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A review of the possible effects of radio frequency nerve ablation for knee osteoarthritis

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Thesis

A REVIEW OF THE POSSIBLE EFFECTS OF RADIO FREQUENCY NERVE ABLATION FOR KNEE OSTEOARTHRITIS

by

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A REVIEW OF THE POSSIBLE EFFECTS OF RADIO FREQUENCY NERVE ABLATION ON KNEE OSTEOARTHRITIS

DANIEL CHAN

ABSTRACT

The knee is the most common site of osteoarthritis (OA) and is one of the leading causes of disability in older adults affecting over 53 million people in the United States and more than 302 million people worldwide. These numbers are only expected to grow because of the rise of diseases such as obesity, demographic shifts to an older population, and a more sedentary lifestyle. The rise of obesity and a more sedentary lifestyle comes with increases in joint loading which along with the aging population creates worse outcomes in proprioception. All of which can contribute to worsening OA. Despite the great costs to quality of life and society, there is no cure for OA. Only treatments exist to treat the symptoms of OA; and since knee pain is one of the most common symptoms of OA, it is a powerful driver for treatment because of the disruptive nature it can have on quality of life. Therefore, many treatments focus on pain relief and exercise to reduce the pain and worsening of OA. Radio frequency nerve ablation (RFA) is a procedure that is increasingly being performed for those who want an alternative before resorting to or are not a good match for total knee arthroplasty (TKA). Because RFA is minimally invasive, it can be performed on an outpatient basis and has been shown to be effective in reducing pain for at least 24 months for most patients. Despite the benefits in pain

reduction, little is known about the biomechanical effects of RFA and its consequences on proprioception. However, based on prior studies into the pain relieving effects of interventions such as celecoxib or HA injections, we can hypothesize that with a decrease in pain, knee loading increases. Therefore, the pain relieving effects of RFA may increase the incidence of OA. Furthermore, because the RFA procedure involves ablating nerves that carry sensory information, changes to proprioception are expected. However, currently there is no information regarding its effect on proprioception. Again, using prior research that studies the consequences of reduced proprioception on those with OA, we can hypothesize that with RFA, proprioception would be further reduced compared to the reductions experienced by people with OA already, and it may also lead to worsening OA outcomes. Despite the possible issue of worsening OA outcomes with RFA, the pain relieving effects cannot be discounted as it is one of the most disruptive symptoms of OA. Therefore, effects of RFA on knee biomechanics and proprioception should be studied to understand the long-term impacts of this procedure.

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LIST OF ABBREVIATIONS

ACL .... Anterior Cruciate Ligament

ACR .... American College of Rheumatology

BW .... Body Weight

CBT .... Cognitive Behavioral Therapy

CI .... Confidence Interval

CRFA .... Cooled Radio Frequency Ablation

GPE .... Global Perceived Effect

GRF .... Ground Reaction Force

GROC .... Global Rating of Change

HA .... Hyaluronic Acid

ht .... Height

IMU .... Inertial Measurement Unit

JPS .... Joint Position Sense

JND .... Just Noticeable Difference

KAM .... Knee Adduction Moment

K/L .... Kellgren Lawrence

MOST .... Multicenter Osteoarthritis Study

MTP .... Metatarsophalangeal Joint

MRI .... Magnetic Resonance Imaging

NRS .... Numerical Rating Scale

NSAID .... Non-steroidal anti-inflammatory drug

OA ....Osteoarthritis

OARSI ....Osteoarthritis Research Society International

PPT .... Pain Pressure Threshold

RFA ....Radio Frequency Ablation

TKA .... Total Knee Arthroplasty

TKR .... Total Knee Replacement

US .... United States

VAS ....Visual Analog Scale

WOMAC .... Western Ontario and McMaster Universities Osteoarthritis Index

XO ....Cross-Over

INTRODUCTION

Knee Osteoarthritis

Osteoarthritis (OA) is the most common type of arthritis and is one of the leading causes of disability in older adults. It is estimated that 53 million adults in the United States who are 18 years and older and 302 million people worldwide are affected by arthritis (Hootman et al., 2017; Kolasinski et al., 2019). With an aging population in the United States, it is estimated that the prevalence of arthritis will rise from about 22.7% of all adults diagnosed with arthritis in 2010-2012 to about 25.9% of all adults diagnosed with arthritis by 2040 based on the US Census data (Hootman et al., 2017). However, when taking into account other factors such as the rise in obesity and other demographic shifts, the actual increase in prevalence of OA by 2040 may be much higher (Hootman et al., 2017).

OA leads to an increased health burden on older adults as there is an increased risk of all-cause mortality due to increased impairment of physical function and loss of quality of life (Wang et al.,2020). When modeled with an OA and Obesity simulation model, those with just knee OA lose almost 2 years in quality-adjusted life-years whereas those with both knee OA and obesity lose just over 3.5 years in quality-adjusted life-years compared to non-knee OA and non-obese people (Losina et al., 2011). OA is associated with a heavy economic burden as well. With just estimating surgical treatment options alone, OA is estimated to cost around $12 billion a year with the aggregate societal impact of absenteeism at work due to OA to cost another $10.3 billion a year (Desai et al., 2019; Kotlarz et al., 2010).

Osteoarthritis (OA) is a disease that is characterized by the damage and remodeling of the tissues of the joint such as bone and articular cartilage leading to synovial inflammation. In the past, it was thought that due to increased loads on a person's joint, it would lead to "wear and tear". This wear and tear would then eventually result in inflammation. But it is now recognized that the risk factors for developing OA are multifactorial (Abramoff and Caldera, 2020).

Now, it is understood that damage to the articular cartilage leads to the development of a persistent low-grade inflammation of the joint and the synovial capsule that projects the joint which further leads to more damage due to the slow healing nature of cartilage. This inflammation can perpetuate itself and activate more inflammation pathways and lead to more damage over time of not only the cartilage, but the bone as well; causing osteophytes or bone spurs, bone remodeling, and sclerosis to occur (Griffin and Scanzello, 2019; Sharma, 2021). On radiographic imaging, a classic sign of OA progression is joint space narrowing and the development of osteophytes, bone marrow lesions, and edema as the cartilage and bone are progressively worn away (Abramoff and Caldera, 2020). The severity of OA is commonly assessed with the Kellgren-Lawrence (K/L) grade (Kellgren and Lawrence, 1957).

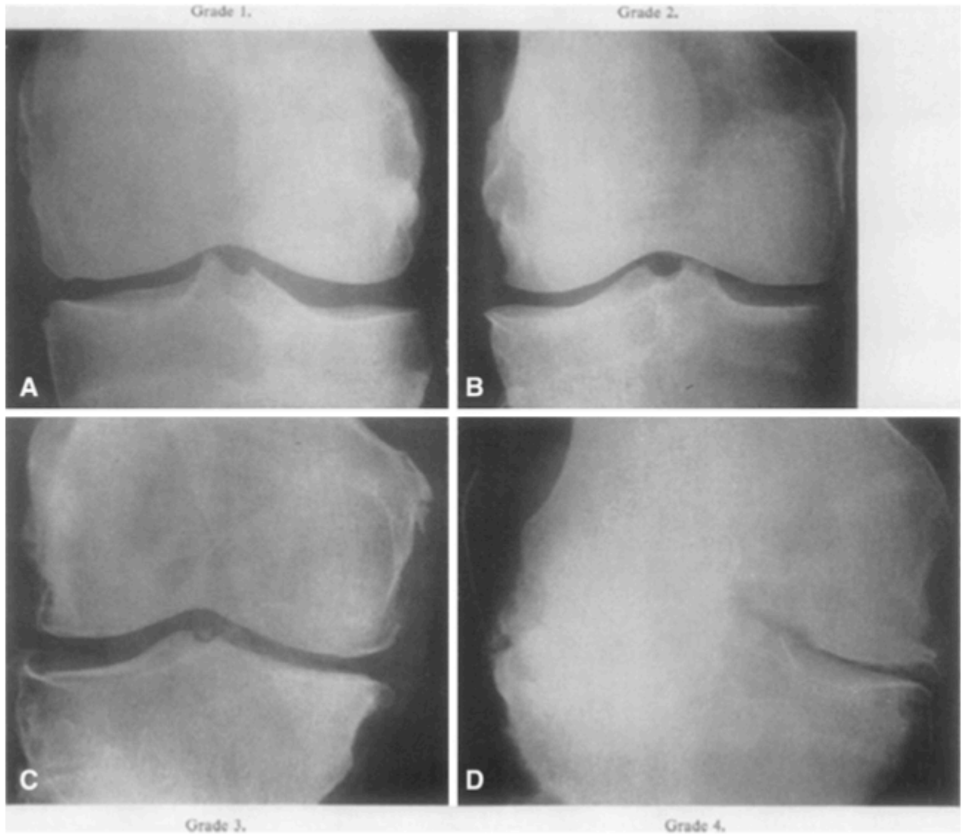

Figure 1. Radiographs of the different severities of knee OA as graded by the Kellgren Lawrence scale (as described by Kohn et al., 2016): (A) Grade 1 demonstrates doubtful narrowing of the joint space and possible osteophyte formation. (B) Grade 2 demonstrates definite joint space narrowing and definite osteophytes. (C) Grade 3 shows definite narrowing of the joint space, moderate osteophyte formation, and possible bony deformation of bony ends. (D) Grade 4 demonstrates large osteophyte formation, severe narrowing of the joint space with sclerosis, and definite deformity of the bony ends. Image reprinted from Kellgren and Lawrence, 1957.

Due to the complex nature in how OA can develop, risk factors are divided into modifiable and non-modifiable factors such as age, gender, ethnicity, genetics, obesity, past injuries, surgery, and physical activity with knees being one of the most commonly affected weight bearing joints most affected (Abramoff and Caldera, 2020; Deshpande et al., 2016).

When considering the non-modifiable risk factors, age and gender are generally the most commonly studied factors. While OA has been traditionally thought of as a condition mainly affecting the elderly, the rate of total knee replacement (TKR) has been found to be rising fastest in those younger than 60 years old (Deshpande et al., 2016). This suggests that the prevalence of OA is increasing in a younger population (Deshpande et al,. 2016; Hootman et al., 2017). OA has also been found to be 1.9. times more prevalent among women over 50 years old compared to men of the same age (Abramoff and Caldera, 2020).

When considering modifiable risk factors, obesity is a major risk factor as obese patients are about 2.96 times more likely to have OA compared to their non-obese counterparts (Abramoff and Caldera, 2020). With the rise of obesity, this factor is a hot topic of discussion as reverting our obesity levels to that of around 2002 would have prevented an estimated 110,000 TKR procedures in people between 50-84 years old by 2012 (Losina et al., 2012). OA has also been found the be more prevalent in those who perform manual labor or play high impact sports (Abramoff and Caldera, 2020). This suggests that the higher loads placed onto our joints may be increasing the risk of developing OA as well.

Presentation and Treatment of Knee OA

Knee OA is one of the most common causes of chronic knee pain (Bannuru et al., 2019). As frequent knee pain affects about 25% of adults, it is often one of the first indicators of knee OA (Nguyen et al., 2011). Stiffness, associated disability, and swelling often follow as knee OA progresses (Abramoff and Caldera, 2020). But, as OA continues to progress, the type of pain experienced and other symptoms may change and become more unstable (Abramoff and Caldera, 2020). All of these symptoms can affect the activities of daily life and lead to avoidance behaviors to try to reduce the pain and symptoms experienced (Abramoff and Caldera, 2020). Even as the symptoms progress, an interesting note is that the structural damage may not be concordant with the symptoms (Abramoff and Caldera, 2020). This means that as some people experience greater pain, swelling, and stiffness, there may not be much structural change that can be seen on imaging.

Despite its prevalence, there is no cure for OA. Currently, only treatments exist to help with symptom management. Additionally, because of the complexity in how OA may arise, there are a broad range of treatments for people with OA. To make sure that treatments have a sound scientific basis, two research bodies, the Osteoarthritis Research Society International (OARSI) and the American

College of Rheumatology (ACR) regularly release recommendations on how to treat patients with OA.

Treatments for OA tend to fit within a few categories. Non-pharmalogical lifestyle modifications are usually first recommended to help reduce the co-morbidities that are associated with OA and include activities such as increasing exercise, diet modification to lose weight, engaging in mind-body exercise such as yoga or Tai-Chi, cane use, kinesiotaping, orthoses/modified shoes, and cognitive behavioral therapy (CBT) (Bannuru et al., 2019; Kolasinski et al., 2019).

Pharmalogical treatments usually start off conservatively with topical and oral non-steroidal anti-inflammatory drugs (NSAIDs), other oral medications such as acetaminophen, or other topical medications such as capsaicin (Bannuru et al., 2019; Kolasinski et al., 2019). As OA progresses, more invasive pharmalogical management techniques are usually pursued such as intra-articular glucocorticoid injections (Bannuru et al., 2019; Kolasinski et al., 2019). Another intra-articular injection that is commonly used is the Hyaluronic acid (HA) injection. Although it is conditionally recommended against for the treatment of knee OA by the ACR (Kolasinski et al., 2019), it is conditionally recommended under the OARSI guidelines (Bannuru et al., 2019).

Finally, if the pain associated with OA is severe enough, a total knee replacement (TKR) also known as a total knee arthroplasty (TKA) can be performed to replace the joint (Aweid et al., 2018). But, due to factors such as co-morbidities and lack of social support, TKR may not be the option for extended pain relief (Desai et al., 2019). Radio frequency ablation (RFA) of the nerves is another treatment option that has recently been increasingly pursued and may be a better option for those who are not the best candidates for TKR due to its minimally invasive nature and ability to help manage pain long term (Desai et al., 2019).

Table 1. Physical, psychosocial, and mind-body approaches for hand, knee, and hip OA as recommended by the ACR. Within the groups, there is no hierarchy for treatment order. Reprinted from Kolasinski et al., 2019.

Intervention	Joint		
	Hand	Knee	Hip
Exercise			
Balance training			
Weight loss			
Self-efficacy and self-management programs			
Tai chi			
Yoga			
Cognitive behavioral therapy			
Cane			
Tibiofemoral knee braces		(Tibiofemoral)	
Patellofemoral braces		(Patellofemoral)	
Kinesiotaping	(First carpometacarpal)		
Hand orthosis	(First carpometacarpal)		
Hand orthosis	(Other joints)		
Modified shoes			
Lateral and medial wedged insoles			
Acupuncture			
Thermal interventions			
Paraffin			
Radiofrequency ablation			
Massage therapy			
Manual therapy with/without exercise			
Iontophoresis	(First carpometacarpal)		
Pulsed vibration therapy			
Transcutaneous electrical nerve stimulation			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

Table 2. Pharmalogical approaches for hand, knee, and hip OA as recommended by the ACR. Within each of the groups, there is no hierarchy for treatment order. Reprinted from Kolasinski et al., 2019.

Intervention	Joint		
	Hand	Knee	Hip
Topical nonsteroidal antiinflammatory drugs			
Topical capsaicin			
Oral nonsteroidal antiinflammatory drugs			
Intraarticular glucocorticoid injection			
Ultrasound-guided intraarticular glucocorticoid injection			
Intraarticular glucocorticoid injection compared to other injections			
Acetaminophen			
Duloxetine			
Tramadol			
Non-tramadol opioids			
Colchicine			
Fish oil			
Vitamin D			
Bisphosphonates			
Glucosamine			
Chondroitin sulfate			
Hydroxychloroquine			
Methotrexate			
Intraarticular hyaluronic acid injection	(First carpometacarpal)		
Intraarticular botulinum toxin			
Prolotherapy			
Platelet-rich plasma			
Stem cell injection			
Biologics (tumor necrosis factor inhibitors, interleukin-1 receptor antagonists)			

Strongly recommended
Conditionally recommended
Strongly recommended against
Conditionally recommended against
No recommendation

Biomechanics of OA

Because knee OA involves the degradation and remodeling of cartilage and bone (Sharma, 2021), the implications of OA are more than just pain. As OA progresses, it interferes with how patients move and perform their activities of daily life at a functional level. As summarized by van Tunen et al. (2018), people with knee OA tend to have skeletal malalignment, muscle weakness and dysfunction, impaired proprioception, and greater joint laxity. Additionally, it was found in at least 10 studies that were assessed, the knee adduction moment (KAM) was found to be elevated. The KAM is a kinematic parameter that is of great interest in lower limb biomechanics as it is used as a surrogate for medial knee loading. Since medial knee OA is the more common than lateral knee OA, KAM is important to help estimate knee loading for most patients.

There are many non-pharmalogical techniques that are used to try to reduce KAM. Knee braces are one of the modalities used to try to delay the progression of OA (Khan et al., 2019). But, the general consensus on whether or not bracing works to decrease KAM seems to be split. Some studies have observed that using a knee brace helps correct malalignment and thus helps decrease the KAM, joint loading, and pain (Cudejko et al., 2019; Lamberg et al., 2016). However, other studies have suggested that although there may be a decrease in pain, there seems to be little to no change in KAM unless other modalities such as lateral wedged shoe insoles and walking with your toes pointed outward are used simultaneously with an added risk of increased discomfort and fall risk (Khan et al., 2019). Another randomized control study reported that there may be no correlation between pain reduction and changes in KAM (Lewinson et al., 2016). Finally, a large study found that despite improvements to pain, the synovitis experienced at the joint did not change (Swaminathan et al., 2017). Meaning that although there is a consensus that knee braces may help with pain reduction, it may not reduce the progression of OA.

Proprioception

Proprioception is considered to be one of the lesser known senses and is often referred to as the "sixth sense." Despite this fact, proprioception is one of the most important senses that we use to help keep balance and maintain our posture. It also serves as our sense of body position and movement. But, as previously noted by Van Tunen et al. (2018), people with OA tend to have impaired proprioception. To help further understand the implications of proprioception, Henry and Baudry (2019) recently published a detailed review of the neural components and circuitry behind lower limb proprioception and how it changes over time with age.

Henry and Baudry (2019) explains that our proprioceptive sense arises from different structures: the muscle, tendons, joint capsule, and skin. All of these structures have special receptors called proprioceptors that identify different types of movements: Ruffini endings/Meissner corpuscles react to static joint position, Pacinian corpuscles react to joint movement and vibrations, muscle spindles detect changes in muscle length, and Golgi tendon organs detect muscle tension. All of these proprioceptors work in unison to provide information to the brain via the large and myelinated 1a and 1b afferent neurons where the information gets integrated at the spinal cord and then the brain and the efferent γ motor neurons help contract the appropriate muscles to keep us steady by countering sway around our ankles if we are standing upright. These myelinated neurons are important as they can carry large amounts of information at very fast velocities through our nervous system.

Henry and Baudry (2019) further explains that as we age, we experience a decline in motor performance and accuracy independent of OA. This is due to alterations in our proprioceptors that make them less sensitive to changes. For example, our muscle spindles, which are housed in capsules, experience capsular thickening, the spindles themselves decrease in diameter, and lose their shape. Signal integration throughout the entire central nervous system also worsens. The reduced sensitivity and reduced conduction velocity of the myelinated neurons makes it difficult to summate the signals from the proprioceptors. The brain also undergo changes that make it more difficult to automatically process this information which then increases the cognitive load. Muscles respond to these changes by increasing the muscle co-activation of agonist/antagonist pairs which increases the stiffening of the legs. All of these changes lead to increased postural instability and reduce the adaptability of our proprioception apparatus, increasing fall risk.

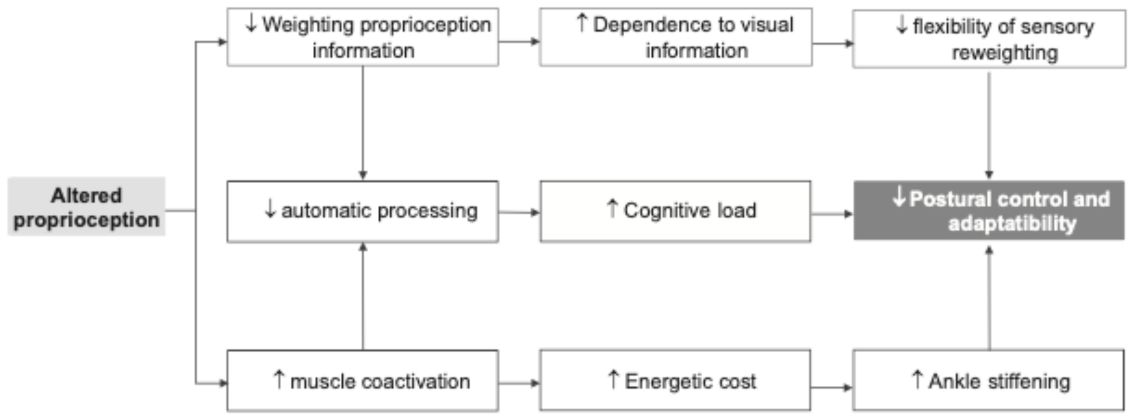

Figure 2. The proposed framework of how altered proprioception leads to a decrease in postural control and adaptability with age. Reprinted from Henry and Baudry, 2019.

Testing Proprioception

As mentioned earlier, proprioception plays an important role in posture and stability. Although as we get older and our proprioception normally becomes impaired over time, people with knee OA have even greater impairment of proprioception compared to healthy controls (Van Tunen et al. (2018). This is because we have proprioceptors such as Ruffini endings, Pacinian corpuscles, and Golgi tendon organs all through our knee joint capsule and ligaments such as the anterior cruciate ligament (ACL) (Mir et al., 2014). As proprioception is increasingly implicated as a factor in knee injury and instability, there is a lot of interest in assessing for proprioceptive deficits (Mir et al. 2014).

Currently, there are a few different ways in how proprioceptive acuity is tested. As Mir et al. (2014) describes, the joint position sense test (JPS) test uses the subject's awareness of their body to recreate a movement. In the case of knee OA, the researcher bends the subject's knee or asks them to bend it until they are told to stop with their eyes closed. Then, the subject recreates the same angle created by their knee. Another common test that is performed as described by Knoop et al. (2011) tests for the just noticeable difference (JND) of perception. With this method, the researcher slowly bends the subject's knee and the subject is supposed to let the researcher know when their knee starts to move or stop as soon as they perceive the movement. Finally, vibratory perception threshold (VPT) testing is more and more commonly used to assess proprioception for knee OA patients after Shakoor, Agarwal, and Block (2008) first used it to assess for sensory deficits in knee OA compared to healthy controls. As Shakoor et al. (2017) explains, vibratory acuity perception follows similar pathways as proprioception, so testing for vibratory acuity would also test proprioceptive acuity as well. Using a device called a biothesiometer (usually used to test for diabetic neuropathy), the investigator can apply a probe to the subject's skin and increase the vibration of the probe until the subject can perceive the vibration. This would then be repeated on other sites of the body (the wrist for example) to provide a vibratory acuity baseline point.

Figure 3. An image of a biothesiometer for use in the VPT test. The probe tip vibrates at a constant rate while the intensity of the vibration is adjusted with changing the voltage.

Despite the various tests that can be used to assess proprioception, Knoop et al. (2011) notes an important issue: each test provides information about a different perspective of proprioception. So although the intra-rater and inter-rater variability is acceptably low for the JPS, JND, and VPT tests, they cannot be compared together. There are also other variations of these tests that also make it difficult to compare results as well. For example, the JPS test has a different variation where it can be performed while weight bearing (standing) or non-weight bearing. Since standing stimulates the proprioceptors more to help with balance, weight bearing results cannot be compared with non-weight bearing results. Thus in the future, there needs to be standardized versions of these tests are essential to allow for better data comparisons and sharing.

AIMS

With OA on the rise, it is important that we learn more about the treatment options that are currently available for patients. Since, RFA is a promising treatment option that is being increasingly performed for people with knee pain that isn't responsive to other treatments, more research is needed into this procedure so that we can better understand the implications. Across many of the publications on RFA, the lack of a standardized methodology and vague descriptions makes it difficult to compare techniques and efficacies across different RFA procedure types. Also, the current literature only focuses on the pain outcomes of RFA with limited information about the biomechanical and proprioceptive effects. Therefore, to further discuss the efficacy and effects of RFA, this thesis has three aims:

1. Describe the techniques that are commonly performed when referring to RFA for knee OA.
2. Discuss what is currently known and unknown about the effects of RFA for knee OA.
3. Hypothesize the possible effects of RFA on knee biomechanics and proprioception using previously published studies.

RADIO FREQUENCY NERVE ABLATION

Radio Frequency Nerve Ablation Background

Radio Frequency Ablation (RFA) of the nerves is a minimally invasive procedure that uses radio waves to generate lesions in nociceptive nerves to halt pain signals from reaching the central nervous system (Gupta et al., 2017). It was originally developed in the 1970's as a treatment for trigeminal neuralgia but was expanded to help treat radiculopathic pain (Gupta et al., 2017). With evidence showing that RFA is effective on patients back pain for at least 12 months, it has become an option for those with painful knee OA who have not responded to other pain management options (Hunter et al., 2020) and is a better option compared to more invasive procedures that accomplish the same goals (such as selective denervation) that have been performed in the past (Dellon, 2014).

Radio Frequency Nerve Ablation Technique

The RFA procedure for genicular nerves is described in great detail by Kidd et al., (2019). RFA is usually performed in 2 basic steps. The procedure starts off with a diagnostic block where lidocaine is injected into the knee to identify the genicular nerves and verifies that the patient is a good candidate for genicular RFA. If the patient reports a pain reduction of at least 50% for the next 24 hours, the RFA is then performed by guiding a cannula with an electrode under fluoroscopy or ultrasound to the same site as the diagnostic block and the genicular nerves are ablated with minimal interruption of the surrounding tissues. Since this procedure is minimally invasive, it can be performed in an outpatient setting and patients can walk immediately after the procedure.

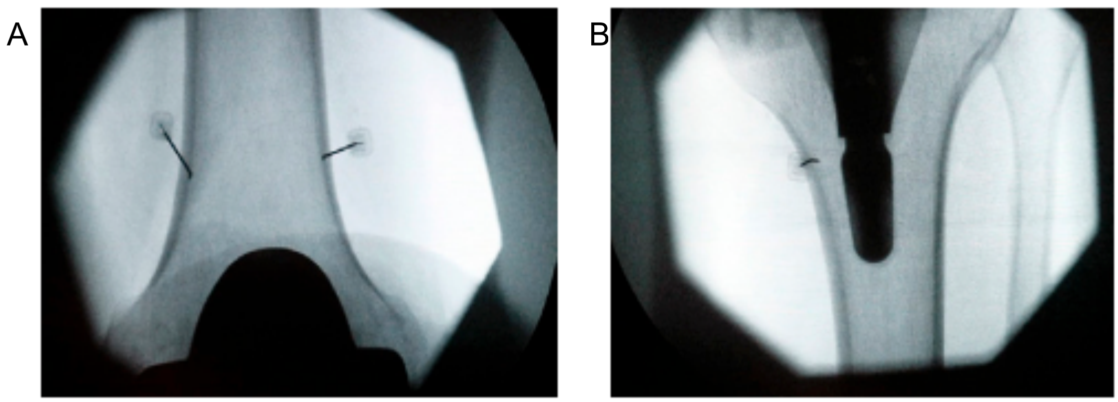

Figure 4. Fluoroscopic placement of the cannulas in a knee for genicular RFA. (A) Placement of cannulas for the superior lateral genicular nerve and superior medial genicular nerve. (B) Placement of cannula for inferior medial genicular nerve. Images reprinted from Kidd et al., 2019.

In terms of the RFA technique, there are 3 RFA techniques that are generally performed as described by Gupta et al. (2017): The conventional RFA technique (which serves as the basis for the other 2 techniques) uses a cannula with an electrode to heat up the surrounding tissue to greater than 47 ºC using radio waves. This destroys the unmyelinated nociceptive nerve fibers and generates normal scar formation a few millimeters around the electrode. If the basal lamina of the Schwann cells are preserved, there may be nerve regeneration over time which may or may not lead to recurrence of pain depending on the fiber type. The pulsed RFA technique, which was later developed in the late 1990's, uses a pulse generator to produce pulses of radio waves. This prevents the electrode from heating up the surrounding tissue as much as the conventional technique. As a result, pulsed RFA provides similar results to the conventional technique while causing less permanent damage to the surrounding tissue. Although this means that pulsed RFA provides a shorter duration of pain reduction. The cooled RFA (cRFA) technique is the third and is the newest technique where water is used to cool the electrode to allow for greater control of the temperature to the surrounding tissue. This allows better control in how the lesion is formed and can target a larger amount of neuronal tissue while allowing for greater sparing of the surrounding tissue; leading to longer pain relief compared to the conventional technique.

The innervation to the knee is highly complex. It involves many branches from the tibial, common peroneal, femoral, saphenous, and obturator nerves meeting to carry sensory information to and from the knee (Kim et al., 2016). But despite the complexity, the innervation pathways across the knee is fairly constant between people (Dellon, 2014). When deciding on which of these nerves to ablate, interventionists have to be careful which to select. Although there have been 3 case series studies involving about 200 patients receiving pulsed RFA on the femoral, saphenous, tibial, or sciatic nerves (Gupta et al., 2017), these nerves are usually considered to be too proximal to the spinal cord and has a high risk for other deficits (Dellon, 2014). More distal and smaller nerve branches serve as more ideal targets for RFA with most studies targeting the genicular nerves, the intra-articular nerves, the lateral retinacular nerve, the medial retinacular, and the infrapatellar branch of the saphenous nerve (Dellon, 2014; Gupta et al., 2017). Since RFA is typically performed under fluoroscopy, visualization of the actual nerves is impossible. Therefore, the genicular nerves (superior lateral genicular nerve, superior medial genicular nerve, and inferior medial genicular nerve) are by far the most common target for RFA due to their proximity to easily identifiable bony landmarks and is considered the standard when performing RFA (Kidd et al., 2019).

Table 3. Nerve innervation within and around the knee joint. Reprinted from Dellon, 2014

TIBIOFEMORAL
CUTANEOUS: (from anterolateral to medial, then posterior)
lateral femoral cutaneous
anterior femoral cutaneous
medial cutaneous nerve of the thigh
infrapatellar branch of saphenous nerve
posterior femoral cutaneous nerve
JOINT: (from anterolateral to medial, then posterior)
lateral retinacular nerve
terminal branch of innervation of vastus intermedius
medial retinacular nerve
popliteal plexus from sciatic nerve
PATELLOFEMORAL
lateral retinacular nerve
terminal branch of innervation of vastus intermedius
medial retinacular nerve
PROXIMAL TIBIOFIBULAR
recurrent genicular branch of common peroneal nerve

Knee pain after RFA

The RFA procedure has been shown to be a cost-effective, safe, and minimally invasive procedure for knee OA patients who may not be the right candidate for TKA (Chen et al., 2020; Desai et al., 2019; Kidd et al., 2019). However, more needs to be learned about the effect of RFA on long term knee pain. While there are a few articles that describe the analgesic effects of RFA up to 12 months, there is only one paper that has followed up with RFA patients after 12 months (Hunter et al., 2020). This combined with differing methodologies between investigations makes it difficult to draw equal comparisons between groups (Gupta et al., 2017). Also, while the genicular nerves are a common target in most published studies, there are more nerves that provide pain innervation to the knee that can also be targeted, further complicating the comparisons made between studies (Chen et al., 2020; Davis et al., 2018; Gupta et al. 2017).

Despite these challenges, RFA is consistently shown to provide pain relief in knee OA patients. According to Iannaccone, Dixon, and Kaufman (2017), using a retrospective chart review, genicular nerve RFA significantly reduced knee pain by an average of 67% by patients who reported relief at 6 months using a visual analog scale (VAS). But, only 52% of patients experienced relief of over 50% by 6 months. Davis et al. (2018) reported a higher efficacy of pain relief using CRFA compared to intra-articular steroid injections. After 6 months, 74.1% of subjects reported at least 50% reduction of knee pain compared to 16.2% of those who received an intra-articular steroid injection.

Hunter et al. (2019) continued following up with the subjects of Davis et al. (2018) and reported that knee pain remained improved through 24 months. Using the numerical rating scale (NRS), knee pain reduced from an average of 6.6 to 3.6. Hunter et al. (2019) also reported that according to the global perceived effect (GPE) scale (used to compare a treatment from one time point to a previous time point), 80% of subjects reported improvement at 18 months and 66.7% of subjects continued to report improvement in their chronic pain after 24 months.

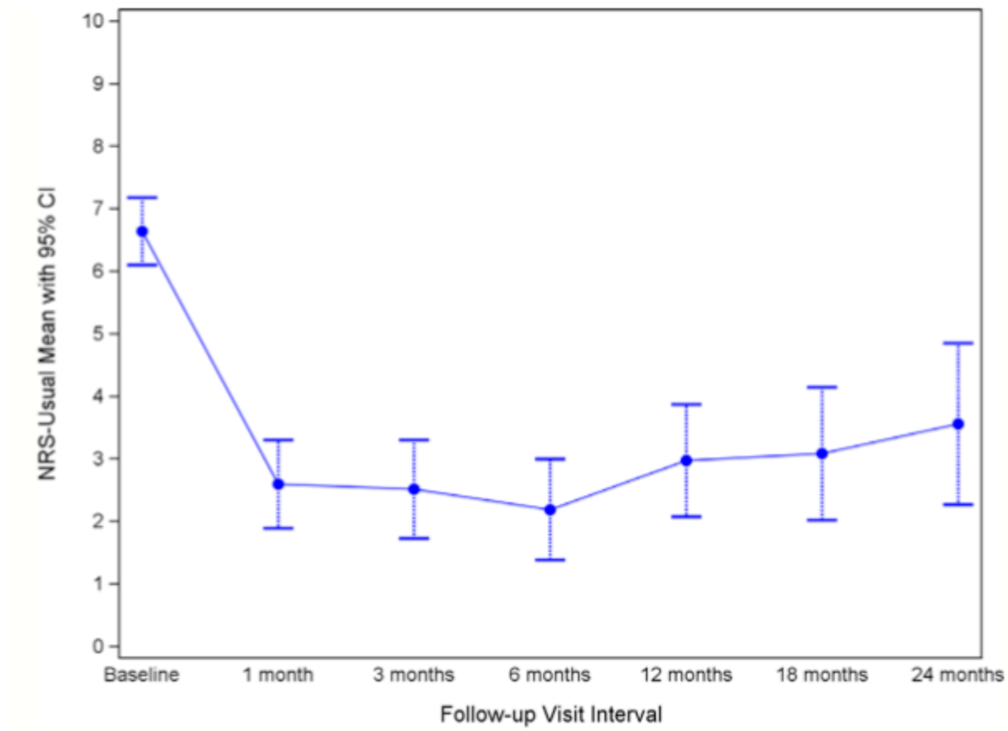

Figure 5. Knee pain on the NRS scale with 95% confidence intervals (CI) over 24 months. Reprinted from Hunter et al., 2019.

Chen et al. (2020) is another study that reports RFA data up to 12 months post procedure. Like Davis et al. (2018), Chen et al. compared CRFA to another intra-articular procedure, hyaluronic acid (HA), rather than intra-articular steroids. Chen et al. (2020) also allowed for subjects randomized to the HA group to cross over to receive the cooled RFA procedure at 6 months. After 12 months 65.2% of subjects reported pain relief of over 50% at 12 months and NRS scores decreased around 4 points as well, which closely matches previously reported data from Davis et al. (2019). Chen et al. (2020) also reports improvements on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale (a tool used to rate pain and functional ability) above the minimum change for clinical improvement. Chen et al. also reports that CRFA consistently provided greater pain relief compared to HA injections at across all time points and when those who crossed over from HA to cooled RFA, there was a significant improvement in pain reduction as well.

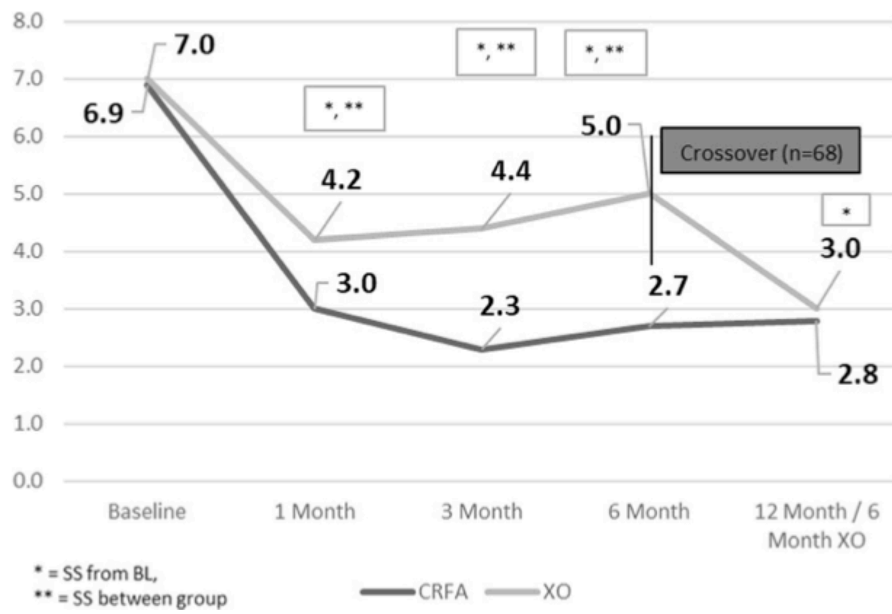

Figure 6. NRS scores from those who received CRFA compared to those wo received HA injections and then crossed over (XO) into the CRFA group at 6 months. Reprinted from Chen et al., 2020

With studies showing that RFA is an effective technique to help with pain management, there are other factors that we still do not know about RFA such as its consequences with knee loading and proprioception. While it is important to understand the role of pain in knee OA, it is only a symptom of the pathogenesis of OA.

CURRENT GAPS IN KNOWLEDGE WITH RFA

Pain Reduction and Biomechanics

Although many studies have shown that RFA is highly efficacious in reducing pain for people with knee OA, pain reduction itself may not reduce the progression of OA. There is evidence that reducing pain may lead to continuing maladaptive adaptations now that pain has been reduced (Orishimo et al., 2012; Debbi et al., 2015; Dixon et al., 2018). Thus, more research is needed into the biomechanics of people who receive RFA so that we could better understand the other components of OA rather than just the effects on pain. With this information, we can include other modalities to help fix the adaptations.

At the present time, there is currently only one study that has studied the effects of RFA on biomechanics which (Lebleu et al., 2020). Although Lebleu et al. (2020) reported an improvement in hip range of motion, knee pain reduction, and stair climbing with no significant changes to gait, this study is difficult to compare to previous studies because the physicians ablated 5 nerves (the recurrent fibular nerve and the infrapatellar branch of the saphenous nerve in addition to the genicular nerves) instead of the typical 3 that is commonly performed as previously noted. Another issue for this study was that the gait and stair climbing tasks were performed only an hour after the procedure, making it difficult to rule out the effects of the lidocaine that was used to numb the skin and surrounding soft tissue performed prior to ablation. Finally, only inertial measurement unit (IMU) data was collected, so kinematic data interpretation is limited since only joint angles and velocities were reported and data on joint loading (e.g., KAM) is not reported.

Using other studies conducted previously, there is a body of evidence that shows that with pain reduction, there may be an increase in loading on the lower extremities while performing some activities. Schrader et al. (2004) reported that with intra-articular corticosteroid injections, although there is a significant decrease in pain on the knee, that there is an increase in loading on the hip and knee after injection. While this improved gait mechanics by increasing the walking velocity and cadence, KAM was significantly increased while walking. In terms of moving up stairs, there was no difference in the hip and knee kinematics pre injection compared to after the injection and the joint angles exhibited were significantly less than healthy controls.

Another study, Henriksen et al. (2006) isolated the effects of pain on biomechanics by using intra-articular lidocaine injections to effectively eliminate pain. As expected, the lidocaine eliminated most of the knee pain in subjects. But, there were shifts during the later stages of gait that increased loading on the knee. Despite a reduction in extensor moments which are usually indicative of decreased loading of the knee, the investigators hypothesized that the increased flexor moments as a result of antagonistic muscle activity compensation or increased reaction forces that created a net increase in loading in the medial compartment of the knee despite KAM experiencing non-significant changes. Compared to the previous study and others, this study is unique in that with lidocaine use, it was possible to isolate the effects of abolishing pain practically completely without other confounding effects of other medications such as the anti-inflammatory effects of corticosteroids or NSAIDS. Conversely, it is this fact that makes it difficult to generalize to a larger population because the medications that are typically prescribed for pain reduction are not as efficacious in pain reduction as lidocaine in addition to the other side effects. As Henrickson et al. (2006) compared their results to previous studies, they found that lidocaine combined with a steroid yielded no changes to extensor moments but increased KAM. Meaning that with the abolishment of pain combined with steroids increased joint loading.

In 2004, Detrembleur et al. performed one of the first double blind studies to investigate the effects of NSAIDs on gait. Using celecoxib, an NSAID that had shown efficacy in reducing pain, they conducted gait trials using a crossover method that had subjects randomly switched from a treatment or placebo group into either subsequent treatment or placebo group again. This study helped establish that celecoxib had clinical efficacy by reducing pain and was shown to increase velocity, cadence, and recovery. Using a locomotor mechanism model to describe the effects of celecoxib, Detrembleur et al. (2004) noted that there was an increased efficiency to how the patients walked. By decreasing knee pain, it allowed the knee to increase stiffness by stretching out the elastic components of muscle. This created a better spring for the body to increase velocity and cadence to a more optimal step frequency as defined by the locomotor model.

While increasing walking velocity and cadence may make OA patients more efficient in matching healthy controls, joint loading still plays an important role in the development of OA. Boyer et al. (2012) conducted a single blinded crossover with washout comparison between celecoxib and oxycodone to isolate the anti-inflammation effects of NSAIDs. Matching Detrembleur et al. (2004), all of the subjects had a faster cadence and velocity with a decrease in pain. It also was found that anti-inflammation plays a role in worsening OA as when the subjects who were on celecoxib experienced higher KAM and ground reaction forces (GRF) compared to when they were on oxycodone which did not experience a significant change in GRF. Also it was found that the groups who were on oxycodone had a different gait pattern compared to those on celecoxib. Despite both groups of subjects experiencing increased gait velocity, those on oxycodone had a smaller step length than those on celecoxib whose faster cadence accounted for the increase in velocity. These changes suggest that the alterations in gait for those with OA may be adaptations to prevent joint pain.

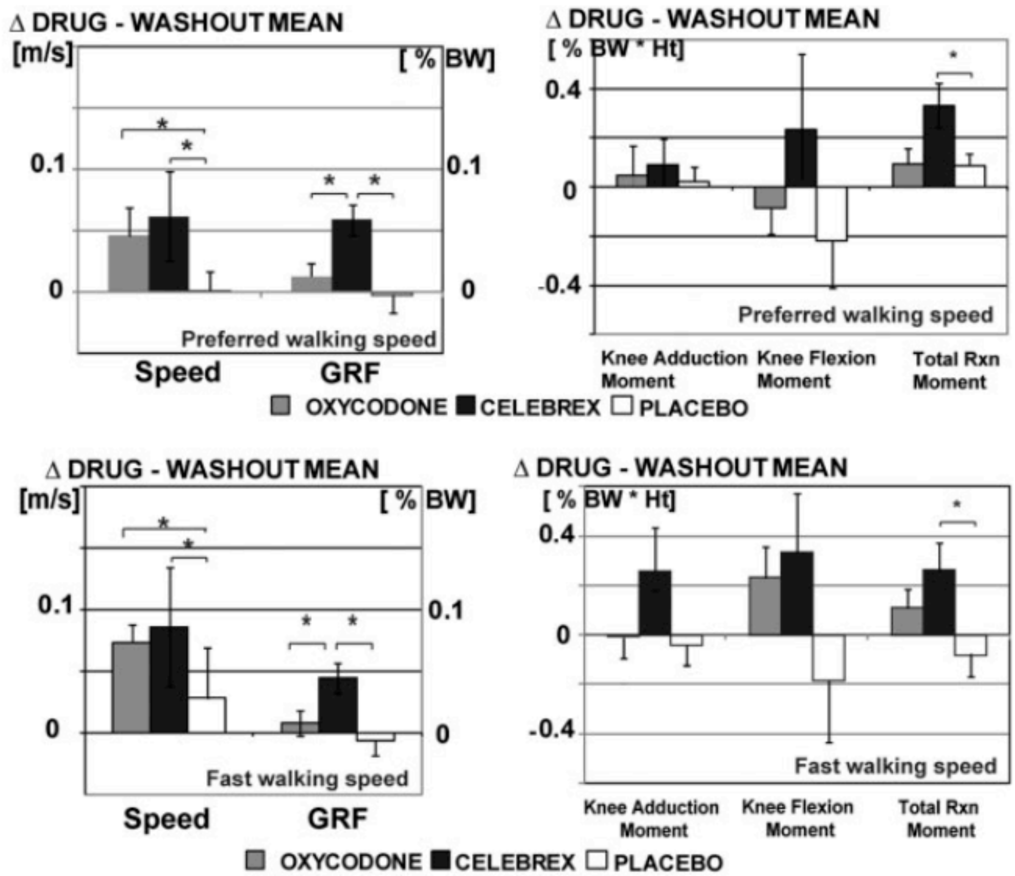

Figure 7. Changes in gait functional outcome measures (left) and joint kinetics (right) at preferred walking speed and a fast walking speed. Reprinted from Boyer et al., 2012.

The relationship between pain and biomechanics has also been studied with hyaluronic acid intra-articular injections. Briem, Axe, and Snyder-Mackler (2009) studied the effects of intra-articular HA injections in OA patients over 6 months. During those 6 months, they separated the subjects into those who responded well (had reduced pain of over 20% and/or functional ability improvements over 20% on the KOOS subscale) to the HA injections and those who did not (pain or functional ability did not change or changes were less than

20% on the KOOS subscale). After performing gait analyses on all of the subjects, it was found that those who responded well to HA injections had an increased KAM and increased muscle co-contraction on the medial side whereas those who did not respond well to HA injections had no significant changes to KAM. This suggests that those who have a decrease in pain may experience more rapid joint deterioration than those who don't.

Finally, the effects of HA injections in biomechanics were again studied again with Tang et al. (2015). HA injections were performed on OA patients and were assessed up to 6 months post injections and compared to healthy controls. At baseline, the OA group walked with a slower velocity and shorter step length and increased KAM compared to the controls. After injection, the OA group showed significantly improved walking speed and step lengths which persisted through the 6 month period. But it was found that KAM further increased significantly over 3 months which then persisted through 6 month period. Again, showing that decreased knee pain leading to increased loading on the knee.

When considering the effects of RFA on pain relief. It seems that there is the high likelihood that ablation of the sensory nerves will lead to a worsening in joint loading. This is supported across all of the studies discussed. Although there were a variety of methodological differences that made them difficult to compare equally, the main outcomes of each papers reported similar findings:

when steps are taken to reduce knee pain in knee OA patients, they tended to have walking parameters that trended toward healthy non OA subjects; these subjects tended to consistently have a faster gait and better cadence. But conversely, there tended to be an increase in joint loading especially if there were steps taken to reduce inflammation. This leads to the idea that was discussed in Boyer et al. (2012) where adaptations to gait when walking on a painful knee may serve a protective purpose to prevent more pain. This idea is consistent with the selective denervation procedures performed and explained on Dellon (2014) where he mentions that selective denervation should only be performed on a stable knee and is contraindicated on unstable knees where denervation could lead to an increased likelihood of falling.

Proprioception Deficits and Biomechanics

Although there currently are no studies specifically involving proprioception and strategies used to reduce pain such as with intra-articular steroids, we can hypothesize what could possibly happen after the RFA procedure based on prior studies dealing with proprioception since RFA deals with ablating sensory nerves that also carry proprioceptive information.

In 2011, Knoop et al. performed a literature review of proprioception in knee osteoarthritis as there had been no recent review of the effects of proprioception on those with knee osteoarthritis. After reviewing 75 studies, it was found that that proprioception plays more of a role than just posture and balance. It also performs functions such as protecting the knee from excessive movements via reflex responses and coordination of complex knee movements. It was also found that there were two basic types of measures used to measure proprioception, there were many variations between them that makes comparisons between methodologies difficult as described above. Another finding is that due to changes in our muscles in OA, it may affect our muscle spindles. For example, muscle atrophy usually led to impaired proprioceptive accuracy. Although it was also found that impaired position sense was found to be not affected by muscle atrophy, this makes sense as position sense is usually detected by different proprioceptors. Finally it was found that proprioception impairment is consistently worse in those with OA compared to healthy controls. It is also a risk factor for worsening OA rather than being one of the factors that lead to its onset.

Felson et al. (2009) conducted one of the first longitudinal studies on proprioception using the Multicenter Osteoarthritis Study (MOST), a large and prospective epidemiological study of people who were at risk or have OA. The goal of MOST is to identify risk factors that lead to OA. Felson et al. assessed 2243 subjects in two major US cities to determine whether or not there was a correlation with loss of proprioceptive acuity and radiographic OA. Proprioception was assessed with a JPS test where the subjects were told to slowly extend their leg from a seated position to a randomly predetermined angle. The subject was to reproduce this angle and other randomly predetermined angles. It was found that over the course of 30 months, there was no correlation between proprioceptive acuity and radiographic OA. But, there was a significant decrease in WOMAC pain and functional ability/physical function scores. Those who had better proprioceptive acuity also experienced a decrease in WOMAC scores as well, but to a lesser degree than the worse quartile.

As mentioned previously, Shakoor, Agarwal, and Block (2008) conducted one of the first studies to assess proprioceptive acuity with VPT testing. Because more traditional proprioception measurements can be confounded by other factors such as patient memory, reaction time, concentration, and joint pain (Shakoor, Agarwal, and Block, 2008), Shakoor, Agarwal, and Block sought for another modality to help assess sensory deficits to also assess for proprioceptive acuity as well. In a comparison between OA subjects matched with controls, it was found that across all 5 testing sites all over the body, the VPT was significantly increased (higher strength of vibration needed to perceive the vibration sensation) in those with OA compared to the normal controls. Because vibratory sense is believed to also travel through the same Type 1a and 1b nerve fibers as proprioception, VPT can be reliable measure to measure proprioception while eliminating the other confounding factors as previously mentioned.

Shakoor et al. (2012) further went on to study how sensory and proprioceptive acuity is related to gait. Again, Shakoor et al. used VPT testing on 58 subjects, of whom 31 also underwent gait analysis. As expected, those who experienced worse VPT scores tended to have worse OA. Interestingly, out of the 5 sites tested on the body, the lack of sensitivity in the metatarsophalangeal joint (MTP) was most correlated with an increased KAM and a higher K/L grade. To explain this, it was hypothesized that the MTP joint would be the most sensitive to medial knee loading changes because it is the closest assessed site that makes contact to the ground, and therefore experiences the full load of the body. Furthermore, not only was there worse VPT acuity across the whole body, there was a direct relationship between a higher K/L grade and worse sensory acuity as assessed by VPT testing at the MTP as well. To explain this, Shakoor et al. suggested that the sensory deficits may be a sign of a greater systemic nervous system involvement rather than just local damage leading to pain. This study is unique in that it also showed a correlation between proprioception and radiographic OA changes as assessed by the K/L grade which was not seen in Felson et al. (2009) But conversely showed no correlation between proprioception and pain which again was not seen in Felson et al. (2009). Which only shows that there is more that needs to be learned to fully understand the connection between sensory acuity, pain, and structural changes.

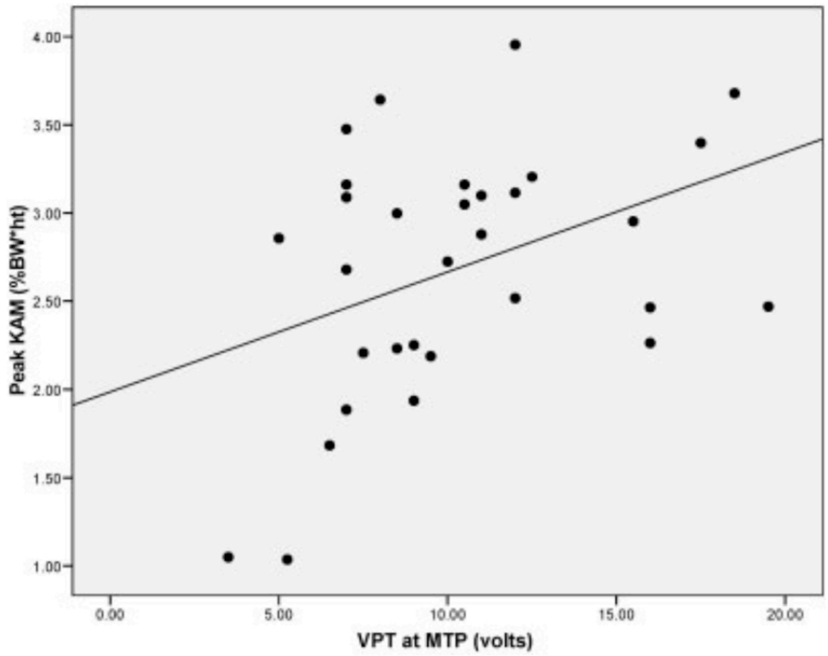

Figure 8. Relationship between the VPT at the MTP of the OA leg expressed in volts and Peak KAM adjusted as percent body weight (BW) times height (ht). Reprinted from Shakoor et al., 2012.

In a larger study involving VPT testing, Shakoor et al. (2017) assessed the relationship between VPT and quadriceps muscle strength in the MOST study. Since the MOST study started asking questionnaires about knee stability at the 60 month visit and subsequent visits, this visit served as the baseline and follow up visits for sensory testing. VPT and quadriceps muscle strength was assessed in 1803 MOST study subjects at the 60 month visit and questionnaires about knee instability were completed. The questionnaires were designed to assess multiple aspects of knee instability such as knee buckling and slipping/shifting and worsening sensations of slipping and buckling over time. The stability questions were asked again in the subject's 72 month and 84 month visits. After completing all of the assessments, it was found that those who had worse vibratory acuity were sensitive to incident and worsening knee buckling specifically rather than worsening instability. Meaning that there is a potential mechanical implication related to the loss of sensory information. It was also found that those with reduced quadriceps muscle strength had worse VPT acuity. Worse quadriceps strength was also associated with greater incidence and worsening knee slipping without knee buckling. In those who had greater quadriceps strength, it was found that there may be a protective effect against knee instability and worsening instability symptoms. These results were as expected and matches with prior literature as worse muscle strength and proprioception can have reduced confidence and functional ability and increased the risk of falling (Knoop et al. 2011; Knoop et al. 2012). Also, since neuromuscular factors play a large role in knee stability, impacts in sensory acuity can have a major role in knee instability (Shakoor et al., 2017).

Again, as mentioned by Shakoor, Agarwal, and Block (2008), proprioception follows the same neuronal pathways as vibratory acuity. So to test for proprioception, vibratory acuity can be used as a surrogate measure. But, somatosensory alterations doesn't just refer to proprioception and vibratory perception, it is a broad term to include other senses as well such as nociception (Dua et al. 2018). As found by Shakoor, Agarwal, and Block (2008) and again in Shakoor et al (2012), those with OA experienced worse VPT scores across all of the sites assessed, meaning that there are body-wide somatosensory deficits rather than deficits localized to the knee. Therefore, to better understand how the worsening in somatosensory acuity relates to proprioceptive acuity, we must further understand somatosensory acuity in general.

Dua et al. (2018) notes a “contradiction” in somatosensory alterations where decreased sensory functions such as proprioception and vibratory acuity are accompanied by an increased sensitivity to other sensations such as pressure and pain. In order to study this “contradiction,” Dua et al. (2018) sought to investigate the relationship between somatosensory alterations and pain perception. Subjects with OA and healthy controls were recruited and tested for different types of pain in addition to VPT. To measure allodynia (experience of pain from a stimulus that is not normally painful), Von Frey monofilaments of different pressures were applied onto different points of the body. Since the filaments are fairly pliable, if the subject experienced pain with the filament, there was the presence of allodynia. Pain pressure detection threshold (PPT) was also tested to measure the pressure required to experience a change of sensation from pressure to pain. Compared to the controls, more OA subjects experienced more allodynia, experienced worse PPT thresholds and experienced more bouts of spontaneous pain. Those lower PPT thresholds also correlated to worse VPT testing at the same sites. VPT threshold was also worse in multiple sites in OA subjects who had allodynia compared to other OA subjects who did not experience allodynia. As shown by these results, poorer sensory acuity was associated with higher pain sensitivity.

After RFA, deficits in proprioception are expected because the procedure involves ablating sensory nerves. Since ablation of the genicular nerves removes the input from about 3 out of the 11-13 sensory nerves that innervates the knee joint capsule, this does not completely suppress proprioception (Lebleu et al., 2020). But, as shown in this section, reductions in proprioception are not innocuous as it can lead to further worsening OA (Knoop et al. 2011), increased loading at the knee (Shakoor et al., 2012), increased pain and worsening functional ability (Felson et al. 2009), altered neuromuscular factors such as muscle weakening and atrophy leading to knee instability (Knoop et al., 2011; Shakoor et al., 2017) and altered muscle co-contraction (Henry Baudry, 2019) and systemic sensitization to pain (Dua et al. 2018). This is in addition to the already reduced proprioception experienced by people with OA (Shakoor, Agarwal, Block, 2008).

CONCLUSION

RFA seems to be a promising procedure that can possibly be a non-invasive alternative to those who do not qualify for TKA, but more needs to be learned before it becomes a common-place procedure such as intra-articular injections and joint replacement.

It is highly effective in reducing pain in those with knee OA and can provide higher amounts of pain relief and improved functional capacity compared to other options such as HA and corticosteroid injections (Davis et al., 2018; Chen et al., 2020). RFA is also capable of providing long term pain relief over the course of at least 24 months (Hunter et al., 2019). The RFA procedure in itself is also considered to be safe as there have been only a small number of complications reported after the procedure if there were any complications at all (Iannaccone, Dixon, Kaufman, 2017; Davis et al., 2018).

Although it has been shown that RFA is highly efficacious in pain reduction, we do not currently know much about the biomechanical effects of RFA. Although there is currently one study that measures the biomechanical effects of RFA (Lebleu et al. 2020), its study design makes it difficult to compare with more popular RFA techniques and it does not include measures of knee loading. Thus as shown with other studies that study the relationship between pain and biomechanics, pain reduction with RFA may lead to worsening knee loading (Schrader et al., 2004; Henriksen et al., 2006; Detrembleur et al. 2005; Boyer et al., 2012; Briem et al., 2009; Tang et al., 2015). Therefore, with the pain reduction shown with RFA may lead to worsening OA later in life.

Finally, as the RFA procedure ablates a few of the sensory nerves of the knee capsule (Lebleu et al., 2020), there are consequences that must be considered in terms of proprioception. Since people with knee OA already have systemically reduced proprioception compared to age matched controls (Shakoor, Agarwal, and Block, 2008), reducing proprioception even more can affect more than just the balance and posture alterations (Henry and Baudry, 2019) of age related proprioception decline. With further reductions of proprioception, there may be a decline in functional ability and worsening pain (Felson et al. 2009), an increase in knee loading which can lead to knee instability (Shakoor et al, 2017), and an increase in pain sensitization which can lead to allodynia (Dua et al., 2018).

Future Directions

The next steps that need to be done in this field is to assess the biomechanical effects of RFA. As mentioned previously, Lebleu et al. (2020) ablated two more nerves than how it has been more popularly performed (Kidd et al. 2019) and assessed the biomechanics of their subjects before and only 1 hour post procedure. In order to test the more long term biomechanical effects of RFA, we can have the subject assessed a few weeks after their RFA instead of 1 hour post-procedure and allow them to become more accustomed to the change in pain. That way, we can have a better picture of the adaptations that occur on knee loading and reduced pain and we can ensure enough time has passed for washout of the diagnostic block or cutaneous block (as performed by Lebleu et al.). Despite walking and stair climbing being important activities that we perform every day, we perform a wider variety of movements that were not assessed by Lebleu et al. More activities such as sit-to-stand, squatting, and balance activities can be assessed to gather a wider picture on what changes biomechanically and sensory testing such as the JPS and VPT test can be performed to further elucidate what happens to joint proprioception after ablation since our joints are richly innervated (Jerosch et al. 1993).

If the biomechanical results of RFA are as what is predicted, it should not eliminate RFA as a treatment option. Since knee pain is the most common reason as to why people opt for a TKA among people with OA (Nguyen et al. 2011), we cannot ignore the pain relieving benefits of RFA. What now can be done is combining other treatment modalities with RFA to try to reduce knee loading and improve proprioception. Gait modification strategies such as such as “medializing” the knee (try to walk in a fashion that reduces medial knee loading), avoiding contralateral pelvic drop, and changing the toe angle are effective strategies that can be trained to help reduce KAM (Boswell et al. 2020). These strategies are most effective when personalized for the subject (Boswell et al. 2020). As mentioned before, Khan et al. (2019) found that there was a significant decrease in loading if subjects combined walking with their toes out and a lateral shoe wedge together. But the main issue with combining these modalities was that it was fairly uncomfortable for their participants. Since RFA would help reduce the pain, it may be more comfortable for knee OA subjects combine these two modalities or a combination of others to help decrease KAM. Proprioception can be improved mainly through exercise. Exercise activities that involve the use of proprioception and weight bearing muscle strengthening exercises have been shown to improve proprioception as well as help with pain management (Knoop et al., 2011). Kinesio taping for knee OA in general was also found to improve proprioception and range of motion especially if proper tension can be achieved on the quadriceps (Cho et al. 2015). Tai chi was found to also be a good option to improve neuromuscular control and proprioception since it requires a very heavy focus on body position and movement (Wang et al. 2013). With the previously mentioned strategies, we can help mitigate the possible issues that may come up with the RFA procedure. But a lot more research needs to be performed even before we reach this step.

LIST OF JOURNAL ABBREVIATIONS

Ann Intern Med ....Annals of Internal Medicine

Arthritis Care Res .... Arthritis Care & Research

Arthritis Rheum.. Arthritis & Rheumatology

BMC Musculoskelet Disord .... BioMed Central Musculoskeletal Disorders

Clin Exp Rheumatol............................... Clinical and Experimental Rheumatology

J Orthop Res .... Journal of Orthopaedic Research

J Orthop Surg .... Journal of Orthopaedic Surgery

J Phys Ther Sci ....Journal of Physical Therapy Science

JBJS Essential Surgical Techniques

..........................Journal of Bone & Joint Surgery, Essential Surgical Techniques

Knee Surg, Sports traumatol, Arthroscopy

.... Knee Surgery, Sports Traumatology, Arthroscopy

N Engl J Med .... New England Journal of Medicine

Orthop Muscul Syst .... Orthopedic & Muscular System: Current Research

Pain Pract ....Pain Practice

Prosthet Orthot Int ....Prosthetics and Orthotics International

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CURRICULUM VITAE

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