Hypoesthesia in Knee Osteoarthritis: Relationship of Pain, Vibration Perception and Proprioception

By
Ali M. Alsouhibani
BS., King Saud University, Riyadh, Saudi Arabia, 2010

THESIS
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Defense Committee:
Carol A. Courtney, Chair and Advisor
Alexander Aruin, Physical Therapy
Sangeetha Madhavan, Physical Therapy
This thesis is dedicated to my parents (Mrs. Norah Alsouhibani and Mr. Mohammed Alsouhibani), without whom it would never have been accomplished.
ACKNOWLEDGMENTS

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Then I would like to thank my thesis committee—Carol Courtney, Alexander Aruin and Sangeetha Madhavan for their unwavering support and assistance. They provided guidance in all areas that helped me accomplish my research goals and enjoy myself in the process.

A number of individuals involved with data collection and analysis were extremely helpful to me during this time; I would like to thank them as well.

Finally, I would like to thank my wife Norah Alsuhaibani who shared every moment of this process and my parents and family who supported me during the last 2 years.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACL</td>
<td>Anterior Cruciate ligament</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
</tr>
<tr>
<td>KOS</td>
<td>Knee outcome survey</td>
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<tr>
<td>MDT</td>
<td>Mechanical detection threshold</td>
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<tr>
<td>NPRS</td>
<td>Numeric pain rating scale</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<tr>
<td>PROM</td>
<td>Passive range of motion</td>
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<tr>
<td>QST</td>
<td>Quantitative sensory testing</td>
</tr>
<tr>
<td>TDPM</td>
<td>Threshold to detection of passive motion</td>
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<tr>
<td>TMD</td>
<td>Temporomandibular joint disorder</td>
</tr>
<tr>
<td>VPT</td>
<td>Vibration perception threshold</td>
</tr>
<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Arthritis Index</td>
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SUMMARY

Purpose: Hypoesthesia, or partial loss of sensitivity to sensory stimuli has been reported in individuals with knee osteoarthritis, with deficits reported in both proprioception (kinesthesia and joint position sense) and vibration perception threshold at the affected knee. The mechanisms underlying these deficits are unclear, however, previous evidence has indicated that diminished somatosensation, such as vibration perception threshold may occur due to altered nociceptive processing. It has been postulated that similar mechanisms may explain deficits in kinesthesia, or the ability to detect passive joint movement in knee osteoarthritis, however this premise has not been examined. It was hypothesized in this study that deficits in vibration perception threshold and proprioception (kinesthesia) would be associated in a subjects with moderate to severe knee osteoarthritis. The purpose of this study was to explore the relationship between somatosensory measures of pain, vibration detection, proprioception and function in persons with knee osteoarthritis.

Methods: Fifteen individuals (mean age, 55.6±7.4y; 8 female; BMI 33.0±7) diagnosed with osteoarthritis of the tibiofemoral joint by their physician (≥ grade II Kellgren and Lawrence radiographic changes) participated. Measurements included vibration perception threshold at the knee using a biothesiometer, proprioception tested via threshold to detection of passive movement, resting pain and worst pain during the week prior to testing examined via Numeric Pain Rating Scale, function using the Knee
Outcome Survey Activities of Daily Living Scale and isometric quadriceps strength.

**Results**: Subjects reported 3.1±3.0 pain at rest and worst pain at 6.2±2.6 on the NPRS, and 56±16% on the Knee Outcome Survey Activities of Daily Living Scale, indicating an average of 50% deficit in function. Quadriceps strength was significantly different between limbs (p<0.05), and significant deficits in vibration and proprioception were demonstrated at the affected knee compared to contralateral knee (p<0.05). These deficits were not correlated (r=.02) however a moderate positive correlation was demonstrated between proprioception deficits and resting pain (r=.54, p<0.05) and worst pain (r=.54, p<0.05), and a weak positive correlation was found between diminished vibration and resting pain (r=.24). No correlation was found between diminished function as measured by the Knee Outcome Survey Activities of Daily Living Scale and both vibratory and proprioceptive deficits.

**Conclusions**: Hypoesthesia, as measured by proprioception and vibration detection was significantly impaired on the painful osteoarthritis limb compared to the contralateral limb and these findings were correlated to resting and worst pain. Functional deficits were only weakly correlated to somatosensory deficits, indicating that diminished function is likely multifactorial in nature. Several factors may contribute to functional deficits found with chronic knee osteoarthritis, however pain related somatosensory deficits may contribute.
I. INTRODUCTION

A. Background

Knee osteoarthritis (OA) is common in the elderly population and pain associated with the disease is considered a major contributor to functional limitations and reduced quality of life (Lawrence et al., 2008). Hypoesthesia, or partial loss of sensitivity to sensory stimuli has been reported in these individuals with deficits reported in both proprioception (see Knoop et al., 2011 for review) and vibration perception threshold (VPT) (Shakoor et al., 2008; 2012; Kavchak et al., 2012) at the affected knee. Both experimental and clinical research has suggested that vibratory hypoesthesia may be due to altered central pain processing rather than peripheral nerve damage (Geber et al., 2008), however hypoesthesia related to movement detection at the joint, i.e., proprioceptive deficits, has not been considered in this manner. Hypoesthesia of the affected knee may result in impaired motor control, leading to ongoing micro damage to painful joints and other tissues (Hurley et al., 1997). In fact, both proprioceptive and vibration detection deficits have been associated with altered joint loading (van der Esch et al., 2006; Shakoor et al., 2012) and perceived instability during functional tasks (Kavchak et al., 2012), however the relationship between impairments in these two sensory modalities has not been examined.
B. Main Objective

The main objective of this thesis was to investigate the relationship between proprioceptive acuity, as measured by threshold to detection of passive motion (TDPM), and vibration perception in knee OA and second, to identify whether these potential somatosensory deficits are correlated with chronicity of the disease and/or activity limitations. Chronicity was operationally defined as the presence of resting pain and/or worst pain at the affected knee in the week prior to testing.

C. Hypotheses

Ia. Proprioceptive deficits measured via TDPM will be correlated with increased VPT (i.e. decreased vibration sense).

Ib. Changes in TDPM and VPT will correlate with chronic pain and activity limitation.

Null hypotheses:

1) No significant correlation will exist between proprioception acuity deficits and vibration perception deficits at the affected knee in individuals with knee OA.

2) No significant correlation will exist between somatosensory (proprioception and vibration) deficits and chronic pain and/or activity limitation in individuals with knee OA.
D. **Rationale**

The rationale for examining somatosensory changes in patients with knee OA arises from research demonstrating reduction of somatic sensation (e.g. vibration and tactile perception) and proprioception in this population and potential associations to chronic pain and functional limitations. Understanding the relationship between altered somatosensation, pain, and functional limitations has the likelihood of developing new strategies and/or treatments to prevent the functional decline in patients with knee OA.

Prior to reviewing the methods of this study, the background section will review the somatosensory changes found in patients with knee OA, and their potential relationship with pain and functional limitations.
II. LITERATURE REVIEW

A. Osteoarthritis: Prevalence and Costs

Osteoarthritis (OA) is the most common form of arthritis, affecting nearly 26.9 million adults in the U.S. aged 25 and above (Lawrence et al., 2008). Radiographic changes are seen in the majority of individuals aged 65 years, and in about 80% of those aged 75 years (Cooper, 1994). It has been estimated that 53% of women and 33% of men above the age of 80 years are diagnosed with radiographic osteoarthritis at the knee (Dahaghin et al., 2005). Approximately 34% of adults in the U.S above the age of 25 years suffer from symptomatic knee OA, which leads to limitation of activity and disability in the elderly (Guccione et al., 1994). In medical care, arthritis and other rheumatic conditions cost the U.S economy about $128 billion annually, and that includes lost wages and productivity (Centers for Disease Control and Prevention, 2007). The total annual cost of OA per person living with OA is nearly $5700 (Maetzel et al., 2004).

Knee OA has been linked with pain (Van Dijk et al., 2009), diminished proprioception (Knoop et al., 2011), muscle weakness (Segal et al., 2010), decreased range of motion (ROM) (Holla et al., 2012), perceived joint instability (Fitzgerald et al., 2004), changes in gait (Astephen et al., 2008) and reduced vibratory perception acuity (Shakoor et al., 2008). However, pain in knee OA was found to have the strongest association with self-reported activity limitations (Van Dijk et al., 2009; Guccione et al., 1994).
B. **Altered Nociceptive Processing in knee OA**

Central sensitization of the nociceptive pathways and impaired pain inhibition has been demonstrated in populations with knee OA (Arendt-Nielsen et al., 2010; Courtney et al., 2009) and it is thought that these mechanisms play a major role in the elevated chronic pain. Furthermore, studies have found an association between proprioception deficits and pain in knee OA (Felson et al., 2009). Joint damage found with knee OA results in noxious input transmitted through (group III, IV) fibers, However, associated inflammation and persistent noxious input from degenerated tissues may result in sensitization of spinal and supraspinal nociceptive processes (Latremoliere and Woolf, 2009). This means that pain is no longer coupled to the magnitude of peripheral noxious stimulus, thereby causing enhanced pain responses and expansion of the receptive area (Bajaj et al., 2001). In addition, a reduction in the effectiveness of the descending inhibiting system may occur, thus minimizing the ability to modulate pain (Kosek and Ordeberg, 2000). Therefore, hyperalgesia, a heightened response to noxious stimuli, is often present in individuals with knee OA (Arendt-Nielson et al., 2010) and is found in regions extending beyond the primary site of joint damage. Clinically, it may be demonstrated by algometric measurement of pressure pain threshold (Kavchak et al., 2012).

Hypoesthesia to vibratory stimulus and proprioceptive deficits has also been found in these populations, both of which represent a deficit or inhibition of non-noxious sensory afference, however the relationship between these sensory impairments is unclear. Recent studies have begun to explore the effect of sustained nociceptive input,
such as found in degenerative joint disease, on altered somatosensation and function in patients with knee OA, specifically non-nociceptive sensory function such as proprioception and vibratory sense (Harden et al., 2013; Kavchak et al., 2012; Hendiani, Shakoor et al., 2008; 2012; Felson, 2009).

C. **Altered Quantitative Sensory Testing (QST) in knee OA**

1. **Proprioceptive Acuity**

Proprioceptive acuity at the joint is believed to be important for movement coordination, body posture, maintenance of balance and postural control, and motor learning and relearning (Gardner, 2000). It is transmitted to the central nervous system through afferent input from cutaneous receptors in the skin, muscles, joint tissues, ligaments, and tendons. However, muscle spindles are known to be the most important contributor to proprioception (Goodwin et al., 1972; Proske and Gandevia, 2009). Two methods of measurement have been described in the literature: joint repositioning (sense of position) measured by active or passive reproduction of joint position, and kinesthesia (sense of motion) measured by threshold to detection of passive joint motion (TDPM). Other types have been described as well (i.e. sense of effort [Weerakkody et al., 2003]). These measurement methods correlate poorly with each other (see Knoop et al. [2011] for review) indicating the distinct nature of the two modalities, potentially both mechanistically and functionally. That being said, individuals with knee OA often show deterioration of proprioceptive acuity in both modalities (Hassan et al., 2001; Hewitt et
al., 2002) and it has been connected to knee pain, activity limitations (Felson et al., 2009), and muscle weakness (Bayramoglu et al., 2007). In particular, van der Esch et al. (2007) demonstrated an increase in TDPM (i.e. decreased proprioception) associated with muscle weakness and reduced functional abilities in individuals with knee OA. However, the mechanisms underlying these associations yet are still unknown.

2. **Vibration Perception Acuity**

Vibratory perception testing examines the patency of somatosensory pathways responsible for transmitting information induced by cutaneous vibratory stimuli. Large myelinated Aα and Aβ sensory fibers are known mediators of vibratory sensation (Saio and Cros 2003). Vibratory testing is most commonly used clinically in the early detection of neuropathy, specifically diabetic neuropathy (Garrow and Boulton 2006). However, recent studies have demonstrated hypoesthesia to cutaneous mechanical detection threshold (MDT) and VPT in populations with chronic knee OA where neuropathy is not manifest (Hendiani et al., 2003; Shakoor et al., 2008; Kavchak et al., 2012). An experimental model of induced pain has shown an increase of VPT (i.e. decreased acuity) in the presence of pain (Apkarian et al., 1994). In addition, thresholds of vibration perception were elevated in patients with temporomandibular (TMD) disorders when higher pain responses to palpation (Hollins et al., 1996). Shakoor et al (2008) found vibratory deficits in patients with knee OA, but did not measure pain intensity as a
component of the study. However all subjects reported walking pain intensities of at least 20/100 mm on the visual analog scale.

**D. Association Between QST, Pain and Function in Knee OA**

Hyperalgesia and hypoesthesia are present in populations with knee OA and both may be elicited by nociceptive input; however, it is thought that the mechanisms underlying these somatosensory findings are distinct (Geber et al., 2008). Westermann et al. (2011) reported tactile hypoesthesia in both limbs but not hyperalgesia on the contralateral limb of patients with knee OA. Accordingly, the demonstration of bilateral hypoesthesia was deemed further evidence that knee OA related sensory deficits were centrally mediated. These findings may have functional repercussions. Kavchak et al. (2012) demonstrated an association between vibration perception deficits and perceived functional instability in patients with knee OA. Shakoor et al. (2012) have shown a relationship between VPT deficits and increased dynamic knee joint loading in knee OA, which may influence function. In addition, they proposed that deficits in VPT may be an indicator of diminished proprioceptive acuity, however, this relationship has not been tested.

The mechanisms underlying pain-related hypoesthesia remain unclear, however spinal, supraspinal and peripheral mechanisms have been proposed. Magerle and Treede (2003) suggested a spinal mechanism. They proposed presynaptic inhibition of primary afferent Aβ-fibers caused by C-fiber input. Specifically, noxious C (Group IV) fiber input
from the periphery may, through interneuronal connections, cause inhibition of sensory information transmitted via Aβ (Group II) fibers at the dorsal horn in the spinal cord. Alternatively, Apkarian (1994) suggested supraspinal mechanisms were likely, considering that touch is mediated primarily through the dorsal column nuclei, which receive input directly from dorsal column tracts that bypass spinal cord processing (Apkarian 1994). However, this is related to his findings of vibratory deficits in response to pain in the upper extremity. It is known that muscle afferents (i.e., information from the muscle spindle) from the lower limbs ascend via Clarke’s column and the dorsal spinocerebellar tract (Proske and Gandevia, 2009). Lower limb afferents synapse at Clarke’s nucleus extends from L3-C8, which may be a site of sensory modulation.

Peripheral mechanisms of hypoesthesia in persons with knee OA have also been proposed. Harden et al (2013) suggested that focal hypoesthesia in persons with knee OA occurred due to peripheral neuropathy. These authors suggested a fiber type specific neuropathy because of the specificity of somatosensory deficits found. However, the findings of hypoesthesia on the contralateral limb by Westermann et al (2011) would seem to challenge this premise, indicating a more regional rather than focal deficit. While hypoesthesia, including proprioceptive and vibratory deficits have been found in persons with knee OA, it is unknown whether these deficits are mediated by similar mechanisms. If so, it would seem that a relationship would exist between these modalities.
E. Background of Proprioception Measures

A variety of modalities for testing proprioception have been described. The two most common are repositioning (position sense) and kinesthesia (motion sense). Muscle spindles, believed to be a main contributor to proprioception, include primary and secondary endings. Primary endings (Ia) sense the change of muscle length and the velocity of this change, while secondary endings (II) only sense the length change of the muscle (Pearson and Gordon, 2013). Position sense is thought to be accomplished by utilizing primary and secondary fibers; whereas, only primary fibers contribute to the sense of motion (Proske and Gandavia, 2009). To measure position sense, the knee is moved (passively or actively) to a specific angle then returned to the initial position. The subject is then asked to reproduce the angle by the same or the contralateral knee. The subject may sometimes show the perceived angle on a knee model (Bayramoglu et al., 2007; Hurley et al., 1997; Lund et al., 2008). Measurement of proprioception using motion sense (detection of movement) requires slow movement of one or both knees. The subject is asked to signal immediately upon detecting the initiation of the movement or a change of the limb’s position. Subjects are sometimes required to note which knee moved and/or the direction in which it moved (Lund et al., 2008; Sharma and Pai, 1997; Pai et al., 1997; van der Esch et al., 2007). In the testing of both modalities, visual, auditory, and cutaneous inputs are eliminated as much as possible. Studies have shown that these two measurements do not correlate with each other (Knoop et al., 2011), even though, both measurements have shown to be reliable (Streiner and Norman, 2003).
III. METHODS

A. Study Design and Subjects

The study was conducted with a convenience sample of individuals with knee OA and tested in a lab setting in the Department of Physical Therapy at the University of Illinois at Chicago. Fifteen individuals (mean age, 55.6±7.4y; range, 42 to 70y; 8 females and 7 males; 12 African American, 2 Hispanic, 1 Caucasian) diagnosed with OA of the tibiofemoral joint by their physician (≥ grade II Kellgren and Lawrence radiographic changes) were included in the study. It has been shown that the prevalence of knee OA among African American was significantly higher than Caucasian and Hispanic individuals (Dillon et al., 2006). Therefore, for better representation of the population, additional African American individuals were included. Patients were recruited by the use of recruitment flyers from the outpatient clinics of the University of Illinois Medical Center at Chicago. Subjects were excluded from the study if they had undergone total knee arthroplasty in either knee, reported any neurological or rheumatoid condition, taken steroid injection within 3 months in either knee, or the presence of diabetes mellitus. Subjects were instructed to avoid anti-inflammatory drugs and/or pain medications 24 hours before the testing and to avoid exercise before testing. The participants were not informed on the working hypothesis and the results were not visible to them during the
testing. The study was approved by the Institutional Review Board (IRB) of the
University of Illinois at Chicago.

**B. Overview of Study Protocol**

Prior to participation, subjects signed a written informed consent, reported their
health history and completed a functional questionnaire, the Activities of Daily Living
Scale of the Knee Outcome Survey (KOS) (Irrgang et al., 1998b). This outcome survey is
a patient-reported measure of functional limitations of the knee during activity of daily
living. The KOS has been determined reliable and valid in patients with knee OA and in
patients after anterior cruciate ligament (ACL) reconstruction (Williams et al., 2012;
Irrgang et al., 1998a). Self reported pain was obtained using a 0 ("no pain") to 10 ("worst
pain imaginable") pain intensity Numeric Pain Rating Scale (NPRS) (Jensen et al., 1999).
Resting pain at the affected knee was obtained by asking the question “when you are at
rest how much would you rate the pain from 0 to 10 with 0 no pain and 10 worst pain
imaginable?” Similarly, worst pain at the affected knee was obtained by asking the
question “how much would you rate the worst pain from 0 to 10 in the past week with 0
no pain and 10 worst pain imaginable?” Passive range of motion (PROM) for knee
flexion/extension was acquired using a standard goniometer. Quadriiceps strength for both
limbs was measured using a MicroFet 2 dynamometer (Hoggan Health Industries Inc,
West Jordan, UT, USA). Specifically, each subject was tested in sitting with the knee
flexed to 90°. The mean value of 3 measurements of isometric knee extension was
recorded. Next, proprioceptive acuity was measured using TDPM (see section C below) in both knees. Vibration acuity was tested in both limbs (see section D) at 5 sites: 1) medial femoral condyle 2) lateral femoral condyle 3) tibial tuberosity 4) medial malleolus 5) lateral malleolus. The testing limb was randomly assigned.

C. **Proprioception Acuity**

Proprioception was determined using TDPM, as has been described previously (Barrack et al., 1983; Courtney et al., 2005; Courtney and Rine, 2006, Courtney et al 2013). This methodology has been reported to be reliable (Hurkmans et al., 2007). Subjects were seated in an adjustable chair of a Biodex Rehabilitation/Testing System 3 (Biodex Medical Systems, Inc, Shirley, NY) with their hips at 70°, tested knee at 45° (popliteal fossa placed 4-6 inches away from the edge of the apparatus), and ankle in neutral position. An air splint was applied to the ankle to minimize cutaneous input with an air pressure of 20 mm Hg. Subjects were blindfolded to prevent visual feedback and listened to white noise to minimize auditory input. Prior to testing and in test position, subjects were instructed to co-contract the tested knee for 10 seconds to eliminate the effect of thixotropy, which has been demonstrated to affect measures of TDPM (Wise et al., 1996). A motor and a pulley system attached to the dynamometer of the Biodex and the air splint was used to perform a passive, slow (0.5°/sec) flexion or extension of the limb after a random delay. Subjects were instructed to press a handheld switch when they detected motion of the limb and/or change of position. A practical trial was performed
then an average of 3 trials on each limb was conducted with random assignment of limb side and direction of movement. After documenting the amount of linear movement of the pulley \((x)\), the threshold to detection \((\theta, \text{ in degrees})\) was calculated using the following formula \(\theta = \tan^{-1}(x/r)\), where \(r\) is the shank length measured from the medial joint line knee to the inferior aspect of the medial malleolus.

**D. Vibratory Acuity**

Vibration perception threshold (VPT) was evaluated at 5 sites of the lower limb (medial and lateral femoral condyle, medial and lateral malleolus, and tibial tuberosity) in each side using a biothesiometer (Bio-Medical, OH) as previously described (Shakoor et al., 2008). A vibratory tip (13 mm cylinder) oscillates at a frequency of 100 Hz at the site of application using the weight of the machine only as the source of pressure. Vibration (in “biothesiometer units” [von Schlippe et al., 2001]) was increased 1 volt per second at the site until the subject reported sensation. While leaving machine in place 2-3 more trials were performed and an average of the trials was documented.

**E. Statistical Analyses**

All data are reported as mean ± SD unless otherwise noted. The Shapiro-Wilk test was used to ensure normality of the data, as this test is considered appropriate for samples less than 50. To analyze differences in vibration acuity a 2-way repeated measure analysis of variance (location by side) was conducted. Post hoc analysis was performed using paired \(t\) tests to determine significant differences in VPT between affected and less
affected side. Similarly, paired $t$ tests were conducted to determine differences in proprioception and strength between limbs. Pearson product moment coefficient of correlation was performed to determine associations between vibration acuity, proprioception acuity, function, and pain in the affected limb. Level of significance was set at $p< 0.05$ for all tests. All Statistical analyses were performed using SPSS software (version 22.0 for Windows; SPSS, Chicago, IL).
IV. RESULTS

A. Subject Characteristics

Fifteen individuals with knee OA participated in the study. Demographics and clinical characteristics are shown in Table 1. Subjects reported $3.1 \pm 3$ pain at rest and worst pain at $6.2 \pm 2.6$ on the NPRS. Five participants had bilateral symptoms, however, all reported one leg with greater symptoms and pain. The average score on the Activities of Daily Living Scale of the Knee Outcome Survey was $53.4 \pm 16.34\%$, indicating an average of almost 50% deficit in function. Accordingly, 40% reported problems with knee giving way during daily activities. Average BMI was $32 \pm 7.2$ km/m$^2$ and ten of 15 individuals reported resting pain.
<table>
<thead>
<tr>
<th>Demographics and clinical characteristics of participants.</th>
<th>Participants (N=15)</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>Age (y)</td>
<td>55.6 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Gender (%female)</td>
<td>53.3%</td>
<td></td>
</tr>
<tr>
<td>BMI*</td>
<td>32 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Dominant leg (% right)</td>
<td>93.3%</td>
<td></td>
</tr>
<tr>
<td>Resting pain§</td>
<td>3.1 (3)</td>
<td></td>
</tr>
<tr>
<td>Worst pain†</td>
<td>6.2 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Passive Range of Motion, in degrees (affected knee/less affected knee)</td>
<td>115.4 (16.6) / 122.4 (13.6)</td>
<td></td>
</tr>
<tr>
<td>Activities of Daily Living Scale on KOS **</td>
<td>53.4 (16.3)</td>
<td></td>
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* BMI indicates body mass index.
** KOS indicates knee outcome survey.
§ Resting pain represents pain at the affected knee when subject is at rest using the numeric pain rating scale.
† Worst pain represents the worst pain subject had at the affected knee in the week prior to testing using the numeric pain rating scale.
B. **Proprioception Acuity and Strength**

Comparison of TDPM between sides with paired $t$ test indicated significant higher thresholds in the affected (6.24±2.68) as opposed to less affected side (4.47±1.53), $t(14) = 3.6$, $p = 0.002$ (Table 2). Likewise, quadriceps strength was significantly different between sides with the affected (32.8±10.6 lbs.) significantly less than the less affected side (41.5±11.03 lbs.), $t(14) = -3.36$, $p = 0.004$ (Table 2).

<table>
<thead>
<tr>
<th>Table II. Comparisons between affected and less affected side in proprioception and quadriceps strength</th>
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<tr>
<td><strong>Affected side Mean (SD)</strong></td>
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<tr>
<td>------</td>
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<tr>
<td>TDPM*</td>
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<td>Strength</td>
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</table>

* Threshold to detection of passive motion in degrees.
C. Vibration Acuity

The 2-way analysis of variance revealed no significant interaction between side and location of vibration ($P = 0.607$). However, a significant main effect of side ($P = 0.035$) and location ($P = 0.027$) was found. Further analysis using paired $t$ tests indicated a significant difference in vibration threshold between affected (32.16±7.3) and less affected (26.81±8.4) side at the medial femoral condyle $t(14) = 4.81, p < .001$; other locations were not significantly different (Figure 1).
Figure 1. Mean vibration perception threshold in OA subjects.
D. Correlation Analyses

There was no significant correlation between TDPM and VPT measures at any of the sites (see Figure 2). However, a significant moderate correlation was found between TDPM and resting pain \( (r = 0.545, p = 0.018; \text{see Figure 3}) \), as well as worst pain \( (r = 0.542, p = 0.018; \text{see Figure 4}) \). Thus, higher proprioception thresholds (i.e. decreased acuity) were associated with increased pain. No significant correlations were found between resting pain or worst pain and diminished vibration sense at any of the sites of the limb. Additionally, no correlations were found between function as measured by the KOS and decreased proprioception acuity \( (r = -0.093) \). There was also no relationship between the KOS and VPT at any of the sites of the knee. A significant weak correlation was found between quadriceps strength and VPT at the lateral femoral condyle of the affected knee \( (r = -0.467, p = 0.040) \). This means that better strength was associated with lower vibratory thresholds (i.e. enhanced vibration sense) at the lateral femoral condyle of the affected knee; however, no significant correlations were found at the other sites (see Table 3). No significant correlation was found between quadriceps strength and TDPM at the affected knee \( (r = 0.178, p = 0.263) \).
Figure 2. Correlation between TDPM and VPT at the medial femoral condyle.
Figure 3. Correlation between TDPM and resting pain in subjects with knee OA.
Figure 4. Correlation between TDPM and worst pain in subjects with knee OA.
Table III. Correlations of the VPT with TDPM, NPRS for resting and worst pain, and function measured by KOS at 5 sites of the lower extremity in patients with knee osteoarthritis.

<table>
<thead>
<tr>
<th></th>
<th>Medial femoral condyle</th>
<th>Lateral femoral condyle</th>
<th>Medial malleolus</th>
<th>Lateral malleolus</th>
<th>Tibial tuberosity</th>
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<tr>
<td><strong>TDPM</strong></td>
<td></td>
<td></td>
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<tr>
<td>Pearson’s $r$</td>
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<td>-0.112</td>
<td>0.046</td>
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<tr>
<td>$P$(one tailed)</td>
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<td>0.241</td>
<td>0.345</td>
<td>0.435</td>
<td>0.322</td>
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<tr>
<td><strong>Resting pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pearson’s $r$</td>
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<td>0.068</td>
<td>0.144</td>
<td>0.320</td>
<td>-0.021</td>
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<tr>
<td>$P$(one tailed)</td>
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<td>0.404</td>
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<tr>
<td><strong>Worst pain</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pearson’s $r$</td>
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<td>-0.210</td>
<td>-0.043</td>
<td>-0.290</td>
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<tr>
<td>$P$(one tailed)</td>
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<td>0.440</td>
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</tr>
<tr>
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<td>0.340</td>
<td>0.416</td>
<td>0.166</td>
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<tr>
<td><strong>Strength</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson’s $r$</td>
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<tr>
<td>$P$(one tailed)</td>
<td>0.398</td>
<td>0.040*</td>
<td>0.210</td>
<td>0.344</td>
<td>0.229</td>
</tr>
</tbody>
</table>

Abbreviations: VPT, vibration perception threshold; TDPM, threshold to detection of passive movement; NPRS, Numeric Pain Rating Scale; KOS, knee outcome survey.

* Significance $P<0.05$
V. DISCUSSION

One of the main findings of this study was that deficits in proprioception as measured by TDPM and VPT, although both present, were not significantly correlated in subjects with knee OA. While these two sensory modalities are believed to be mechanistically distinct, this finding suggests that the pathomechanisms underlying these somatosensory changes are potentially distinct. Additionally, proprioceptive hypoesthesia had a significant moderate correlation with self-reported pain at rest and worst pain. This is concurrent with previous studies reporting similar results (Felson et al., 2009).

A. Proprioception Acuity

Proprioception in our study was measured by TDPM and a significant difference found between limbs with a greater deficit in the ability to detect joint movement demonstrated at the affected limb. Thresholds of proprioception were found to be similar to those reported previously (van der Esch et al., 2007; Hurkmans et al., 2007). This indicates greater deterioration of proprioception of the affected limb in these individuals, even though some individuals reported bilateral symptoms. In addition, TDPM in the less affected limb was also deficient when compared to normative data from previous studies (Sharma and Pai, 1997). This may support a centrally mediated mechanism underlying this sensory deficit. Animal model studies of induced pain demonstrating bilateral effects,
have suggested this is mediated at spinal and supraspinal levels (De Silva, 2010; Radhakrishnan, 2003), however hypoesthesia has been less studied in the animal model, likely due to the difficulty in measurement. Previous studies have shown proprioception deficits in the non-affected limb, when compared to age-matched controls in unilateral OA subjects. Of those, van der Esch et al. (2007) and Sharma and Pai (1997) have demonstrated deficits when using TDPM as a measurement of proprioception in both limbs compared to controls. Interestingly, Lund et al. (2008) observed proprioception deficits of the non-affected limb in patients with knee OA when using TDPM as a measurement of proprioception but not when using re-positioning.

B. **Vibration perception threshold (VPT)**

Hypoesthesia to vibration stimuli found in this study was similar to results demonstrated in previous studies (Shakoor et al., 2008). It was found that the OA affected limb required increased stimulus to perceive vibration. In particular, the medial femoral condyle was the site that revealed a significant difference between the limbs, which is in agreement with previous studies (Shakoor et al., 2008; Kavchak et al., 2012). Interestingly, this is often the area of most pain in persons with knee OA (Thompson, 2009; Kavchak et al., 2012). As with proprioception, results from the less affected limb were elevated when compared with normative data from previous studies (Shakoor et al., 2008; Kavchak et al., 2012). This may suggest a central, rather than peripheral focal neuropathy. Vibration perception deficits have been linked to pain and functional deficits
in several studies (Apkarian et al., 1994; Hollins et al., 1996; Kavchak et al., 2012).
Apkarian et al. (1994) demonstrated an increase in vibratory thresholds when experimental pain was induced. Hollins et al. (1996) showed an association between vibrotactile and pain thresholds in individuals with temporomandibular (TMD) disorder. Results in the present study found only weak correlations between vibration thresholds and pain (see Table 2). These results, which are inconsistent with previous studies, may be due to use of different pain measures (NRPS) in this study. In addition, average BMI was $32\pm7.2$ km/m$^2$ in this study. Therefore, increased adipose tissue at the site of measurement may have altered the vibratory perception. Although, vibratory deficits were shown to have links to pain in healthy and individuals with TMD, no relationship was found in individuals with knee OA. While Kavchak et al. (2012) demonstrated a relationship between both pain and vibratory deficits to perceived instability, a correlation between pain and vibratory threshold was not reported.

C. **Associations between vibratory and proprioceptive hypoesthesia, pain and function**

This study has found moderate correlations between pain and proprioceptive hypoesthesia measured by TDPM in individuals with knee OA. Patients who reported higher pain had greater proprioception deficits. These findings are in agreement with findings of earlier studies (Felson et al., 2009). However, as mentioned above, vibration was not found to correlate with pain. Therefore, a salient result of the study was the lack
of correlation between vibratory deficits and proprioceptive deficits. Thus, our hypothesis was not supported. This result may indicate the pathomechanism of hypoesthesia in this population are potentially different, although both may be triggered by nociceptive input.

As previously described, both peripheral and central mechanisms have been proposed. Localized peripheral neuropathy may result in the ongoing hypoesthesia in these individuals (Harden et al., 2013). However, since the results from this study and previous studies (Westermann et al., 2011) have observed bilateral deficits in patients with knee OA, this suggests that the findings may be centrally mediated. Central plasticity may include spinal and/or supraspinal (i.e. cortical) mechanisms (Geber et al., 2008). Apkarian et al. (1994) suggest that supraspinal mechanisms may possibly be achieved by afferent input bypassing the dorsal horn via the dorsal column tracts. The authors suggest that this mechanism may either happen in the dorsal column nuclei or in the lateral thalamus were there is convergence of noxious and innocuous input. However in the lower extremity, proprioceptive input synapses at Clarke’s nucleus in the spinal cord (Proske and Gandevia, 2009), which gives less support to Apkarian’s arguments. Further research which examines neurophysiological mechanisms underlying pain related hypoesthesia is warranted.

The absence of correlation between proprioception deficits and vibratory deficits in subjects with knee OA suggests that hypofunction of these two modalities are distinct in pathomechanism, even though both may be centrally mediated. In this study
Quadriecps strength was found to be significantly weak in the affected limb compared to the less affected limb. Research suggests that muscle weakness may decrease muscle spindle sensitivity and thereby possibly affect proprioception acuity (Hurley et al., 1997; Marks, 1996). In addition, studies have demonstrated selective enhancement of proprioceptive acuity following a specific motor learning training (Wong et al., 2011) and in athletes involved in skilled activities (Lephart et al., 1996; Barrack et al., 1984; Courtney et al., 2013). Furthermore, van der Esch et al. (2007) have found a significant correlation between impaired proprioception measured by TDPM and weakness of quadriiceps and hamstring muscles in patients with knee OA. They have also found that impairment in proprioception and weakness of the muscles together directly affected functional ability. Therefore, strength impairments as found in our study population may have possibly affected proprioceptive acuity in the affected limb. It is notable that van der Esch et al. (2007) did not find a direct relationship between impaired proprioception and functional ability; the affect of proprioception on functional ability was indirect through weakness of muscles. The absent of correlation found in this study between proprioception deficits and functional limitations measured by the KOS concur with van der Esch et al. (2007) findings. However, the lack of correlation between muscle weakness and function in our study may be hampered by the different measurement of function (KOS) and the measurement of only one group of muscles (quadriiceps). Since van der Esch et al. (2007) used a composite score of hamstring and quadriiceps strength, this may have generated more of a comprehensive view of the affect. In addition, the
results of this study suggest that function in this population is likely affected by several factors. Thus, deficits in proprioception in chronic knee OA may be multi-factorial in underlying pathomechanism, which would explain the lack of correlation found between impaired VPT and TDPM in this study.

Interestingly, this study found a correlation between quadriceps strength and vibration perception threshold at the lateral femoral condyle site only of the affected knee. We would expect a correlation between strength and vibration deficits in the medial femoral condyle, since this anatomical site was found the most deficient in vibration perception. However, intriguingly, Shakoor et al. (2012) have found a correlation between Kellgren/Lawrence grade of radiographic severity and vibration perception deficits as measured by VPT in patients with knee OA at the lateral femoral condyle site but not the medial femoral site. This correlation remained significant even after adjustment of age, sex, BMI, and Western Ontario and McMaster Universities Arthritis Index (WOMAC) score for knee pain. In addition, it has been shown that muscle strength, specifically strength of quadriceps and hip flexors, were associated with less loss medial and lateral femoral cartilage volume in individuals with knee OA (Ding et al., 2007). The exact reason for the correlation found in this study at only the lateral femoral condyle site is unclear but most likely reflects some pathophysiological differences between anatomical sites.
D. Limitations

One limitation of the study is the absence of a control group. Although, results in this study were in agreement with previous studies and results were compared to normative data from previous studies, use of a group of asymptomatic knee OA would have allowed for more robust analyses and comparisons. Specifically, it would allow us to determine if somatosensory deficits in this population is potentially caused by pain. The sample size used in this study was relatively small. Future investigations should include larger sample sizes to improve the ability to detect correlations of lower magnitude that may have been significant.

The results for functional ability are limited to the type of measurement used in this study (e.g. KOS). Inclusion of other physical tests and/or scales of functional limitations may yield results that are relevant to different aspects of function. Also, weakness measures in this study are limited to measurements of isometric quadriceps strength only. Measurements of hamstring strength may potentially provide a comprehensive and detailed insight of the effect of specific muscles on sensory input.

Finally, it should be acknowledged that neither this study nor previous studies have established a causal relationship between hypoesthesia to vibration stimuli and/or motion detection and the development or progression of knee OA. Therefore, it is unknown whether proprioceptive and vibratory deficits precede or follow development or progression of knee OA.
E. Conclusions

Proprioception, as measured by TDPM, and vibration detection was impaired in both limbs with the painful OA limb significantly more impaired than the contralateral limb. Both represent measures of hypoesthesia. These deficits were not correlated to each other. However, proprioception impairments were moderately correlated with resting pain and worst pain. This relationship was not found with vibration deficits. Peripheral and central mechanisms have been suggested for the underlying pain-related hypoesthesia. While peripheral mechanisms suggest that peripheral hypoesthesia were possible due to neuropathy. However, hypoesthesia found in the contralateral side in this study, as well as previous studies, may suggest a central mechanism. Future research is recommended to expand on the current project with larger sample sizes, more extensive examinations using different proprioceptive measures (such as position sense) and different vibration frequencies, and detailed analysis.

Conclusions from this study cannot indicate the neurophysiological mechanism underlying these somatosensory deficits, however the regional nature of hypoesthesia found in this population would support a central mechanism.
CITED LITERATURE


VITA

NAME: Ali Mohammed Alsouhibani

EDUCATION: MS., University of Illinois at Chicago, 2014 (expected)
BS., King Suad University, Riyadh, Saudi Arabia, 2010

PROFESSIONAL
MEMBERSHIP: American Physical Therapy Association
Saudi Physical Therapy Association

CLINICAL
EXPERIENCE: King Khaled University Hospital 2009-2010
King Faisal Specialist Hospital and Research Center 2010-2011