.1 for the fatigue severity, and 4.1 ± 2.7 for the distress from fatigue. For 25% of the sample, fatigue occurred every day. More than half of the sample (59.1%) reported fatigue was unchanged during the course of a week, and most often fatigue affected walking (mean = 4.7, SD = 2.7), doing household chores (mean = 4.3, SD = 2.5), shopping (mean = 4.3, SD = 2.7), and exercise (mean =3.8, SD =2.4). Sex differences in reported fatigue were examined and are presented in (Table 4). Women reported significantly higher fatigue scores in all dimensions than men ($p < 0.05$).

4.4 Description of Factors Associated with Fatigue

Means, standard deviations, and observed ranges of the variables associated with self-reported fatigue are shown in Table 5 . With respect to the depressive symptoms, the mean score for the CES-D was 10.5 (SD = 8.4, range 0-39). Ten (23%) of the respondents scored 16 or above on CES-D indicating that they were possibly depressed as defined by Radloff in 1977.[99]

During the quadriceps fatigue test, both the MVIC and SES torques gradually declined relative to their initial values (Figure 3) Simple linear regression was used to calculate the rate of decline (i.e., the slope parameters) for the MVIC and SES torques for each subject. The mean rate of decline in MVIC torque, which is a measurement of quadriceps fatigue, was 7.1 %/min

(SD = 5.1, range 0.98 – 21.9). The mean rate of decline in SES torque was 5.5 %/min (SD = 3.7, range 0.67 – 17.50). The mean endurance time (i.e., exhaustion) for the quadriceps fatigue test was 7.39 ± 4.74 min (range, 2 to 23 min). To determine the mechanisms of quadriceps fatigue, a paired samples t-test was performed to detect differences among the rates of decline in MVIC and SES torques at each subject's endurance time (Figure 4). The rates of decline were statistically different (p <.001). Therefore, it was concluded that fatigue was central in nature.

Because the time to fatigue was different as shown in (Figure 5), the rates of decline in torques were compared at 2, 5, and 7 minutes of the fatigue task. The rates of decline in torques were compared at 2 minutes of the fatigue task because all the subjects were able to perform the test for at least 2 minutes, thus all subjects were included in this analysis. The rate of decline in torques were also compared at 5 minutes of the fatigue task, which corresponded to the mode of time to fatigue and at 7 minutes of the fatigue task, which corresponded to the mean time to fatigue. Significant differences were found between the rates of decline in torques when the calculations were based on 2, 5, or 7 minutes of the fatigue task (p <.05). Means and standard deviations of the rates of decline in torques at 2, 5, and 7 minutes of the fatigue task are presented in Table 6. Thus, it was concluded that time to fatigue did not affect the conclusion that fatigue was central in nature.

4.5 Relationships among Variables

The direction, strength, and statistical significance of the bivariate correlations between fatigue and the independent variables of interest are listed in Table 7. Fatigue was not significantly correlated with age (r = -.04, p = .81). Sex was positively and significantly

correlated with self-reported fatigue (r = .52, p <.001). Women had higher levels of fatigue than men. Fatigue was positively and significantly associated with pain (r = .62, p < .001), depression (r = .47, p < .05), and anxiety (r = .54, p < .05), indicating that high levels of pain, depression, and anxiety were associated with greater fatigue. Additionally, fatigue was negatively and significantly associated with cardiorespiratory endurance (r = -.55, p <.001), indicating that poor cardiorespiratory endurance was associated with greater fatigue. However, fatigue was weakly and not significantly associated with quadriceps fatigue (r = .01, p = .71).

4.6 Hypothesis Testing

Hypothesis 1 stated that individuals with knee OA would report significantly higher fatigue scores than those individuals who do not have knee OA and similar levels of fatigue as individuals with rheumatoid arthritis. These hypotheses were tested with independent samples t-tests. The magnitude and dimensions of self-reported fatigue in this study were compared to those of controls and patients with RA obtained from a previous study that used the same fatigue scale (i.e., MAF) used in this study to measure fatigue.[12] The control group included 46 individuals (91% females) with a mean age of 42 years who had not been diagnosed with rheumatic disease. The RA group included 51 patients (85% females) with a mean age of 43 years who had been diagnosed by their physician with RA. Individuals with knee OA reported significantly higher fatigue than controls (Table 8) and significantly lower fatigue than RA patients (Table 9). (p < 0.05).

Hypothesis 2 stated that when controlling for age, sex, pain, depression, and anxiety, individuals who have less quadriceps fatigue would report significantly less fatigue compared to individuals who have more quadriceps fatigue. A two-step hierarchical regression analysis was used to test this hypothesis. The dependent variable for the model was the GFI. The GFI is a composite score of the five dimensions of fatigue; degree, severity, distress, impact, and timing. Six independent variables were grouped into two sets. Table 10 show the results of the hierarchical regression analysis to determine the influence of quadriceps fatigue on self-reported fatigue after controlling for age, sex, pain, depression, and anxiety. The first set of variables entered into the model included age, sex, pain, depression, and anxiety. The first step accounted for 55% of the variance of self-reported fatigue ($F = 9.12$, $p < .001$). In the second step, quadriceps fatigue was entered into the model. Addition of the quadriceps fatigue did not provide any additional explanation of the variability in fatigue. Therefore, this hypothesis was not supported. In other words, after controlling for age, sex, pain, depression, and anxiety, quadriceps fatigue did not have any influence on self-reported fatigue. The standardized beta coefficients for the final model including quadriceps fatigue are reported in Table 11. The strongest individual predictors of fatigue were sex and depression.

Hypothesis 3 stated that when controlling for age, sex, pain, depression, and anxiety, individuals who have better cardiorespiratory endurance would report significantly lower fatigue scores than individuals who have poorer cardiorespiratory endurance. A two-step hierarchical regression analysis was used to test this hypothesis. The dependent variable for the model was the GFI. Six independent variables were grouped into two sets. Table 12 shows the results of the hierarchical regression analyses to determine the influence of cardiorespiratory endurance on

self-reported fatigue after controlling for age, sex, pain, depression, and anxiety. The first set of variables entered into the model were age, sex, pain, depression, and anxiety, which accounted for 61% of the variance in self-reported fatigue ($F = 11.75$, $p < .001$). In the second step cardiorespiratory endurance was entered into the model, which did not explain any additional variation in self-reported fatigue. Therefore, this hypothesis was not supported. In other words, after controlling for age, sex, pain, depression, and anxiety, the addition of cardiorespiratory endurance did not have any influence on self-reported fatigue. The standardized beta coefficients for the final model including cardiorespiratory endurance are reported in Table 13. The strongest individual predictors of fatigue were sex and depression.

A stepwise regression analysis was performed to determine the "best" regression model for prediction of fatigue. The standardized beta coefficients and the statistical significance of each variable in the "best" model for prediction fatigue are reported in Table 14. Pain, sex, and depression constituted the "best" model for prediction fatigue and accounted for 53% of variance in fatigue.

4.7 Testing Assumptions of the Statistical Model

Tests were conducted to check for violations of the statistical assumptions. Residual scatterplots were reviewed for outliers, homogeneity of variance, and linearity. The correlation matrix was examined for multicolinearity.

Residual scatterplots showed no outliers, which are any data points greater than three standard deviations from the mean of the residuals.[71] In reviewing the residual scatterplots, a check for homogeneity of variance revealed constant variability over the range of dependent values. No heteroscedasticity was noted.

Another assumption tested was that of linearity. Residual scatterplots as a function of predicted value were examined for linearity and no evidence of curvilinear relationships was found. Multicolinearity occurs when there are high intercorrelations among the independent variables.[71] A correlation matrix of independent variables was generated as shown in Table 7. Correlations between variables ranged from .05 to .56 (ignoring directions). Based on the magnitudes of these relationships it appears that multicolinearity was not a problem in this data set. Based on these analyses, it appears that the assumptions of homogeneity of variance, linearity, and independence were met.

5 DISCUSSION

5.1 Introduction

This chapter includes an interpretation of study's primary findings and a discussion of their significance. There is also a discussion of the implications of the study for physical therapy, and recommendations for further research.

The purposes of this study were threefold; 1) to describe the magnitude and dimensions of self-reported fatigue in individuals with knee OA, 2) to determine the influence the quadriceps fatigue on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety and 3) to determine the influence of the cardiorespiratory endurance on self-reported fatigue in individuals with knee OA, while accounting for potential confounders such as age, sex, pain, depression, and anxiety.

5.1.1 Interpretation and Significance of Findings

The sample consisted of 44 older adults (75% females) with a mean age of 65 years who had radiographically confirmed knee OA. The presence of fatigue was a significant problem in this study sample. Fatigue occurred every day, was consistently present during the course of the week, and affected activities of daily living.

Bivariate correlations revealed that fatigue was significantly associated with sex (greater fatigue in females), pain, depression, and anxiety. These factors that were associated with self-reported fatigue in individuals with knee OA were also found to be associated with fatigue in individuals with a spectrum of rheumatic disesases.[12,13,25,34,64,74,75,89,93,101,114,115,118,123]

5.1.1.1 Magnitude of Self-Reported Fatigue

Since no prior reports offer comparable detail on fatigue in OA, no direct comparison can be made. However, the observation of fatigue in individuals with knee OA was compared to previous studies that addressed fatigue in RA patients and controls (no rheumatic disease) using the same fatigue scale.[12] This comparison was based on the fact that both OA and RA are common joint diseases that have similar clinical manifestations such as pain, stiffness, and functional limitations. Individuals with knee OA in this study reported significantly lower fatigue than RA patients but significantly higher fatigue than controls. However these results must be interpreted carefully due to differences in the mean age between the studies. The mean age of the knee OA group was 65 years, whereas the mean age of the RA group was 43 years and the mean age of the controls group was 42 years. This may raise a question regarding the effect of age on fatigue. Evidence showed that fatigue was not related to age in individuals with RA[13,64] nor in individuals without rheumatic diseases.[81] Consistent with the findings of other investigators[13,64,81], we found that age was not related to fatigue ($r = -.04$, $p = .81$).

5.1.1.2 Magnitude and Mechanisms of Quadriceps Fatigue

To our knowledge, this quadriceps fatigue protocol has not been used to measure fatigue in individuals with knee OA prior to this study. Therefore, it was not possible to compare the degree of quadriceps fatigue in this sample to comparable population. However, this technique was used to investigate quadriceps fatigue in 9 individuals (mean age 29 years) diagnosed with FM.[90] In contrast to our findings, the mean rate of decline in MVIC torque in individuals with FM was found to be 1.7 %/ min, while the mean rate of decline in MVIC torque in individuals with knee OA was found in this study to be 7.1 %/min. This difference could be attributed to the

fact that fatigue exercise was performed at 30% of MVIC by young people with FM, while in the present study it was performed at 50% of MVIC on elderly people with knee OA.

The significant difference between the rates of decline in MVIC and SES torques during quadriceps fatigue test in this study led to the conclusion that fatigue was central in nature. In contrast to our results, quadriceps fatigue in patients with FM was observed to be peripheral. This may be explained by the fact that OA is a joint disease whereas FM is a muscular disease. In the present study, quadriceps fatigue was central which may lead to the expectation that depression and anxiety would have contributed to the lack of motivation. Data in this study did not support this conjecture.

5.1.1.3 Influence of Quadriceps fatigue on Self-Reported Fatigue

Self-reported fatigue was not significantly associated with quadriceps fatigue. An attempt was made in this study to determine the influence of quadriceps fatigue on self-reported fatigue after controlling for age, sex, pain, depression, and anxiety. This was accomplished by performing a hierarchical regression analysis. The results revealed that quadriceps fatigue had no influence on self-reported fatigue above and beyond demographic, physiological, and psychosocial variables. This can be explained by the lack of a bivariate association between quadriceps fatigue and self-reported fatigue. As a result of this, the functional significance of quadriceps fatigue in knee OA must be questioned.

The lack of association between quadriceps fatigue and self-reported fatigue may be due to differences in the method of measurement between the two variables. Self-reported fatigue was reported by the patient as his/her perception of general fatigue, while quadriceps fatigue was a performance-based measure of local muscular fatigue. Several investigators have

demonstrated that self-reported and performance-based measures of the same phenomenon are at most moderately related to each other indicating that they may measure different aspects of the same construct.[33,43,100,103,104] In this study, self-reported fatigue reflected the individual's perception of fatigue that may encompasses the whole body, whereas the quadriceps fatigue test examined the quadriceps muscle's ability to sustain the required level of muscle force during an repeated isometric contractions of the quadriceps. The lack of association between the two measures indicated that they measured different unrelated aspects of fatigue that we hypothesized would be related. Our observations did no support this hypothesis. Because quadriceps fatigue may limit the distance a person can ambulate, we evaluated the relationship between the single item on the MAF that queried the subject on the impact of fatigue on walking and the results of the quadriceps fatigue test. If quadriceps fatigue is related to self-reported fatigue in any manner, we would expect that there would be a relationship between quadriceps fatigue and the item that was most directly related to function of the quadriceps muscle (i.e. impact of fatigue on walking). The bivariate correlation between quadriceps fatigue and the subject's self-report of the impact of fatigue on walking was .08 (p=.61). Thus quadriceps fatigue does not appear to be in any way related to self-reported fatigue by subjects with knee OA.

5.1.1.4 Functional Significance of Quadriceps fatigue

Given the lack relationship between quadriceps fatigue and self-reported fatigue and the lack of any significant associations between quadriceps fatigue and any of the other variables as shown in Table 7 , we must question the functional significance of quadriceps fatigue in subjects with knee OA. Quadriceps fatigue, when measured as the ability to maintain a maximal

isometric contraction for 90 seconds, has been found to be related to the time required to walk 50 ft, but not to the degree of dependence, difficulty, or pain experienced during a variety of daily activities.[48] The failure to demonstrate the functional significance of quadriceps fatigue, measured as the ability to maintain a maximal isometric contraction for 90 seconds, was thought to be due to the fact that most daily activities do not require a single maximal isometric contraction of the quadriceps and the demands of normal daily functional activities on muscles are more closely reproduced by repetitive, submaximal exercise. In our preliminary work, we developed a fatigue test that consisted of repeated submaximal quadriceps contractions at 50% of maximal effort (unpublished data). Quadriceps fatigue was operationally defined as the number of contractions an individual could perform before he or she was no longer able to generate 50% of the MVIC quadriceps torque. Using that procedure to measure quadriceps fatigue, we were unable to demonstrate a relationship between quadriceps fatigue and concurrent self-reported or performance-based measures of physical function. Concurrent self-reported measures of physical function included the WOMAC physical function and total scores, the ADLS scale of the Knee Outcome Survey, and the physical components summary scores of the SF-36 and the performance-based measure of physical function consisted of the "get-up and go" test.

To further the investigation of the effect of knee OA on quadriceps fatigue, in this study we defined quadriceps fatigue as a progressive decline of the maximum voluntary contraction over the course of time. Based on this definition, quadriceps fatigue in this study was found to be negatively related to quadriceps muscle strength normalized to body mass index (BMI) ($r = -.35$, $p = .02$), but not to the degree of difficulty ($r = -.02$, $p = .93$), or pain ($r = -.05$, $p = .74$) experienced during activities of daily living as measured by WOMAC physical function and pain subscales respectively. In contrast, quadriceps muscle strength normalized to

BMI was negatively related to the degree of difficulty (r = -.39, p = .009), and pain (r = -.42, p = .005) experienced during activities of daily living, indicating that individuals with a strong quadriceps muscle relative to body mass index had less difficulty and pain during daily activities but had greater quadriceps fatigue. This relationship between muscle strength and endurance can be explained by the age-related morphological adaptation of the human muscle. Evidence indicates that with aging, human muscle tends to have a greater proportion of type I fibers (fatigue-resistance) than type II fibers (fatigable).[26,37,38,70] This fiber-type shift may explain the inverse relationship between muscle strength and endurance in the elderly.

The consistent findings of the studies that we have performed over the last four years to investigate the effects of knee OA on quadriceps fatigue implies that quadriceps fatigue, as we operationally defined and measured it, does not influence the function of individuals with knee OA. Given this, the value of continued investigation of the effect of knee OA on quadriceps fatigue is limited.

5.1.1.5 Magnitude of Cardiorespiratory Endurance

Our results confirm previous findings that people with knee OA have impaired aerobic capacity. Previous studies have shown that individuals with knee OA are markedly deconditioned compared to healthy, age-and sex-matched peers.[9,96] Beals et al[9] reported significant differences in VO_2 max mean between subjects with knee OA and sedentary age-and sex-matched controls. The mean VO_2 max was 17.8 ± 2.3 and 20.5 ± 2.1 ml/kg/min for knee OA and controls groups respectively (p <.05). In a recent study by Philbin et al[96] it was reported that patients with knee OA had significantly lower VO_2 max mean scores compared to age-and sex-matched controls (12.8 ± 3.7 versus 17.6 ± 5.2 ml/kg/min, p <0.0005). In our study, VO_2 max

in individuals with knee OA was 16.5 ± 5.6 ml/kg/min. The values of VO_2 max obtained in the three above studies were all lower than the published norms of VO_2 max relative to age and sex, indicating lower fitness level for persons with knee OA.[52]

5.1.1.6 Influence of Cardiorespiratory Endurance on Self-Reported Fatigue

Results in this study demonstrated that fatigue was negatively related to cardiorespiratory endurance (r = -.55, p <.001), indicating that poor cardiorespiratory endurance was associated with greater self-reported fatigue. However, hierarchical regression analysis revealed that adding cardiorespiratory endurance to the model after controlling for age, sex, pain, depression, and anxiety did not explain any additional variance in fatigue. Although cardiorespiratory endurance is related to self-reported fatigue, it did not appear to influence fatigue after controlling for demographic, physiological, and psychosocial variables. This is due to the fact that cardiorespiratory endurance was found to be related to sex (r = -.60, p <.001) (poorer cardiorespiratory endurance in females), pain (r = -.54, p<.001), depression (r = -.34, p =.03), and anxiety (r = -.35, p =.02). These relationships precluded cardiorespiratory endurance from providing any additional contribution to the prediction of fatigue after those variables were added to the model.

5.1.1.7 Functional Significance of Cardiorespiratory Endurance

The functional significance of cardiorespiratory endurance was evident by its relationship with quadriceps muscle strength, physical function, and pain. Cardiorespiratory endurance was found to be positively related to quadriceps muscle strength normalized to BMI (r = .66, p <.001), and negatively related to the degree of difficulty (r = -.35, p = .02), and pain (r = -.54, p <

.001) experienced during activities of daily living. These relationships and the relationships between cardiorespiratory endurance, self-reported fatigue, depression, and anxiety seem to fit into the theoretical model put forward by Dekker et al[36] to explain the role of muscle weakness in mediating the relationship between psychosocial variables and pain and disability experienced by individuals with osteoarthritis. It is hypothesized that patients with knee OA tend to avoid physical activity because increased levels of physical activity are associated with pain. This in turn contributes to progressive muscle weakness and disability. As a result, patients may feel frustrated and hopeless by this vicious cycle and be at risk of developing psychological distress. Depression and anxiety may serve to amplify this loop by increasing the degree of avoidance. Prolonged depression and anxiety may, by resulting in persistent attempts to avoid knee pain, lead to further muscle wasting, cardiovascular deconditioning and a sensation of generalized fatigue during normal activities of daily living. Our data fully support this hypothesis.

5.1.2 Implications for Physical Therapy

The focus for health care providers in primary care is to minimize the consequences of chronic illness such as OA and maximize individual's capability for independent living.[29] Given this, and the results of this study which demonstrate the magnitude of fatigue, its association to psychosocial variables as well as to cardiorespiratory endurance, primary care health providers should attend to complaints of self-reported fatigue in OA population. Individuals with characteristics similar to those that participated in this study may benefit from strategies to reduce the sensation of fatigue through better management of pain, psychosocial issues, and/or cardiorespiratory endurance.

The findings that self-reported fatigue, pain, and physical function were related to quadriceps strength but not to quadriceps fatigue have implications for physical therapy management of patients with knee OA. In particular, these data indicate that exercises to improve quadriceps function should be focused at increasing strength (i.e. torque production) not endurance (i.e. the ability to sustain torque production). Often physical therapy programs for individuals with knee OA include low to moderate resistance-high repetition exercises for the quadriceps, which are aimed at improving the ability to sustain torque production. Focusing quadriceps exercises on high resistance-low repetition exercises (i.e. exercises with resistance that subjects can perform for 6 to 8 repetitions) may be more advantageous for patients with knee OA. Further research is needed to test this hypothesis.

5.1.3 Recommendations for Further Studies

This study explored fatigue in individuals with knee OA using a one group cross-sectional research design. The results of the study revealed the magnitude and dimensions of fatigue in individuals with knee OA. The level of self-reported fatigue that we observed in individuals with knee OA appears to be greater than the fatigue observed in normal healthy individuals, although the control group used for this comparison was younger. Therefore, future research is warranted to explore fatigue using a case-control design research. Future research is also warranted to test the hypothesized role of psychosocial variables in modifying the relationship between quadriceps strength and/or cardiorespiratory endurance with pain and physical function.

Data from this study indicated that the primary muscle dysfunction in individuals with knee OA was a deficit in quadriceps strength and not quadriceps fatigue. Traditionally exercises

to improve quadriceps function in individuals with knee OA have made use of low to moderate resistance-high repetition exercises, which would be expected to primarily address quadriceps fatigue, not deficits in quadriceps strength. Exercises aimed at improving quadriceps strength should make use of relatively high resistance performed for few repetitions. To determine which mode of exercise is most beneficial for individuals with knee OA that have quadriceps weakness, a randomized clinical trial is needed to investigate the effect of high resistance-low repetition exercises versus low to moderate resistance-high repetition exercises for the quadriceps on pain and physical function in individuals with knee OA.

5.1.4 Conclusion

This cross-sectional study was an initial attempt to explore self-reported fatigue in individuals with knee OA. The results of this study demonstrated that fatigue is common in individuals with knee OA. Quadriceps fatigue is not related to fatigue. Cardiorespiratory endurance is related to fatigue, but not after controlling for age, sex, pain, depression, and anxiety.

Table 1. Demographic Characteristics (n=44)

	Mean	SD	Range	Number	%
Age (yrs)	65.32	8.9	50-86		
Sex					
Female				33	75
Male				11	25
Marital Status:					
Single				1	2.3
Married				30	68.2
Divorced/Separated				5	11.4
Widowed				8	18.2
Education:					
Less than high school				0	0
High School graduate				13	29.5
Some college				12	27.3
College graduate				7	15.9
Some post-graduate education				1	2.3
Post-graduate degree				11	25.0
Employment:					
Full time regular duty				13	29.5
Part time regular duty				4	9.1
Light duty or part time modified duty				2	4.5
Unable to work or retired due to health status				3	6.8
Retired				17	38.6
Homemaker				1	2.3
Unemployed				4	9.1
Work type:					
Mostly sedentary				16	36.4
Somewhat sedentary with substantial walking required				3	6.8
Moderately active, walking, some lifting and carrying				22	50.0
Demanding physical activity, heavy lifting and carrying				3	6.8
Years with knee OA:					
Less than 1 year				0	0
1-2 years				1	2.3
3-5 years				12	27.3
5-10 years				19	43.2
More than 10 years				12	27.3
Current Exercise:					
Walking				21	47.7
Jogging				2	4.5
Stretching				21	47.7
Step Machine				12	27.3
Weights				11	25
Aerobic exercise				4	9.1
Water exercise				13	29.5

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Table 2. Parameters for Multiple Regression Power Analysis

Assumptions	
Alpha	0.05
Power	0.80
Covariates	
Number of variables	5
R^2	0.49
Main set	
Number of variables	1
Increment to R^2	0.10
Total Model	
Number of variables	6
R^2	0.59
Outcome	
Sample size	40

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Table 3. Means and Standard Deviations of Fatigue Scores

Descriptor	Mean	SD	Observed Range
GFI[a]	23.6	10.4	1-40[b]
Degree	5.3	2.1	1-10[c]
Severity	4.6	2.5	1-9[c]
Distress	4.1	2.7	1-10[c]
Impact	3.3	1.7	1-8.5[c]
Timing	6.3	3.0	1-10[c]

[a] GFI = Global Fatigue Index
[b] Possible range of scores 1 (no fatigue) to 50 (extreme fatigue)
[c] Possible range of scores 1 (not at all) to 10 (great deal)

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Table 4. Means and Standard Deviations (SD) of Males and Females Fatigue Scores

	Males (n=11)	Females (n= 33)		
Descriptor	**Mean (SD)**	**Mean (SD)**	**t**	***p* value***
GFI	14.3 (10.3)	26.7 (8.5)	-3.59	<.01
Degree	3.8 (2.4)	5.8 (1.7)	-2.52	<.05
Severity	2.6 (2.3)	5.2 (2.2)	-3.21	<.01
Distress	1.6 (1.5)	4.9 (2.6)	-4.95	<.001
Impact	2.2 (1.8)	3.7 (1.5)	-2.66	<.05
Timing	4.1 (3.4)	7.0 (2.5)	-2.64	<.05

* Significance tested with independent samples t-test

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Table 5. Means and Standard Deviations of Factors Associated with Fatigue

Variables	Mean	SD	Observed Range
Pain	6.7	3.8	0-14[a]
Depression	10.5	8.4	0-39[b]
Anxiety	7.1	6.3	0-28[c]
Cardiorespiratory Endurance[d]	16.5	5.6	9.4-30.9
Quadriceps Fatigue[e]	7.1	5.1	0.98-21.9

Possible range of scores; [a] (0-20), [b] (0-60), [c](0-63)
[d] Measured as maximum oxygen consumption (VO2 max) (ml/kg/min)
[e] Measured as rate of decline of maximum voluntary isometric contraction (MVIC) (%/min)

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Table 6. Means and Standard Deviations of the Rates of Decline in Maximum Voluntary Isometric Contraction (MVIC) and Superimposed Electrical Stimulation (SES) Torques at 2, 5, and 7 Minutes of the Fatigue Task.

	MVIC	SES		
Time (min)	**Mean ± SD**	**Mean ± SD**	**t**	***p* value***
2	11.56 ± 5.3	9.03 ± 3.7	4.79	<.001
5	7.75 ± 4.6	6.2 ± 3.2	4.12	<.001
7	5.87 ± 3.4	4.72 ± 3.2	2.03	<.05

* Significance tested with paired samples t-test

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Table 7. Bivariate Associations among Variables (n=44)

	GFI	Age	Sex	Pain	Depression	Anxiety	CRE[a]	QF[b]
GFI	1	-.04	.52**	.62**	.47**	.54**	-.55**	.01
Age		1	-.06	.24	.07	.10	-.07	.24
Sex			1	.34*	.19	.21	-.60**	.11
Pain				1	.33*	.56**	-.54**	-.05
Depression					1	.54**	-.34*	.18
Anxiety						1	-.35*	.09
CRE[a]							1	-.18
QF[b]								1

* Pearson Product Moment Correlation (p <.05) (2-tailed)
** Pearson Product Moment Correlation (p <.001) (2-tailed)
[a] Cardiorespiratory Endurance
[b] Quadriceps fatigue

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Table 8. Means (SD) of Fatigue Scores for OA Patients and Controls[a]

	OA (n=44)	Controls (n= 46)		
Descriptor	**Mean (SD)**	**Mean (SD)**	**t**	***p* value***
GFI	23.6 (10.4)	16.4 (11.5)	3.11	< 0.01
Degree	5.3 (2.1)	4.2 (2.0)	2.56	< 0.05
Severity	4.6 (2.5)	3.2 (1.9)	3.02	< 0.01
Distress	4.1 (2.7)	3.0 (1.8)	2.29	< 0.05
Impact	3.3 (1.7)	2.6 (1.7)	1.97	< 0.05
Timing	6.3 (3.0)	5.3 (2.3)	1.80	< 0.05

[a] Controls fatigue scores were obtained from a previous study by Belza[12]

* Significance tested with independent samples t-test

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Table 9. Means (SD) of Fatigue Scores for OA and RA Patients[a]

	OA (n=44)	RA (n= 51)		
Descriptor	**Mean (SD)**	**Mean (SD)**	**t**	***p* value***
GFI	23.6 (10.4)	27.8 (10.5)	-1.96	< 0.05
Degree	5.3 (2.1)	6.3 (1.7)	-2.57	< 0.05
Severity	4.6 (2.5)	5.4 (1.8)	-1.81	< 0.05
Distress	4.1 (2.7)	4.9 (1.7)	-1.76	< 0.05
Impact	3.3 (1.7)	4.2 (2.1)	-2.28	< 0.05
Timing	6.3 (3.0)	7.3 (2.1)	-1.91	< 0.05

[a] RA fatigue scores were obtained from a previous study by Belza[12]

* Significance tested with independent samples t-test

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Table 10. Hierarchical Regression Analysis: Influence of QF[a] on GFI[b].

Model	R^2	R^2 Δ	F -Ratio	p Value
Model 1				
(Age+ Sex + Pain+ Depression + Anxiety)	**.55**	**.55**	**9.12**	**< .001**
Model 2				
(Age +Sex + Pain + Depression + Anxiety +QF)	**.55**	**.00**	**.12**	**.732**

[a] QF = Quadriceps Fatigue
[b] GFI = Global Fatigue Index

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Table 11. Standardized Beta Coefficients for the model including QF[a]

Variables	Standardized Beta	t	*p* value
Age	-.183	-1.5	>.05
Sex	.280	2.3	<.05
Pain	.399	2.7	.<.01
Depression	.198	1.5	>.05
Anxiety	.157	1.1	>.05
QF	.042	.35	>.05

[a] Quadriceps Fatigue

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Table 12. Hierarchical Regression Analysis: Influence of CRE[a] on GFI[b].

Model	R^2	R^2 Δ	F -Ratio	p Value
Model 1				
(Age+ Sex + Pain+ Depression + Anxiety)	**.61**	**.61**	**11.75**	**< .001**
Model 2				
(Age +Sex + Pain + Depression + Anxiety +CRE)	**.62**	**.01**	**.18**	**.673**

[a] CRE = Cardiorespiratory Endurance
[b] GFI = Global Fatigue Index

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Table 13. Standardized Beta Coefficients for the model including CER[a]

Variables	Standardized Beta	t	*p* value
Age	-.151	-1.4	>.05
Sex	.298	2.3	<.05
Pain	.367	2.6	<.05
Depression	.182	1.4	>.05
Anxiety	.180	1.3	>.05
CRE	-.062	-.43	>.05

[a] Cardiorespiratory Endurance

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Table 14. Stepwise Regression Analysis to determine the "best" model

	Variables	Standardized Beta	t	*p* value
Step 1	Pain	.42	3.45	<.01
Step 2	Sex	.34	2.88	<.01
Step 3	Depression	.26	2.25	<.05

Overall R^2 = .53

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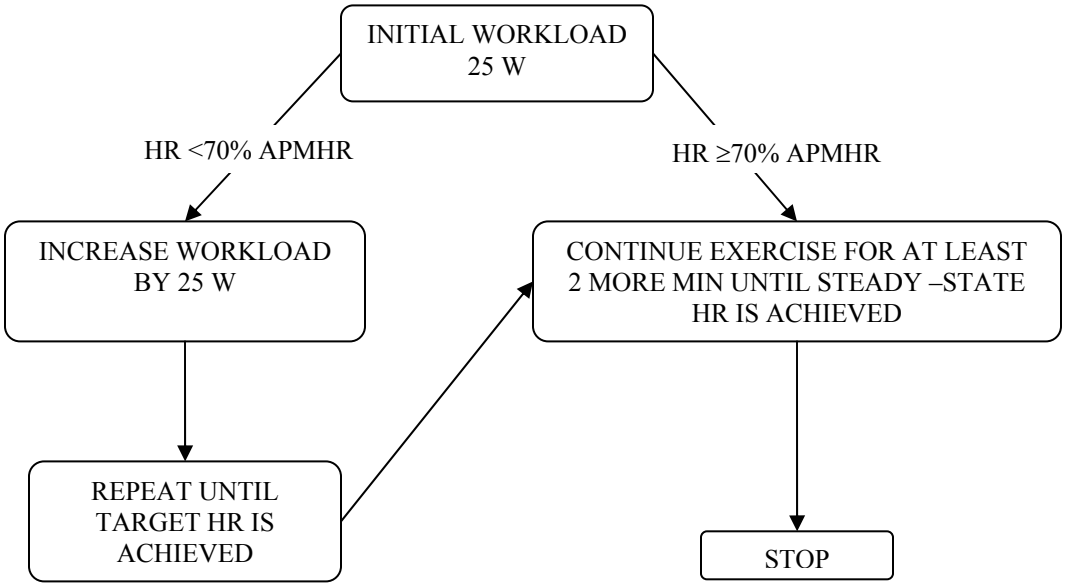

Figure 1. Schematic Illustration of the Cardiorespiratory Endurance Test

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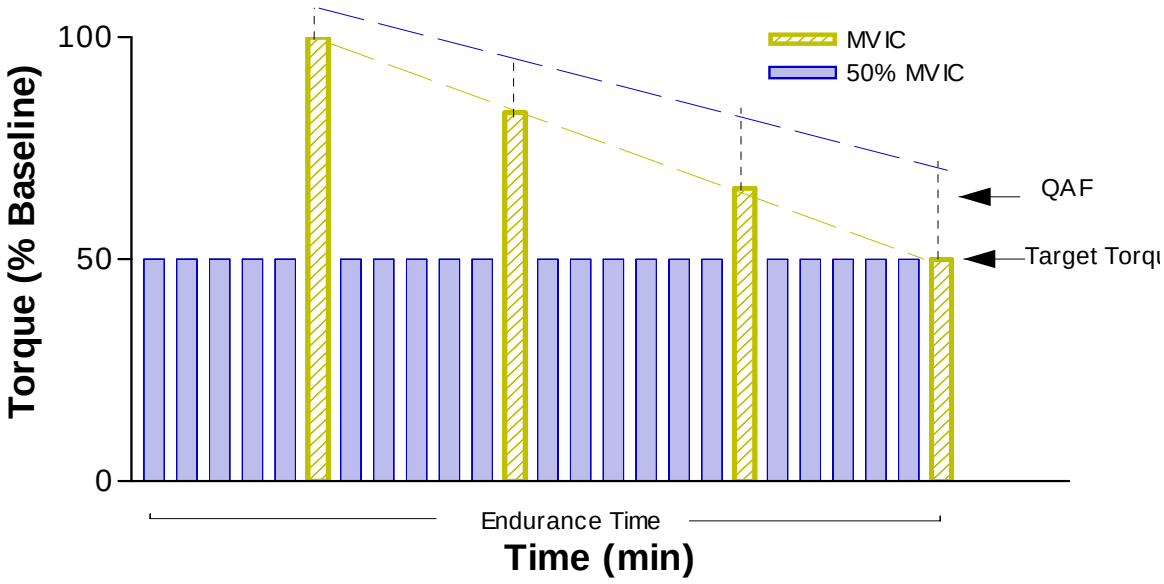

Figure 2. A schematic Illustration of the Quadriceps Fatigue Test.

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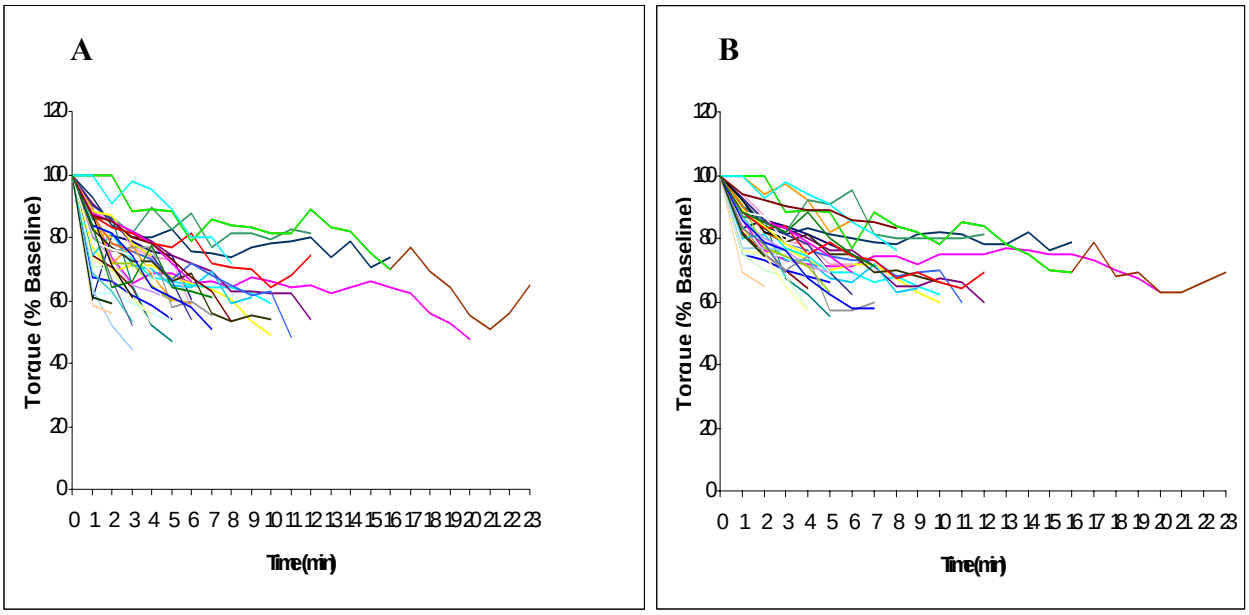

Figure 3. (A) Maximum Voluntary Isometric Contractions (MVIC) and, (B) Superimposed Electrical Stimulation (SES) torques over time during repeated isometric contractions at 50% of SES. Each line represents a plot of the MVIC (A) or SES (B) torques over time for each individual subject.

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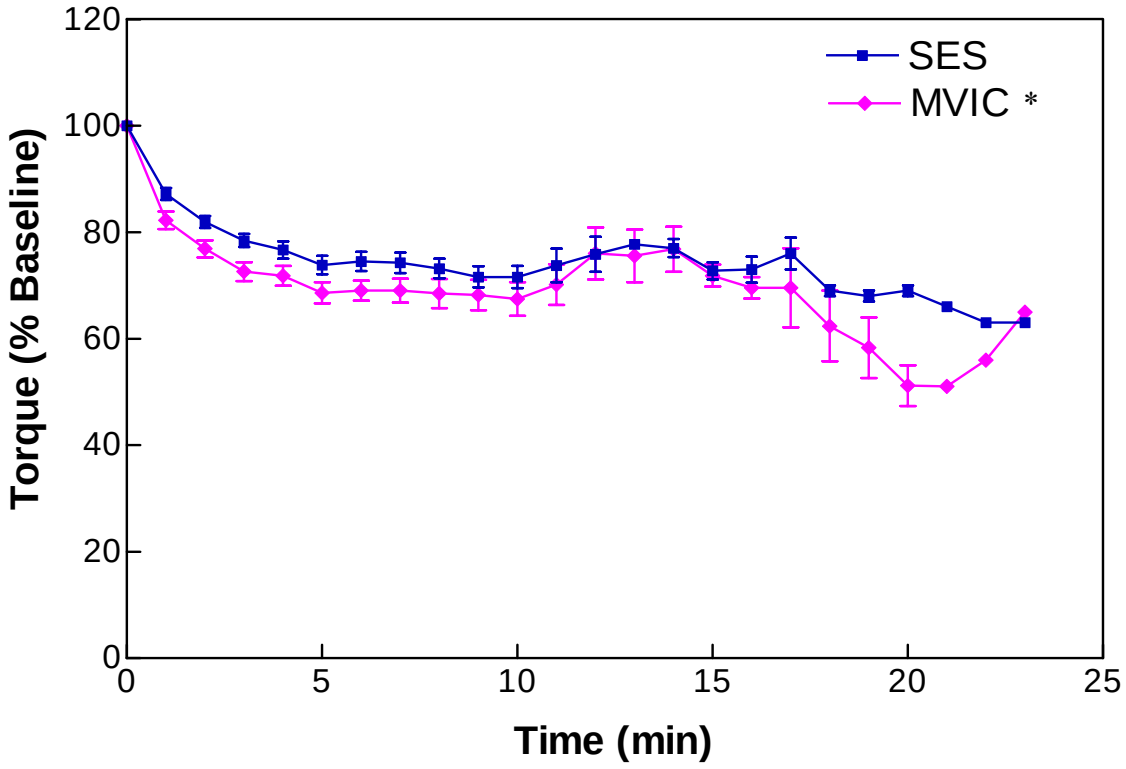

Figure 4. Maximum Voluntary Isometric Contraction (MVIC) and Superimposed Electrical Stimulation torques over time during repeated isometric contractions at 50% of SES. Data represents aggregate data across all 43 subjects at endurance time. Each data point represents mean ± SE of the corresponding torque at one minute intervals**.**

***** Significant difference between rates of decline in torques at each subject's endurance time ($p <$ .001).

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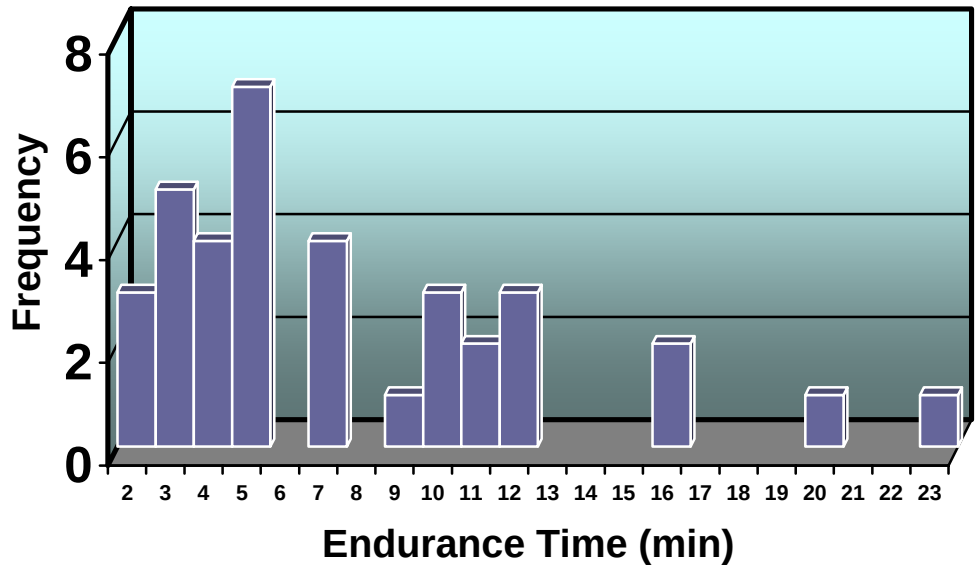

Figure 5. Histogram of time to fatigue during quadriceps fatigue test

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APPENDIX A

LETTER TO POTENTIAL SUBJECTS

Dear Research Participant

We are currently conducting a study in the Department of Physical Therapy at the University of Pittsburgh School of Health and Rehabilitation Sciences. The purpose of this research study is to look at the level of fatigue in individuals with knee osteoarthritis. Specifically, we want to determine if individuals with knee osteoarthritis frequently complain of fatigue and to determine the relationship between fatigue and age, gender, pain, depression, anxiety, aerobic capacity and thigh muscle fatigue. The result of this study will allow us to develop improved exercise programs for the treatment and prevention of arthritis affecting the knee.

Because you have participated in our previous studies and were diagnosed with knee osteoarthritis, we would like to invite you to participate in this new study which is part of a series of studies we are conducting related to knee osteoarthritis.

Participation in this study requires you to attend two testing sessions at University of Pittsburgh Medical Center (UPMC) Center for Sports Medicine ***(see directions on the back)***. The first testing session will last approximately 90 minutes and the second session will last approximately 30 minutes. You will be reimbursed $20 for each session for a total of $40 for your time and travel.

During the first session, you will be asked to complete several questionnaires regarding your current level of fatigue and pain, your mood state including levels of depression and anxiety, levels of nervousness and fear of pain and further injury to your knee. You will undergo a test on a bike in which you will pedal at a moderate level of exertion to measure your fitness and a test to measure the strength of your thigh muscle. During the strength test you will be asked to straighten your knee as hard as possible and a very brief electrical stimulus will be applied to your thigh ensure that you are pushing with maximum effort.

During the second testing session, you will undergo a test to determine the endurance of your thigh muscle. During this test you will repeatedly attempt to straighten your knee with a submaximal effort until you are no longer able to generate 50% of your maximal strength and a very brief electrical stimulus will be applied to your thigh ensure that your thigh muscle have fatigued.

If you are interested to participate or you would like further information concerning this study, you can contact **FAWZI at (412) 383-6712.** We hope that you will consider participating in the study.

Sincerely,

James Irrgang PhD, PT, ATC
Assistant Professor
Department of Physical Therapy
School of Health and Rehabilitation
University of Pittsburgh

Kelley Fitzgerald, PhD, PT, OCS
Assistant Professor
Department of Physical Therapy
School of Health and Rehabilitation
University of Pittsburgh

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APPENDIX B

MEDICAL RELEASE FORM

MEMORANDUM

TO:

FROM: Fawzi Bouzubar MS, PT and James Irrgang, PhD, PT, ATC

DATE:

RE: Patient Participation in a Research Study

CC:

We are conducting a research study that has been approved by the University of Pittsburgh IRB to describe the prevalence of self-reported fatigue in individuals with knee osteoarthritis and to determine the relationships between fatigue and age, gender, pain, negative affect, cardiorespiratory endurance and neuromuscular fatigue of the quadriceps. Your patient, _____ has agreed to volunteer as a subject in this study. Before scheduling your patient for testing, we want to be certain that there are no medical conditions that you believe would prevent your patient from safely participating in the study. The study is described below.

Please return this form by fax at your earliest convenience so that we may schedule test sessions as soon as possible. Our fax number is 412-383-6629. If you have further questions, I can be contacted at 412-383- 6712. Thank you for your assistance with this project.

Please indicate if you believe there are any medical conditions that would prevent your patient from participating in the study.

_____ The above named patient may participate in the study.

_____ The above named patient may not participate in the study for the following reason:

Description of Study:

Your patient will participate in two testing sessions. During the first session, the patient will fill out a series of questionnaires related to fatigue, pain and negative affect. Then he/she will undergo a **quadriceps femoris strength test in which a brief electrical stimulus** will be superimposed on the patient's voluntary maximum isometric contraction of the quadriceps muscle. This procedure will allow us to determine the maximal voluntary contraction torque output that will be used in the quadriceps fatigue test during the second session. Finally in the first testing session, the patient will perform a **submaximal cycle ergometer test to estimate**

VO_2 max as a measure of cardiorespiratory endurance. The submaximal exercise test will be terminated if systolic blood pressure fails to increase with increased exercise intensity or if systolic blood pressure exceeds 170 mm Hg or diastolic blood pressure exceeds 110 mm Hg or if the heart rate exceeds 85% of the subject's age-predicted maximum value. This test will take approximately 5 to 10 minutes to complete.

The second session will be scheduled within one week after completing the first testing session. During the second session, the patient will perform a **quadriceps fatigue test**, in which the patient will perform submaximal isometric contractions of the quadriceps at 50% of his/her maximum voluntary isometric torque for 6 seconds followed by a 4-second rest period. The contractions will be continued for a minimum of 5 minutes. The test will be stopped after 5 minutes if the subject can no longer generate torque output equal to 50% of the maximum isometric torque output, otherwise the subject will continue the contractions until he/she can longer generate the target torque for successive contractions. During the sixth contraction and every minute thereafter, subjects will be instructed to push with a maximum effort and a burst of electrical stimulation will be superimposed upon the maximal effort of quadriceps contraction. The quadriceps fatigue test will be terminated if systolic blood pressure exceeds 170 mm Hg, if diastolic blood pressure exceeds 110 mm Hg or if heart rate exceeds 85% of the age predicted maximum value.

_____ Date:_____

(Physician's Signature)

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APPENDIX C

INCLUSION/EXCLUSION CRITERIA FORM

Subject ID:_____

Inclusion Criteria:

	Yes	No
Age 45 or older?	☐	☐
Diagnosed with Knee OA?	☐	☐
If yes, please complete the following:		
▪ Meets 1986 ACR criteria (Knee pain and at least 3 of the following):		
1. Age 50 or older?	☐	☐
2. Morning stiffness less than 30 minutes?	☐	☐
3. Crepitus with active motion of the knee (i.e. squatting)?	☐	☐
4. Tenderness of bony margins of the joint?	☐	☐
5. Bony enlargement noted on examination?	☐	☐
6. Lack of palpable warmth of the synovium?	☐	☐

Exclusion Criteria:

	Yes	No
Knee flexion ROM < 70º?	☐	☐
Undergone total knee arthroplasty?	☐	☐
Uncontrolled hypertension? (i.e. systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg)	☐	☐
History of cardiovascular disease? (e.g. myocardial infarction, angina, arrhythmias, stroke)	☐	☐
History of patellar or quadriceps tendon rupture?	☐	☐
History of patellar fracture?	☐	☐
Have had any surgical procedures involving the patella, quadriceps tendon or patellar tendon?	☐	☐
Have had a steroid injection of the patellar or quadriceps tendons in the past 6 months?	☐	☐
Pregnant female?	☐	☐
If no, Post-Menopausal for at least one year?	☐	☐
Home pregnancy test positive?	☐	☐

☐	Subject meets all inclusion/exclusion criteria and **<u>is eligible</u>** for participation in study
☐	Subject does not meet all inclusion/exclusion criteria and **<u>is not eligible</u>** for participation in study

_____ _____

Investigator reviewing Inclusion/Exclusion criteria

Date

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APPENDIX D

SUBJECT DEMOGRAPHIC DATA SHEET

Subject ID #:_____ Date:_____

Age:_____ Height (cm):_____ Weight (kg):_____

2. Sex:

— Male
— Female

3. Involved Knee:

— Right
— Left
— Both (If both, which one causes more pain and disability: ___Right ___left)

4. List other joints in your body with osteoarthritis:

5. Ethnic Origin:

— Black/African American
— Hispanic
— Asian/Pacific Islander
— Native American
— White/Caucasian
— Other

6. Marital Status:

— Married
— Living with significant other
— Divorced
— Widowed
— Single(never married)

7. Level of education (Mark the highest level obtained):

— Less than high school
— Graduated from high school
— Some college
— Graduated from college
— Some post-graduated course work
— Completed post-graduated degree

8. Current Employment Status (Check one category that best describes current work status):

— Work regular duty full time
— Work regular duty part time
— Work light duty or modified position full time
— Temporary unable to work due to health status
— Permanently unable to work or retired due to health status
— Retired (not due to health status)
— Unemployed
— Homemaker (not working outside the home)
— Student (not currently working)

9. Which statement best describes the type of work you do (or used to do):

— Mostly sedentary
— Sedentary; substantial amount of walking required
— Moderately active; walking, some lifting and carrying
— Demanding physical activity, heavy lifting and carrying

10. Have you smoked at least 100 cigarettes in you entire life?

— Yes (go to question 11)
— No (go to question 14)
— Don't know (go to question 14)

11. If yes, on the average during all the years that you have smoked, how many cigarettes have you usually smoked per day?

— 1-10
— 11-20
— 21-40
— More than 40

12. If yes, do you smoke cigarettes now?

— Yes
— No

13. If yes, except for the time you quit, for how many years all together have you smoked cigarettes?

— 0-5 years
— 6-10 years
— 11-20
— More than 20 years

14. The following are a list of health problems. Do you currently have, or have previously had the problems?

a. Heart	— Yes	— No
b. High Blood Pressure	— Yes	— No
c. Stroke	— Yes	— No
d. Congestive Heart Failure	— Yes	— No
e. Lung Disease	— Yes	— No
f. Diabetes	— Yes	— No
g. Stomach ulcer	— Yes	— No
h. Kidney Disease	— Yes	— No
i. Liver Disease	— Yes	— No
j. Anemia or other Blood Disease	— Yes	— No
k. Cancer	— Yes	— No
l. Depression	— Yes	— No
m. Back Pain	— Yes	— No
n. Memory Problem	— Yes	— No
o. Previous Hip Fracture	— Yes	— No
p. Other medical Problems	— Yes	— No

15. How long have you had symptoms (pain) of arthritis in your knee?

— Less than 1 year
— 1-2 years
— 3-5 years
— 5-10 years
— More than 10 years

16. When did you first see a physician about arthritis in your knee?

— Less than 1 year
— 1-2 years
— 3-5 years
— 5-10 years
— More than 10 years

17. Prior knee injuries or surgeries (please provide type of injury or surgery and date or estimate date)

a. Type:_____ Date:_____
b. Type:_____ Date:_____
c. Type:_____ Date:_____
d. Type:_____ Date:_____
e. Type:_____ Date:_____

18. Current medications for knee osteoarthritis:

— a. Over the counter analgesics (Tylenol, Aspirin_free tablets, etc.)
— b. Arthritis creams
— c. Over the counter non-steroids (aspirin, Ibuprofen, Aleve, Orudis, etc.)
— d. Prescription analgesics (Codeine, Percocet, Darvocet, Ultram, etc.)
— e. Prescription non-steriodals (Celebrex, Voltaren, Naprosyn, Daypro, Ibuprefen, Lodine, Oruvial)
— f. Other:_____

19. Please list other Medications you take for conditions other than osteoarthritis of your knee.

a.
b.
c.
d.

20. Current exercise to help lessen the pain and stiffness of arthritis?

a.	Walking program	— Yes	— No
b.	Jogging program	— Yes	— No
c.	Stretching exercise, Yoga	— Yes	— No
d.	Treadmill, Nordic Trak, Stairmaster, etc.	— Yes	— No
e.	Weight Machines	— Yes	— No
f.	Aerobics	— Yes	— No
g.	Water exercises	— Yes	— No

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APPENDIX E

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE

Subject ID #:_____ Date:_____

Instructions: These questions are about fatigue and the effect of fatigue on your activities.

For each of the following questions, circle the number that most closely indicates how you have been feeling during the past week.

For example, suppose you really like to sleep late in the mornings. You would probably circle the number closer to the "a great deal" end of the line. This is where I put it:

Example: To what degree do you usually like to sleep late in the mornings?

1	2	3	4	5	6	7	(8)	9	10

Not at all A great deal

Now please complete the following items based on **the past week.**

---

1. To what degree have you experienced fatigue?

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

If no fatigue, stop here.

2. How severe is the fatigue which you have been experiencing?

1	2	3	4	5	6	7	8	9	10

Mild Severe

3. To what degree has fatigue caused you distress?

1	2	3	4	5	6	7	8	9	10

No distress A great deal of distress

CONTINUED ON NEXT PAGE →

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

Circle the number that most closely indicates to what degree fatigue has interfered with your ability to do the following activities in the past week. For activities you don't do, for reasons other than fatigue (e.g. you don't work because you are retired), check the box.

In the past week, to what degree has fatigue interfered with your ability to:

(NOTE: Check box to the left of each number if you don't do activity)

☐ **4. Do household chores**

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

☐ **5. Cook**

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

☐ **6. Bathe or wash**

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

☐ **7. Dress**

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

☐ **8. Work**

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

☐ **9. Visit or socialize with friends or family**

1	2	3	4	5	6	7	8	9	10

Not at all A great deal

CONTINUED ON NEXT PAGE →

MULTIDIMENSIONAL ASSESSMENT OF FATIGUE (MAF) SCALE (Continued)

(NOTE: Check box to the left of each number if you don't do activity)

☐ **10. Engage in sexual activity**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **11. Engage in leisure and recreational activities**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **12. Shop and do errands**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **13. Walk**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

☐ **14. Exercise, other than walking**

1 2 3 4 5 6 7 8 9 10

Not at all A great deal

15. Over the past week, how often have you been fatigued?

4 Every day

3 Most, but not all days

2 Occasionally, but not most days

1 Hardly any days

16. To what degree has your fatigue changed during the past week?

4 Increased

3 Fatigue has gone up and down

2 Stayed the same

1 Decreased

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* Used with permission from Belza[12]

APPENDIX F

BURST SUPERIMPOSITION MVC TEST DATA FORM

Subject ID:_____ Date:_____

Involved Extremity: R L Limb Weight (NM):_____

Weight (kg):_____ Height (cm):_____ BMI (W/H^2): _____ Age:_____

B.P.: _____/_____mmHG H.R.: _____bpm Rhythm: ( )Reg. ( )Irr.

Biodex Moment Arm:_____

Biodex Chair Back:_____

Biodex Chair Height:_____

Biodex Chair Floor:_____

Dynamometer Position:_____

Resting E-stim Torque (Nm):_____

Practice MVC (Nm):_____

Trial 1:

	Torque	Torque / BMI
E-stim Torque		
Voluntary Torque		
Voluntary/E-stim		

Trial 2:

	Torque	Torque / BMI
E-stim Torque		
Voluntary Torque		
Voluntary/E-stim		

Trial 3:

	Torque	Torque / BMI
E-stim Torque		
Voluntary Torque		
Voluntary/E-stim		

Trial 4:

	Torque	Torque / BMI
E-stim Torque		
Voluntary Torque		
Voluntary/E-stim		

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APPENDIX G

SUBMAXIMAL CYCLE ERGOMETER TEST DATA SHEET

Subject ID #:_____ Date:_____

Gender: F M Age: _____yrs

70% of APMHR:_____ bpm 85% of APMHR:_____ bpm

Pre-exercise HR: _____ bpm Pre-exercise BP_____/_____mmHg

HR	BP
1 min_____ bpm	_____/____mmHg
2 min_____ bpm	_____/____mmHg
3 min_____ bpm	_____/____mmHg
4 min_____ bpm	_____/____mmHg
5 min_____ bpm	_____/____mmHg
6 min_____ bpm	_____/____mmHg
7 min_____ bpm	_____/____mmHg
8 min_____ bpm	_____/____mmHg
9 min_____ bpm	_____/____mmHg
10 min_____ bpm	_____/____mmHg

Average HR _____ bpm Post-exercise BP:_____/_____ mmHg

Test duration: _____min Final workload _____Watts

Preliminary VO_2 max _____ L/min

(Men VO_2 max= 0.348(Prel. VO_2 max) -0.035(age)+3.011)
(Women VO_2 max=0.302(Prel. VO_2 max)-0.019(age)+1.593)

Age & gender corrected VO_2 max _____ L/min

VO_2 max _____mL/kg/min (VO2 max *1000/kg)

Rating:

1. Excellent
2. Good
3. Above average
4. Average
5. Below average
6. Poor
7. Very poor

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APPENDIX H

QUADRICEPS FATIGUE TEST DATA FORM

Subject ID:_____ Date:_____

Involved Extremity: R L Limb Weight (Nm):_____

Maximum Voluntary Torque (Nm):_____

Maximum E-stim Torque (Nm):_____

Resting E-stim Torque (Nm):_____

CAR (%):_____

Time (min)	E-stim Torque	Voluntary Torque

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