

# Assessment of Central Sensitization using Pain Pressure Threshold and Its Association with Disability and Quality of Life in Patients with Knee Osteoarthritis

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**Background & methods:** Osteoarthritis (OA) is associated with increased pain, disability, and functional limitations. The chronic pain processing in OA could be associated with pathophysiological condition called “central sensitization”. Our study objectives were to compare PPT (Pressure pain threshold) in OA patients and in age sex matched healthy individuals and correlating their PPT with pain sensitivity and quality of life. Study design was Crosssectional observational comparative study. 35 participants in each group were included & Assessed for PPT measurements using sphygmomanometer cuff algometry at dermatomes, myotomes, sclerotomes around knee. Pain intensity was assessed by NRS, QOL life by KOOS (KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE) . **Results & conclusions:** PPT values were significantly lower in the knee OA patients versus the healthy controls ( $P < 0.001$ ). Similar PPT values of Dermatomal, Myotomal & Sclerotomal structures between all diseased knees i.e.in bilaterally affected as well as unilateral OA patients i.e. there is presence of hyperalgesia in knee OA patients. Suggestive of central sensitization mediated hyperalgesia. There was an inverse relationship of pain intensity with PPT values in knee OA group and no relationship of QOL with PPT values in knee OA group.

**Keywords:** (Maximum Five): Knee osteoarthritis, Dermatome, Myotome, Sclerotome, Pain pressure threshold

## 1. Introduction

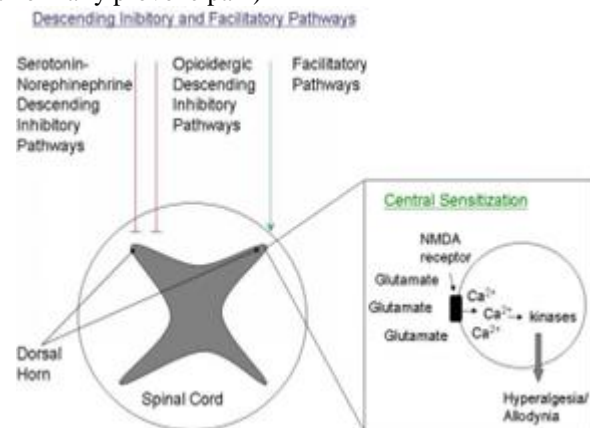
Osteoarthritis (OA) is the most common form of arthritis. Symptomatic knee osteoarthritis (OA) is a condition commonly associated with increased pain, disability, and functional limitations.<sup>(6,12,22)</sup> Osteoarthritis is the second most common rheumatologic problem and Incidences of OA in India has been reported to 22% with people falling more in age group of above 45 years.[WHO report 2002].

The understanding of pain in OA and of its modulation and treatment is important to physical therapist practice, as physical therapists usually manage patients affected by this disease. Although pain is a very common complaint in people with OA, pain severity and the unclear relationship between pain and structural damage have raised the issue of the existence of other mechanisms responsible for the pain in OA. The concepts of peripheral and central sensitization as they relate to knee OA pain<sup>(6, 13)</sup>

Recently, it has been recognized that constant and intense nociceptive sensory information, generated by painful and inflamed deep somatic structures, produces significant neurochemical and metabolic changes, as well as neurologic reorganization within spinal cord segments<sup>(6, 20)</sup>. These changes include an increased excitability of dorsal horn neurons, which in turn produces pain hypersensitivity in segmental distribution. This increased excitability is also known as central sensitization, and both it and peripheral sensitization cause neurons to respond to stimuli in a more intense fashion.<sup>(19, 16)</sup>

## Descending pain pathways and central sensitization:

Descending pain pathways and central sensitization modulate the pain response in the dorsal horn of the spinal cord. Descending analgesic pathways include the serotonin-norepinephrine and opioidergic descending pathways, which dampen pain sensitivity response. Loss of descending analgesia leads to hyperalgesia and allodynia. Central sensitization occurs through the action of glutamate on the N-methyl-D-aspartate (NMDA) receptor, resulting in an increase in intracellular calcium levels and kinase activation, leading to hyperalgesia (abnormally heightened sensitivity to pain and allodynia (triggering of a pain response from stimuli which do not normally provoke pain)



Recent evidence on the role of central sensitization plays in OA pain comes from a study by Graven-Nielsen et al, who conducted a protocol of pain assessment measuring pressure pain threshold(PPT) in people with knee OA. Widespread

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hyperesthesia, enhanced spatial summation, and loss of conditioned pain modulation were observed, which imply sensitized central pain mechanisms in these patients<sup>(6,12)</sup>

Traditional rehabilitation treatments for OA typically are directed to the periphery (i.e., joint and surrounding structures) through interventions such as joint injections, joint protection, analgesic medication, manual therapy, exercise, or transcutaneous electrical nerve stimulation.

Interventions such as cognitive-behavioural therapy and neuroscience education potentially target cognitive-emotional sensitization (and descending facilitation), and exercise therapy can improve endogenous analgesia (descending inhibition) in patients with osteoarthritis.

There for the accurate and appropriate rehabilitation programme will reduce the treatment time and will improve quality of life of these patients.<sup>(7,18)</sup>

## 2. Literature Survey

### 1) **Padmaja Durga<sup>1</sup>, Sreedhar Reddy Wudaru 2016**

Validation of simple and inexpensive algometry using sphygmomanometer cuff and neuromuscular junction monitor with standardized laboratory algometer. There was a good inter-rater reliability ( $\alpha > 0.7$ ) for the three techniques. There was a good correlation with  $r > 0.65$  ( $P < 0.001$ ) between the measurements of standardized pressure algometer and the two techniques being tested as alternatives for algometer to measure pain. The sphygmomanometer cuff technique and electrical stimulation with the peripheral nerve stimulator to measure pain threshold and tolerance provide a simple, efficient, repeatable measure of pain intensity and can be used as suitable alternatives to standard algometers.

### 2) **Ewa M. Roosand Sören Toksvig-Larsen 2016**

Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement.

The Knee injury and Osteoarthritis Outcome Score (KOOS) is a valid, reliable, and responsive outcome measure in total joint replacement. In comparison to the WOMAC, the KOOS improved validity and may be at least as responsive as the WOMAC.

### 3) **Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J Towheed T, Welch V, Wells G, Tugwell P et al 2012**

Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee.

These recommendations are based on the consensus judgment of clinical experts from a wide range of disciplines, informed by available evidence, balancing the benefits and harms of both nonpharmacologic and pharmacologic modalities, and incorporating their preferences and values. It is hoped that these recommendations will be utilized by health care providers involved in the management of patients with OA.

### 4) **Graven-Nielsen T, Wodehouse T et al 2012**

Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement.

PPTs at the knee and at sites away from the knee were reduced in OA patients as compared with healthy pain-free control subjects ( $P < 0.0001$ ). Cuff PPTs were decreased in OA patients as compared with the healthy controls ( $P < 0.05$ ), who also exhibited a greater degree of spatial summation ( $P < 0.05$ ). Whereas an elevation of PPTs was noted in the healthy controls in response to experimental arm pain ( $P < 0.0001$ )

### 5) **Lee YC, Nassikas NJ, Clauw et al 2011**

The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia.

The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther.* 2011; 13:211. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther.* 2011; 13:211. Central pain mechanisms play important roles in wide-spread pain syndromes, including fibromyalgia. The role of these mechanisms in rheumatologic diseases such as OA and RA is not well understood. A few small studies, utilizing quantitative sensory testing and fMRI, have documented loss of descending analgesic activity and alterations in CNS activity among OA patients.

### 6) **Mease PJ, Hanna S, Frakes EP, Altman RD. 2011**

Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment.

In this literature review, the mechanisms underlying pain associated with osteoarthritis (OA) are discussed, along with evidence for the efficacy of medications thought to act centrally to relieve OA pain. We survey the cascade of events from inflammation to activation of nociceptive and neuropathic pathways, to the development and maintenance of central and peripheral sensitization. Preclinical and clinical evidence for the sensitization hypothesis is discussed, along with recently identified genetic variations that may increase sensitivity to pain in patients with OA. Evidence is presented for the efficacy of centrally acting analgesics for OA pain (opioids, antiepileptics, tricyclic antidepressants, and serotonin/norepinephrine receptor inhibitors).

### 7) **Nijs J, Paul van Wilgen C, Van Oosterwijk J, et al. 2011**

How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: practice guidelines.

Central sensitization provides an evidence-based explanation for many cases of 'unexplained' chronic musculoskeletal pain. Prior to commencing rehabilitation in such cases, it is crucial to change maladaptive illness perceptions, to alter maladaptive pain cognitions and to reconceptualise pain. This can be accomplished by patient education about central sensitization and its role in chronic

pain, a strategy known as pain physiology education. Pain physiology education is indicated when: 1) the clinical picture is characterized and dominated by central sensitization; and 2) maladaptive illness perceptions are present. Both are prerequisites for commencing pain physiology education. Face-to-face sessions of pain physiology education, in conjunction with written educational material, are effective for changing pain cognitions and improving health status in patients with various chronic musculoskeletal pain disorders. These include patients with chronic low back pain, chronic whiplash, fibromyalgia and chronic fatigue syndrome. After biopsychosocial assessment pain physiology education comprises of a first face-to-face session explaining basic pain physiology and contrasting acute nociception versus chronic pain (Session 1). Written information about pain physiology should be provided as homework in between session 1 and 2. The second session can be used to correct misunderstandings, and to facilitate the transition from knowledge to adaptive pain coping during daily life. Pain physiology education is a continuous process initiated during the educational sessions and continued within both the active treatment and during the longer term rehabilitation program.

**8) Imamura M, Imamura ST, Kaziyama HH et al.2008**

Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: a controlled analysis.

Patients with knee OA had significantly lower PPT over all evaluated structures versus healthy control subjects ( $P < 0.001$ ). Lower PPT values were correlated with higher pain intensity, higher disability scores, and with poorer quality of life, except for the role-emotional and general health status. Combined PPT values over the patellar tendon, at the S2 subcutaneous dermatome and at the adductor longus muscle were the best predictors for visual analog scale and Western Ontario and McMaster Universities Osteoarthritis Index pain scores.

**9) Arendt-Nielsen L, Graven-Nielsen T et al 2007**

Central sensitization in fibromyalgia and other musculoskeletal disorders.

Muscle hyperalgesia and referred pain play an important role in chronic musculoskeletal pain. New knowledge on the involved basic mechanisms and better methods to assess muscle pain in the clinic are needed to revise and optimize treatment regimens. Increased muscle sensitivity is manifested as pain evoked by a normally non-nociceptive stimulus (allodynia), increased pain intensity evoked by nociceptive stimuli (hyperalgesia), or increased referred pain areas with associated somatosensory changes. Some manifestations of sensitization, such as expanded referred muscle pain areas in patients with chronic musculoskeletal pain, can be explained from animal experiments showing extrasegmental spread of sensitization. An important part of the pain manifestations (eg, tenderness and referred pain) related to chronic musculoskeletal disorders may result from peripheral and central sensitization, which may play a role in the transition from acute to chronic pain.

**10)P. Bajaj, P. Bajaj, T. Graven-Nielsen, L. Arendt-Nielsen et al 2001**

Osteoarthritis and its association with muscle hyperalgesia: an experimental controlled study.

Hypertonic saline effectively excites muscle nociceptors. Muscle hyperalgesia was assessed in osteoarthritis (OA) by intramuscular infusion of 0.5 ml hypertonic saline (6%) into the tibialis anterior muscle in humans. Patients ( $n=14$ ) with OA in the lower extremities were compared with an equal number of age- and sex-matched healthy controls. Ten of the 14 OA patients had pain in the knee joint as the most common presenting complaint. Visual analogue scale (VAS) pain intensity and assessment of pain areas were recorded before infusion and immediately, 2, 5, 10 and 20 min after infusion, and then every 10 min, until the pain vanished. The mean pain offset time in OA patients ( $11.3 \pm 7.9$  min) was larger as compared with the control subjects ( $6.04 \pm 2.1$  min) ( $P=0.025$ ). OA patients had increased pain intensity VAS after the infusion in the right leg compared with controls ( $P < 0.05$ ). Referred and radiating pain areas at 2 min post-infusion increased in OA patients and not in controls as compared with the local pain areas ( $P < 0.05$ ). It is concluded that muscle hyperalgesia and extended pain areas might be due to central sensitization caused by painful osteoarthritis.

**11)Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA, et al.2000**

Osteoarthritis: New Insights. Part 2: Treatment Approaches.

They studied the treatment approaches; evidence for the efficacy of commonly used oral therapies is reviewed and information on alternative therapies, including nutraceuticals and acupuncture, is presented. Biomechanical interventions, such as exercise and bracing, and behavioral interventions directed toward enhancing self-management are reviewed. Current surgical approaches are described and probable future biotechnology-oriented approaches to treatment are suggested

**12)Woolf CJ, Salter MW. 2000**

Neuronal plasticity: increasing the gain in pain.

We describe those sensations that are unpleasant, intense, or distressing as painful. Pain is not homogeneous, however, and comprises three categories: physiological, inflammatory, and neuropathic pain. Multiple mechanisms contribute, each of which is subject to or an expression of neural plasticity-the capacity of neurons to change their function, chemical profile, or structure. Here, we develop a conceptual framework for the contribution of plasticity in primary sensory and dorsal horn neurons to the pathogenesis of pain, identifying distinct forms of plasticity, which we term activation, modulation, and modification, that by increasing gain, elicit pain hypersensitivity.

**13)Schadrack J, Neto FL, Ableitner A, Castro-Lopes JM, Willoch F, Bartenstein P, et al. 1999**

Metabolic activity changes in the rat spinal cord during adjuvant monoarthritis.

Adenosine 5'-triphosphate (ATP) has a ubiquitous role in

metabolism and a major role in pain responses after tissue injury. We investigated the changes in basal and KCl-evoked ATP release from rat dorsal root ganglia (DRG) after peripheral neuropathy induction by unilateral sciatic nerve entrapment (SNE).

Results:

After SNE, rats develop long-lasting decreases in ipsilateral hind paw withdrawal thresholds to mechanical and thermal stimulation. At 15–21 days after neuropathy induction, excised ipsilateral L4-L5 DRG display significantly elevated basal extracellular ATP levels compared to contralateral or control (naïve) DRG. However, KCl-evoked ATP release is no longer observed in ipsilateral DRG. We hypothesized that the differential SNE effects on basal and evoked ATP release could result from the conversion of extracellular ATP to adenosine with subsequent activation of adenosine A1 receptors (A1Rs) on DRG neurons. Adding the selective A1R agonist, 2-chloro-N<sup>6</sup>-cyclopentyladenosine (100 nM) significantly decreased basal and evoked ATP release in DRG from naïve rats, indicating functional A1R activation. In DRG ipsilateral to SNE, adding a selective A1R antagonist, 8-cyclopentyl-1,3-dipropylxanthine (30 nM), further increased basal ATP levels and relieved the blockade of KCl-evoked ATP release suggesting that increased A1R activation attenuates evoked ATP release in neurons ipsilateral to SNE. To determine if altered ATP release was a consequence of altered DRG metabolism we compared O<sub>2</sub> consumption between control and neuropathic DRG. DRG ipsilateral to SNE consumed O<sub>2</sub> at a higher rate than control or contralateral DRG.

**14) Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. 1986**

Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee.

For the purposes of classification, it should be specified whether osteoarthritis (OA) of the knee is of unknown origin (idiopathic, primary) or is related to a known medical condition or event (secondary). Clinical criteria for the classification of idiopathic OA of the knee were developed through a multicenter study group. Comparison diagnoses included rheumatoid arthritis and other painful conditions of the knee, exclusive of referred or para-articular pain. Variables from the medical history, physical examination, laboratory tests, and radiographs were used to develop sets of criteria that serve different investigative purposes. In contrast to prior criteria, these proposed criteria utilize classification trees, or algorithms.

**15) Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. 1978**

Studies with pain rating scales.

The correlation was maintained when presentation of the scales was separated by a series of questions and by physical examination. There is good evidence that the 4 scales are measuring the same underlying pain variable as they calibrate well. There is also evidence that an 11-point (0-10) numerical rating scale performs better than both a 4-

point simple descriptive scale and a continuous (visual analogue) scale.

- Problem Definition:
- **Dermatome:** the skin area supplied by one dorsal root. (Susan B O'sullivan, Thomas J Schmitz, Physical rehabilitation fifth edition, page no.124. published by Jitendar P Vij. 2006)
- **Sclerotome:** the area of a bone innervated from a single spinal segment.
- **Myotome:** muscle or group of muscles innervated from a single spinal segment.
- **Pressure pain threshold:** the minimum force applied which induces pain

### 3. Methodology / Approach

- Research Design: Cross-sectional observational comparative study
- Sample Size: 70 subjects (35 in each group)
- 35 in OA group and 35 age sex matched healthy individuals.
- The sample size was calculated using the sample size calculator ([www.nss.gov.au](http://www.nss.gov.au)) with OA population size 48 Confidence interval 0.1 Standard error 0.05102
- The calculated sample size was 32 and was rounded to 35.

#### Sample Population:

- For OA group: patients coming with chronic knee pain in OPD of Tertiary health care hospital.
- For control group: Relatives of patients coming in OPD of Tertiary health care hospital.

**Type of Sampling:** Convenient sampling

**Source of Sampling:** OPD of tertiary health care hospital

**Place of Study:** Physiotherapy OPD of tertiary health care hospital

**Duration of Study:** 6 Months

#### Inclusion Criteria for OA Group

- Patients suffering from chronic knee pain more than 3 months.
- Age group of 45-65 years of either gender participants with an established diagnosis of knee OA according to the American College of Rheumatology criteria. (21)
- Patients required to have a pain score  $\geq 4$  on a 10 on NRS. (13)
- Voluntary consent to participate.

#### Exclusion Criteria for OA Group

- Any other musculoskeletal impairment.
- Any neurologic conditions.
- Any systemic inflammatory disease.
- Any cognitive impairment.
- Any metabolic disorder like Diabetes mellitus

#### Inclusion Criteria for Control Group

- Healthy age sex matched individuals of age group 45-65 years.



- No reported pain in the lower back or in the lower extremities for the previous year.
- Voluntary consent to participate.

#### Exclusion Criteria for Control Group:

- Clinical manifestations of OA in knee joint.

#### Materials Used

- 1) A well ventilated and lit room.
- 2) High plinth.
- 3) Pen.
- 4) Good quality camera.
- 5) Sphygmomanometer.
- 6) Circular metal bottle stopper of 2 mm height with smooth corrugated edges.



#### Specification of Instruments & Outcome Measures

- NUMERIC RATING SCALE (NRS) (13) (correlation coefficients ranging from 0.79 to 0.96).
- Pressure pain threshold measurements (PPT) using sphygmomanometer cuff algometry. (1) (There was a good inter-rater reliability ( $\alpha C > 0.7$ ) :
- Dermatomes around knee: L3, L4, S2.
- Mayotomes around knee: Adductor longus, tibialis anterior.
- Sclerotome around knee : Patellar tendon.
- Quality of life by using KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS).(2) (test-retest reliability intraclass correlation coefficients ranging from 0.78 to 0.97)

#### Methodology

Approval from the Ethics Committee was sought. A written consent was taken from the participants after explaining the study procedure.

Participants were included in the study after screening for inclusion and exclusion criteria.

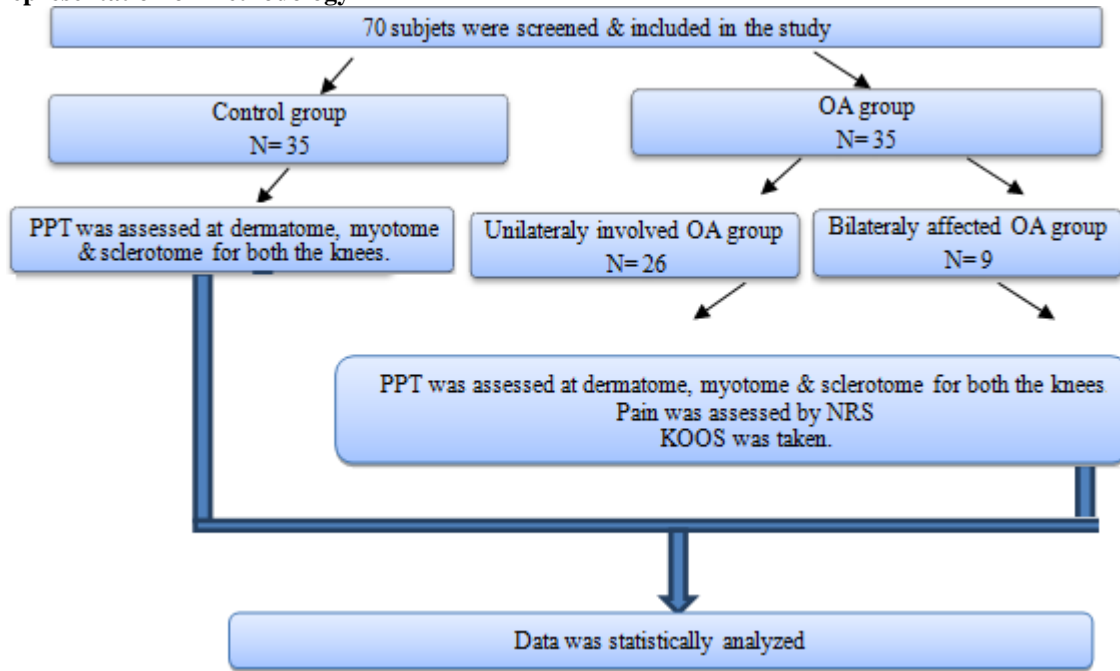
The basic personal information, history of present illness, comorbidities were recorded.

Patients were classified by established diagnosis of knee OA according to the American College of Rheumatology criteria. (21)

- Patients NUMERIC RATING SCALE (NRS) (13) was taken for pain severity.
- KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS). (2) In English, Hindi and Marathi versions were taken.
- Pain pressure threshold was tested by using cuff pressure of the sphygmomanometer<sup>(1)</sup>, a 2.5 cm × 2.5 cm circular metal bottle stopper of 2 mm height with smooth corrugated edges was placed according to:
- Dermatomes (L<sub>3</sub>,L<sub>4</sub>, S<sub>2</sub>).
- Myotomes (adductor longus, tibialis anterior).
- Sclerotome (patellar tendon).
- Both lower limb was tested and the manometer cuff was wrapped around the lower limb. The cuff of the sphygmomanometer was inflated until the subject perceived pain at the site of the metal stopper (gauze piece had been kept between the skin and metal stopper at the site of evaluation to avoid direct contact of metal stopper to skin.) Dermatome (L<sub>3</sub>,L<sub>4</sub>, S<sub>2</sub>), Myotomes(adductor longus, tibialis anterior) and Sclerotome (patellar tendon) were assessed.
- The minimum pressure reading at which the subject complained of pain was noted in mm of Hg. This was called the pressure pain threshold (PTT).
- Three independent readings were taken at intervals of at least 30 seconds between readings.
- The mean of the three readings were taken for analysis.
- PPT was taken for both right and left side for control group.
- PPT was taken for OA group as unilateral OA for both involved and non-involved side and also for bilateral OA for both more affected and less affected side.
- After completion of data collection of control group and OA group, data summery sheet was prepared.



Schematic Representation of Methodology



4. Results & Discussion

- 1) Data was analyzed using Graph pad prism 7 software.
- 2) Descriptive analysis of data was done.

- 3) Data was tested for normality using the Shapiro wilk Test.
- 4) Pain pressure threshold which is interval scale, data was tested for normality.

PPT of Control Group

Shapiro-Wilk normality test												
W	0.977	0.964	0.978	0.948	0.971	0.939	0.971	0.958	0.969	0.959	0.951	0.93
P value	0.658	0.314	0.7	0.099	0.498	0.052	0.493	0.208	0.422	0.223	0.121	0.029
Passed normality test (alpha=0.05)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P value summary	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

PT of OA Group

Shapiro-Wilk normality test												
W	0.933	0.920	0.964	0.976	0.969	0.973	0.976	0.986	0.965	0.980	0.960	0.955
P value	0.234	0.414	0.428	0.650	0.416	0.541	0.649	0.935	0.333	0.777	0.243	0.170
Passed normality test (alpha=0.05)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
P value summary	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

- 5) It passed normality and hence data within group were analyzed using Parametric test.
- 6) Between groups the data were analyzed using Unpaired T Test as comparison was between control group and knee OA group.
- 7) It passed normality and hence data within group were analyzed.
- 8) using Paired T Test for each Dermatome(L3,L4,S2), Myotome (Adductor longus, Tibialis anterior), and Sclerotome (Patellar tendon) level. (for control group comparison was done within their right & left knee, for OA involved group comparison was done within their involved & noninvolved knee and for OA affected group comparison was done within more affected and less affected knee).
- 9) The correlation between PPT & NRS, PPT & QOL were analyzed using Spearman r correlation Test as data didn't pass normality.
- 10) The level of significance was set at 0.05.

Tables and Graphs

For study purposes the groups are named as follows:

- a) CONTROL GROUP (Age sex matched healthy individuals)
- b) OA GROUP (Unilaterally & bilaterally involved individuals)
  - OA UNILATERALLY INVOLVED GROUP (involved & noninvolved knee)
  - OA BILATERALLY AFFECTED GROUP (more affected & less affected knee)

Demographic Data

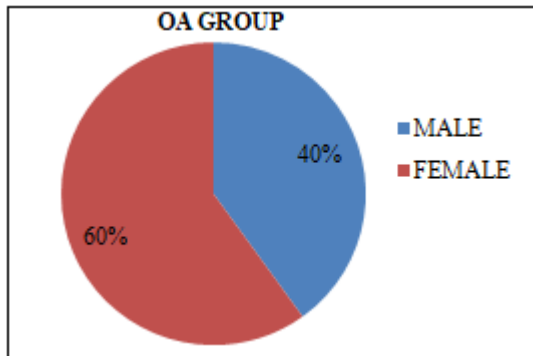
Table 1: Age Distribution

	Control	OA Unilaterally + Bilaterally	OA Unilaterally Involved	OA Bilaterally Involved
Mean ± SD	52.05 ± 6.08	53.88 ± 7.43	54.73 ± 6.76	51.44 ± 9.11
Standard Error	1.02	1.25	1.32	3.03

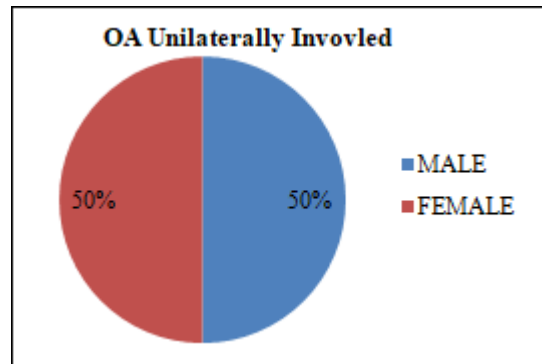
Analysis of Gender Distribution

Table 2: Gender Distribution

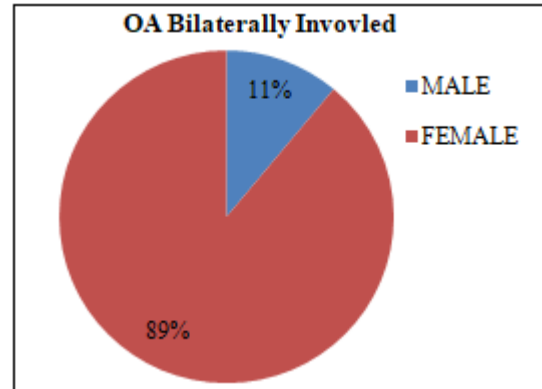
	Control	OA Unilaterally Involved	OA Bilaterally Involved	Total
Male	23	13	1	37
Female	12	13	8	33
Total	35	26	9	70



Graph 1: Gender Distribution in Knee OA Group:



Graph 2: Gender Distribution in OA Unilaterally Involved Group



Graph 3: Gender distribution in OA Bilaterally Involved Group

5. Analysis of PPT (Pain pressure threshold)

1) Summary of PPT means in knee OA group (subgroups- U/L & B/L) & control healthy group :

Table 3:

Variables	Knee OA Group				Control Group	
	Unilateral Involved N=26	Unilateral Noninvolved N=26	Bilateral More Affected N=9	Bilateral Less Affected N=9	Right N=35	Left N=35
<b>Dermatomal</b>						
L3	69.22	77.48	77.39	70.36	150.9	151.7
L4	76.27	80.63	77.57	71.1	134.6	140.9
S2	71.65	77.86	63.32	72.76	124.6	121.7
<b>Myotomal</b>						
Add longus	70.31	76.72	68.68	73.68	139.1	138.3
Tib ant	75.82	79.41	80.91	75.53	132.6	137.1
<b>Sclerotomal</b>						
Patellar tendon	70.37	74.79	70.91	75.72	124	121.7

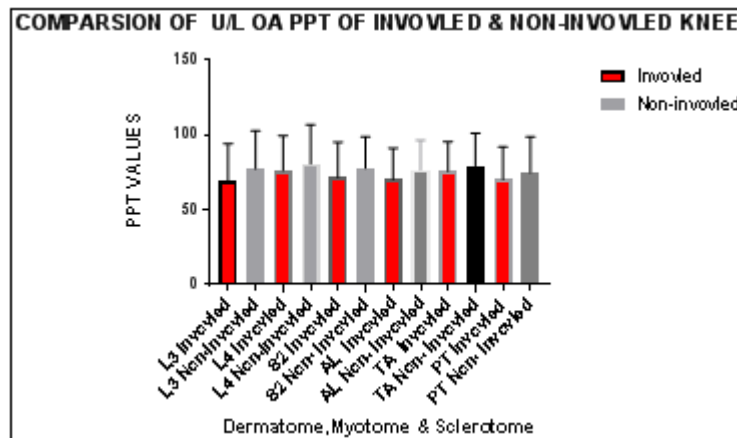
Inference

From table 3 we can infer that the mean PPT values at all Dermatomal, Myotomal & Sclerotomal structures are lower in OA group (subgroup- Unilaterally involved & bilaterally involved OA group) compare to Healthy control group.

2) Analysis of PPT within OA Unilateral group for their involved & noninvolved knee by using Paired T Test as follows:

Table 4

Variables	P value
<b>DERMATOMAL</b>	
L3	0.037
L4	0.258
S2	0.068
<b>MYOTOMAL</b>	
ADDUCTOR LONGUS	0.206
TIBIALIS ANTERIOR	0.086
<b>SCLEROTOMAL</b>	
PATELLAR TENDON	0.187



Graph 4: Comparison of PPT In Involved & Noninvolved Knee In Unilateral OA Group

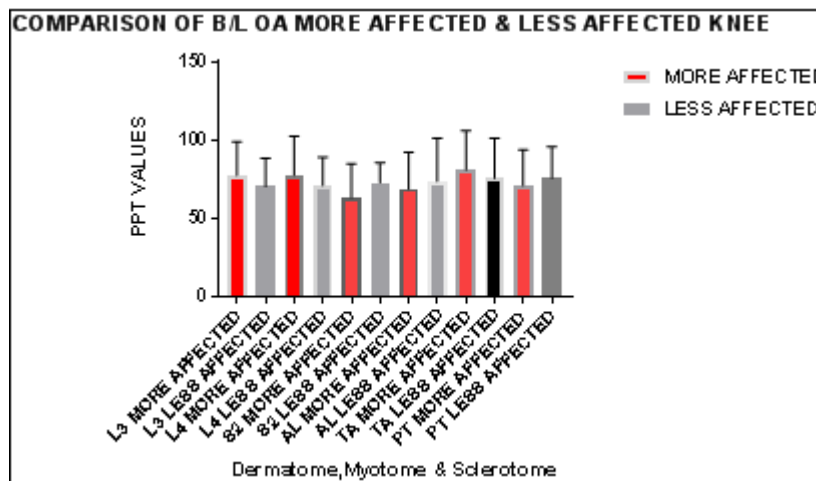
**Inference:**

From table 4 we can infer that the P values at all Dermatomal, Myotomal & Sclerotomal structures are not significant. (P value > 0.05). This indicates there is a no difference within PPT values of involved & noninvolved knees in the OA unilateral group, shown in graph 4.

3) Analysis of PPT within OA Bilateral group for their more affected & less affected knee by using Paired T Test as follows:

**Table 5**

Variables	P value
<b>DERMATOMAL</b>	
L3	0.284
L4	0.350
S2	0.175
<b>MYOTOMAL</b>	
ADDUCTOR LONGUS	0.061
TIBIALIS ANTERIOR	0.534
<b>SCLEROTOMAL</b>	
PATELLAR TENDON	0.053



Graph 5: Comparison of PPT in More Affected & Less Affected Knee in Bilateral OA Group:

**Inference:**

From table 5 we can infer that the P values at all Dermatomal, Myotomal & Sclerotomal structures are not significant. (P value > 0.05). This indicates there is a no difference within PPT values of more affected & less affected knees in the OA bilateral group, shown in graph 5.

4) Analysis of PPT within control group for their Right & Left knee by using Paired T Test as follows:

**Table 7:**

Variables	P value
<b>DERMATOMAL</b>	
L3	0.802
L4	0.068
S2	0.373
<b>MYOTOMAL</b>	
ADDUCTOR LONGUS	0.164
TIBIALIS ANTERIOR	0.802
<b>SCLEROTOMAL</b>	
PATELLAR TENDON	0.565



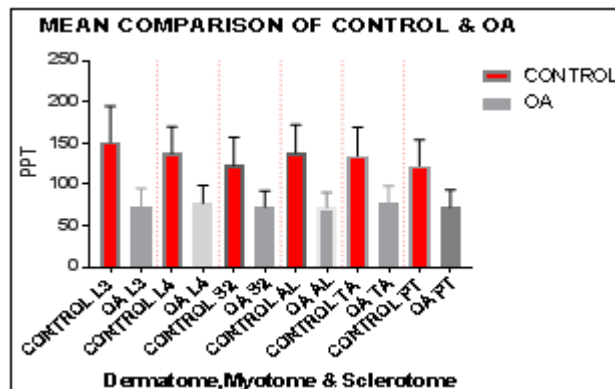
**Inference:**

From table 3 we can infer that the P values at all Dermatomal, Myotomal & Sclerotomal structures are not significant. (P value > 0.05). This indicates there is no difference within PPT values of right and left knees in healthy control group.

5) Analysis of PPT between control group and OA group for their Right & Left knee by using Unpaired T Test as follows:

**Table 6**

Variables	P value
<b>DERMATOMAL</b>	
L3	0.00
L4	0.00
S2	0.00
<b>MYOTOMAL</b>	
ADDUCTOR LONGUS	0.00
TIBIALIS ANTERIOR	0.00
<b>SCLEROTOMAL</b>	
PATELLAR TENDON	0.00



**Graph 6:** Comparison of PPT in Control & OA Group

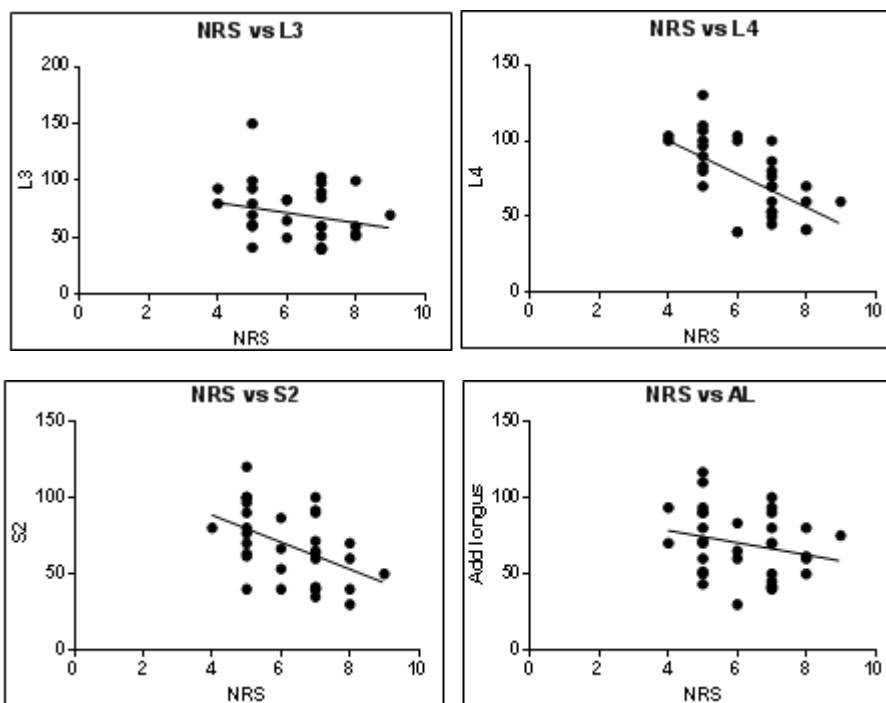
**Inference:**

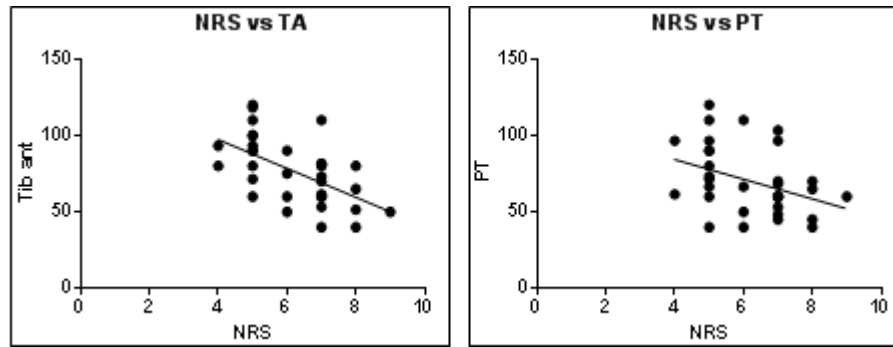
From table 6 we can infer that the P values at all Dermatomal, Myotomal & Sclerotomal structures are statistically significant. (P value < 0.05). This indicates there is a marked difference between PPT values of control group & OA group shown in graph 6.

**6) Correlation of OA KNEE PPT to NRS:**

**Table 8**

	PAIN NRS vs. L3	PAIN NRS vs. L4	PAIN NRS vs. S2	PAIN NRS vs. AL	PAIN NRS vs. TA	PAIN NRS vs. PT
Spearman r	-0.2481	-0.621	-0.5033	-0.584	-0.2477	-0.414
95% confidence interval	-0.5442 to 0.103	-0.7944 to 0.3539	-0.7213 to -0.1944	-0.772 to 0.3021	-0.5439 to 0.1034	-0.6624 to 0.08351
P (two-tailed)	0.1507	<0.0001	0.0021	0.0002	0.1514	0.0134
P value summary	ns	****	**	***	ns	*
Exact or approximate P value?	Approximate	Approximate	Approximate	Approximate	Approximate	Approximate
Significant? (alpha = 0.05)	No	Yes	Yes	Yes	No	Yes
Number of XY Pairs	35	35	35	35	35	35





**Graph 7:** Scattered Diagrams Of Correlation Between NRS & L3, L4, S2, ADD LONGUS (AL), TIB ANTERIOR (TA) & PATELLAR TENDON (PT)

**Inference:**

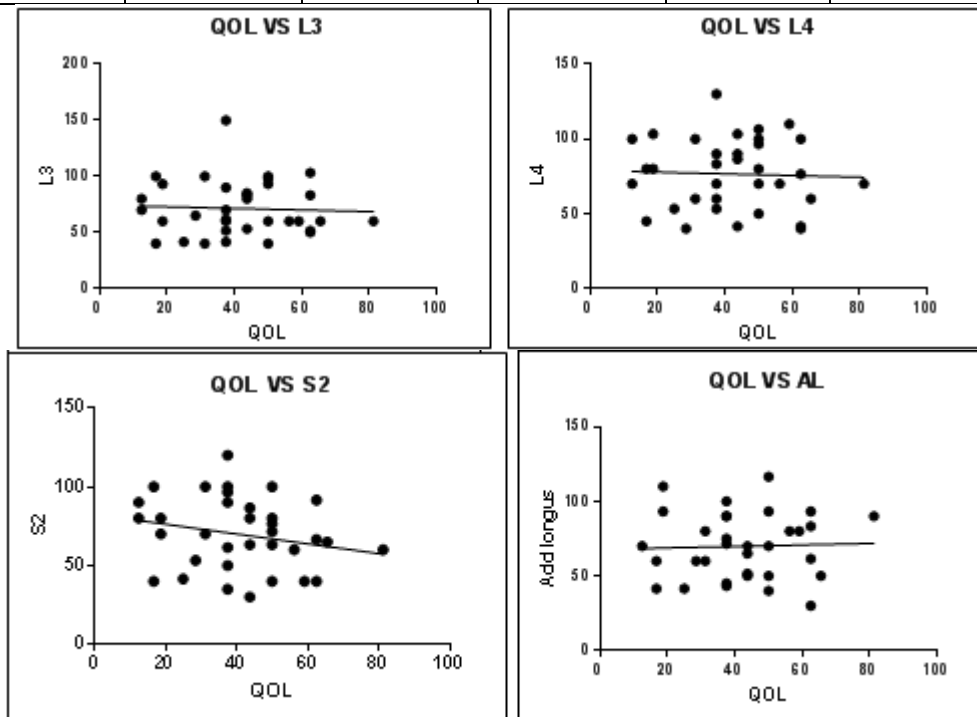
From table 8 we can infer that the P values at dermatome L4, Myotome Adductor longus, dermatome S2, Sclerotome Patellar tendon are statistically significant. (P value <0.05). This indicates there is negative relationship between NRS &

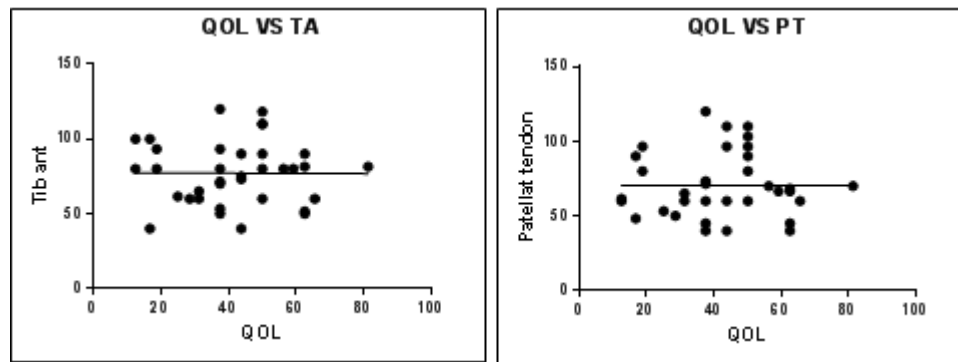
PPT values at dermatome L4, Myotome Adductor longus, dermatome S2, Sclerotome Patellar tendon i.e. when PPT values are low pain intensity is high.

**7) Correlation of OA KNEE PPT TO QOL**

**Table 9**

	QOL vs. L3	QOL vs. L4	QOL vs. S2	QOL vs. AL	QOL vs. TA	QOL vs. PT
Spearman r	-0.04528	-0.02155	-0.2537	0.06139	0.01786	0.0701
95% confidence interval	-0.3817 to 0.3017	-0.3612 to 0.3232	-0.5484 to 0.09708	-0.287 to 0.3954	-0.3265 to 0.358	-0.2789 to 0.4028
P (two-tailed)	0.7962	0.9022	0.1415	0.7261	0.9189	0.6891
P value summary	ns	ns	ns	ns	ns	ns
Exact or approximate P value?	Approximate	Approximate	Approximate	Approximate	Approximate	Approximate
Significant? (alpha = 0.05)	No	No	No	No	No	No
Number of XY Pairs	35	35	35	35	35	35





**Graph 8:** Scattered diagrams of correlation between QOL & L3, L4, S2, ADD Longus (AL), TIB Anterior (TA) & Patellar Tendon (PT)

### Inference

From table 9 we can infer that the P values at all Dermatome, Myotome & Sclerotome structures are not significant. (P value >0.05). This indicates there is no relationship between QOL in OA knee patients & their PPT values. Thus null hypothesis can be accepted.

- 1) The demographic data of the patients and healthy controls age distribution are shown in Table 1. Nine patients had bilateral knee OA, fifteen had knee OA on the right side, and eleven on the left side. In patients with bilateral knee OA, the more symptomatic knee was considered the more affected one. The right side was more involved in 6 and the left side in 3 patients with bilateral involvement. Shapiro wilk Test demonstrated a normal distribution for all of the studied variables. The difference of mean between healthy control group & OA group was analyzed using unpaired t test. The difference of mean within unilateral (involved & noninvolved knees) & bilateral (more affected & less affected) OA group were analyzed using paired t test as data passed normality. The relationship between PPT & NRS, PPT & QOL were analyzed using spearman correlation test as data didn't pass normality.
- 2) **Dermatome hyperalgesia:** Analysis of Dermatome hyperalgesia (25,26) showed that PPT values were statistically significantly lower in all subcutaneous dermatomes of the knee OA patients when compared with healthy controls ( $P < 0.001$ ) (Table 6). In the healthy control group, right and left sides presented similar PPT values ( $P > 0.05$ ). In the knee OA group, no difference was observed among diseased knees (more or less affected in bilateral knee OA, and affected in unilateral OA,  $P > 0.724$ ) or between involved and the noninvolved knees in unilateral knee OA ( $P > 0.949$ ).
- 3) **Myotome hyperalgesia:** Analysis of Myotome structures (25,26) revealed that PPT values were significantly lower in the knee OA patients versus the healthy controls ( $P < 0.001$ ) (Table 6). In addition to finding similar PPT values between left and right sides in healthy controls ( $P > 0.05$ ), we found similar PPT values between all diseased knees i.e. in bilaterally affected ( $P > 0.785$ ) as well as the noninvolved sides in the unilateral OA patients ( $P > 0.444$ ).
- 4) **Sclerotome hyperalgesia:** Analysis of Sclerotome hyperalgesia (25,26), as measured at the patellar tendon, revealed significantly lower PPT measurements at all

evaluated structures in the knee OA patients when compared with healthy controls ( $P < 0.001$ , Table 6). Within the healthy control group, the right side presented a similar PPT value than the left side. Similar PPT values between all diseased knees i.e. in bilaterally affected ( $P > 0.641$ ) as well as the noninvolved sides in the unilateral knee OA patients ( $P > 0.488$ ).

### 5) Evaluation of pain and quality of life:

- **Correlation in pain intensity & PPT values at Dermatome, Myotome & Sclerotome structures:** We tried to identify the PPT variables that significantly influenced pain intensity (NRS) in OA patients. All independent variables were tested separately. We found highly statistically significant correlations in NRS & PPT values, table 8 shows at L4 dermatome ( $P < 0.0001$ ), following at adductor longus Myotome ( $P$  value = 0.0003), following at S2 dermatome ( $P$  value = 0.002), following at patellar tendon Sclerotome ( $P$  value = 0.02). There was no statistically significant correlation found at L3 dermatome & at Tibialis anterior Myotome ( $P$  value >0.05).
- **Correlation in quality of life (KOOS QOL) & PPT values at Dermatome, Myotome & Sclerotome structures:** We tried to identify the PPT variables that significantly influenced QOL in OA patients. All independent variables were tested separately. We found there was no statistically significant correlation in QOL & PPT values of variables, shown in table 9.

## 6. Discussion

- 1) The aim of this study was focusing on an approach to clinically identify nervous system hyperalgesia in patients with disabling knee OA pain; **Imamura et al** demonstrated that the differential PPT threshold between knee OA patients and in healthy controls was significantly lower at the Dermatome, Myotome, and Sclerotome structures. Lower PPT values were correlated with higher pain intensity. (12) study demonstrated a generalized state of hyperalgesia, both in superficial and deep structures, in knee OA patients when compared with healthy controls. This suggests that the peripheral and central nervous system might be involved in the maintenance of the chronic pain state.

- 2) **Suputtitada et al & Moss p et al** demonstrated the clear understanding of the mechanisms involved in how knee OA pain is generated, and how the sensory information is processed from peripheral receptors to cerebral cortex, might provide useful insights that can lead to clinical benefits in the future. Initially, hypersensitivity is found at the site of damage; however when the disease process is not controlled, such as in patients with OA and refractory pain, the central nervous system undergoes plastic changes that are responsible for sustaining chronic pain. It then becomes independent from the peripheral pathologic process. Usually, repeated stimulation causes most sensory organs to become fatigued and less responsive (3,4).
- 3) **Suputtitada et al** demonstrated High threshold polymodal C fibers involved in nociception, however, show the opposite response (3,4). In fact, with repeated nociceptive stimulation, nerve endings undergo changes that result in enhanced sensitivity, lowered threshold to stimulation, and prolonged and enhanced response to the stimulation, also known as after-discharge. This phenomenon is called sensitization and it is responsible for sustained pain, tenderness, and segmental and suprasegmental reflex responses (3).
- 4) **Suputtitada et al , Moss p et al, Graven-Nielson et al** demonstrated findings demonstrated that centrally induced neuroplastic changes measured by a decreased PPT over superficial and deep structures occurred also in sites distant from the knee area. We showed that PPT values were significantly lower in all evaluated structures. It should be underscored that sensitization associated with chronic pain is observed in all levels of the nervous system, from peripheral structures (receptors and nerves) to central structures (spinal cord and brain). In fact, spinal segmental sensitization is a hyperactive state of the spinal cord caused by repeated stimulation of nociceptive receptors from impulses sent by sensitized damaged tissue to the dorsal horn neurons (central nervous system sensitization). The mechanisms of spinal segmental sensitization include neuron hypertrophy and up-regulation of excitatory neurons and of prohyperalgesic peptides, and neurotransmitters at the dorsal horn of the spinal cord. This results in a mismatch of inflammation and pain, as pain does not indicate worsening of inflammation and vice versa. Knowledge of the segmental distribution of sensory nerve fibers is important in managing patients with pain (4). Each segment of the spinal cord and its corresponding spinal nerves have a consistent segmental relationship that allows the clinician to ascertain the probable spinal level of dysfunction based on the pattern of dermatomal, myotomal, and sclerotomal hyperalgesia (3,4,6).
- 5) **Moss P et al** demonstrated PPT over anatomic structures innervated by different segmental spinal nerves and divide them into 3 different categories based on the segmental innervations: dermatomal, myotomal, and sclerotomal (4). For the myotomes, we chose to evaluate the PPT over muscles innervated by different spinal nerves., and adductor longus as muscle innervated by the L2–L3–L4 spinal nerve roots; tibialis anterior by L5–S1 spinal nerves; For the dermatomes we followed those described

by **Keegan and Garrett**(23), and the ones described by Bonica j j for the sclerotomes. Our data suggested that hyperalgesia over some structures presented a stronger correlation to pain.

- 6) **Bajaj p et al, Shah JP et al** demonstrated another possible explanation of lower PPT values over a spontaneously painful human skeletal muscle presents significantly elevated levels of Substance P, calcitonin gene-related peptide, bradykinin, tumor necrosis factor , interleukin-1\_, serotonin, and norepinephrine versus nonpainful, healthy subjects (16).The concentration of selected inflammatory mediators, neuropeptides, cytokines and catecholamines also differ quantitatively from a remote, uninvolved site (14).
- 7) Our findings demonstrated no relationship in QOL & pain intensity that has been described by **Palo N et al** in their study as more than 60% population in our society continued to work, this could be attributed to the financial stress, large family size, low Gross Domestic Product (GDP), and per capita income in our country due to which most elderly patients cannot afford a relaxing retirement time.(5)

## 7. Conclusion

- PPT values at all Dermatomal, Myotomal & Sclerotomal structures are lower in OA group (subgroup- Unilaterally involved & bilaterally involved OA group) compare to Healthy control group i.e. there is presence of hyperalgesia in knee OA patients.
- The results demonstrated that even when OA was unilateral; both extremities were equally affected in terms of hyperalgesia as there was no significant difference between PPT values of OA group (subgroup- Unilaterally involved & noninvolved knees, bilaterally more affected & less affected knees in OA group) suggestive of involvement of central nervous system mediated hyperalgesia.
- There was an inverse relationship of pain intensity with PPT values in knee OA group.
- There was no relationship of QOL with PPT values in knee OA group, could be because of patients personal or environmental factors affecting there QOL.

## 8. Future Scope

Further detailed studies are necessary to confirm our findings and fully investigate the mechanisms of the nervous system that enhance patient's reported pain. These insights may then encourage further studies to assess new therapeutic approaches to control pain in knee OA.

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