

# Knee Osteoarthritis: An Overview of Recent Interventions

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**Abstract** - Knee Osteoarthritis (OA) is one of the most common forms of arthritis contributing to the burden of physical disability. This review focuses on the general and managerial aspects of knee OA. Different electrotherapeutic modalities which are commonly employed to alleviate symptoms of knee OA are Ultrasound therapy (0.5-5MHz), Transcutaneous Electrical Nerve Stimulation (2-10 Hz) and Neuromuscular Electrical Stimulation (50-100 Hz). Pulsed Electrical Stimulation (PES) is another electrotherapy treatment where low frequency current (100 Hz) is believed to promote synthesis of chondrocyte Type 2 collagen and aggrecan, and suppression of matrix metalloproteinases and Interleukin 1(IL 1), hence having a positive effect on chondrocyte function through gene regulation. In this paper, the effectiveness of electrotherapeutic modalities along with physiotherapy, surgery and other measures are reviewed. It has been found that available studies on PES have discussed limited conclusions about its role. Hence, our study aims to understand the effectiveness of PES on knee OA in comparison to commercially available technologies to overcome proposed gaps and may be treated as better therapeutic modality in near future. The data collected or conclusions drawn were through literature survey only. No experimental study or practical usage of the different devices was conducted, which could be considered in future.

**Keywords:** Osteoarthritis, PES, Pulsed Electrical Stimulation, Quadriceps, WOMAC.

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## 1. Introduction

Osteoarthritis (OA) is a dynamic process and differs from simple wear and tear as it is asymmetrically distributed, often localized to only one part of a joint and associated with abnormal loading rather than frictional wear [1]. Whenever there is overwhelming imbalance between breakdown and repair of joint tissue, OA occurs [2]. Some common causes that can lead to development of OA are age related cartilage degeneration [3],[4], genetic inheritance [5],[6], trauma, previous inflammatory conditions, quadriceps weakness[7],[8] and vascular changes [9]. One of the common joints where OA occurs is the knee. OA of the knee may be accelerated if there is a vascular disease in the subchondral bone, either through direct ischaemic effects on bone or by any alteration in the cartilage nutrition [10].

This paper is a review paper, and hence all the conclusions and inferences made were based only on literature survey. Many articles, of last twenty (20) years, related to the study were studied, compared and have been discussed. On many occasions, the results obtained from various studies done or experiments conducted have been shown and comparisons made. The advantages and disadvantages have been studied and reflected. Many studies had some limitations, which have also been shown. Overall, only study has been done on this paper and no practical or experimental study done to verify different aspects mentioned, but has been planned for in the near future.

### 1.1. Prevalence

OA is the commonest of all joint diseases, a true universal disorder affecting sexes and all races.

However, symptoms and radiographic changes are poorly correlated in OA [11]. The burden of OA on the society is physical, psychological and socioeconomic. It can be associated with significant disability, such as a reduction in mobility and activities of day-to-day life. Psychologically distress, devalued self-worth, and loneliness are the main factors. Given the high frequency of OA in the population, its economic burden is large on the society [12]. Symptomatic knee, hand, and hip OA prevalence was significantly higher among women than men and increased significantly with age [13]. Symptomatic knee OA was also found to be significantly more common in the rural compared to urban and suburban populations [14]. In a study conducted globally, hip and knee OA ranked 11th highest contributor to global disability. The standardized global age prevalence of knee OA was 3.8% [15]. In another study, high prevalence of knee OA was found among elderly subject in Beijing, especially women, where 150 million persons age  $\geq 60$ , as compared to elderly subjects in Framingham, Massachusetts [16]. In the Indian scenario, a study was conducted by M S Radha et al., 2015, to measure the prevalence of knee OA patients and identification of risk factors among the age group of 40 to 65 years in Mysore City, Karnataka and compared the Body Mass Index (BMI), Erythrocyte Sedimentation Rate (ESR) and (WOMAC) criteria. Out of 150 knee OA patients, 95 were females and 55 were males. Age group of 60-65 and 40-45 years showed the highest prevalence of knee OA, whereas the least prevalence was shown within the age group of 50-55 years. About 46% of the patients were having normal BMI and 23.33% were found to be overweight [17].

### 1.2. Risk factors

There are many risk factors associated with knee OA, commonly - joint dysplasia [31], intra articular fractures [18], meniscal injuries [19] etc. OA has often been found to be associated with occupation involving repetitive stress to the joint in the form of bending activities [20-21], operation of heavy vibrating tools, long term farming etc [22]. Researchers have proven that OA is more commonly seen in females than males, one of the reasons being obesity, which is more commonly seen in females [23-24]. J Dequeker et al., 1993, observed that, bone mineral density is increased, not only around the affected joints but also in generalised osteoarthritis. The change in bone mineral density is associated with a change in the mechanical properties of bone. These altered mechanical properties

of the underlying subchondral bone may cause cartilage degeneration and affect the progress of disease [25]. Deborah J Hart, 1994 in his study found out that osteoarthritis and osteoporosis are inversely related, although the mechanisms remain unclear [26-27].

### 1.3. Pathophysiology

As the name suggests, pathophysiology is a convergence of pathology and physiology. It thus describes the operating mechanism of the structure and the abnormal or undesired conditions prevailing. Overall pathophysiology explains the mechanisms whereby such conditions develop and progresses. In the case of a normal knee joint, it consists of femoropatellar articulation, which consists of the knee cap known as patella and patellar groove, medial and lateral femorotibial articulations linking the femur with the tibia [28]. For the smooth sliding of the bones, cartilage tissues, which are of two types - meniscus and hyaline cartilage, are present. It is the cartilage that wears out eventually. The menisci protect the bones from rubbing on each other and also help in shock absorption. Along with the menisci, ligaments help in protection of the joint [29-30]. Figure 1 shows all the above mentioned parts of the normal knee joint. Abnormal joint loading is a major reason for the development of knee OA. Disparity between the joint load and the ability to cope up with the stress causes the destruction of cartilage along with other factors. Mechanical and enzymatic factors are thought to impair chondrocyte function and damage the cartilaginous matrix [31].

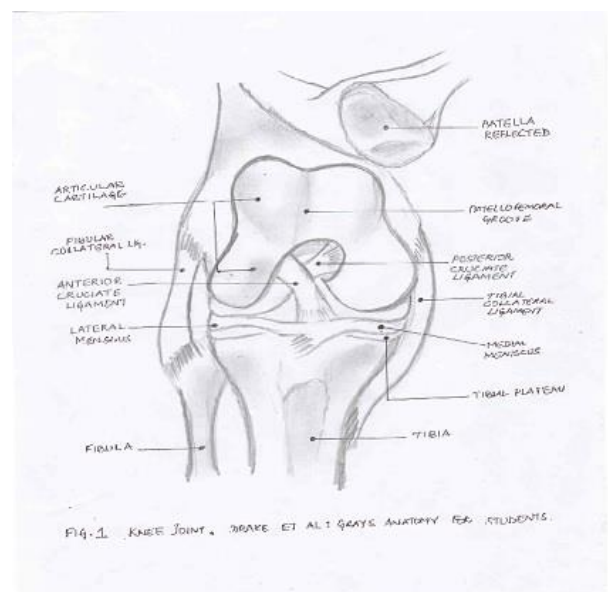


Figure 1. Normal knee joint [135].

## 2. Diagnosis

Though the effects of OA can show up during later stages of life, the onset of the process can be quite early. Early detection can help a lot to prolong the process. If diagnosis is done at an earlier stage, proper measures can be taken to improve the conditions. The major elements of the diagnostic evaluation are the history, physical examination, imaging studies, and, in some cases where special questions arise, laboratory testing is employed.

### 2.1. History and Physical Examination

The criteria laid down by the American College of Rheumatology (ACR) are widely followed in the diagnosis of OA. They are, knee pain, radiographic osteophytes and at least 1 of the following 3 items: Age >50 years, morning stiffness of 30 minutes or less and crepitus on motion [32]. The physical examination of the knee ligaments consists of testing of the lateral ligaments with the varus or valgus stress test [33-34] and testing of the anterior and posterior cruciate ligaments with the drawer test [35]. Likewise, the menisci should be diagnostically tested manually using Apley compression test [36] and McMurray test [37]. The patella-femoral joint is assessed by employing test like Zohlens [38].

### 2.2. Imaging Studies

Despite the development of newer imaging techniques, the radiograph remains the most accessible tool in the evaluation of the OA joint. X-ray imaging studies are used both for primary diagnosis and to assess the progression of the disease. The typical radiological signs of knee osteoarthritis that can be seen on plain films are incorporated in the staging system of Kellgren and Lawrence [39-41]. The staging of osteoarthritis of the knee, after Kellgren and Lawrence scale can be classified as: Stage 0(no abnormality), Stage 1(incipient osteoarthritis, beginning of osteophyte formation on eminences), Stage 2( moderate joint space narrowing, moderate subchondral sclerosis), Stage 3( >50% joint space narrowing, rounded femoral condyle, extensive subchondral sclerosis, extensive osteophyte formation), Stage 4(joint destruction, obliterated joint space, subchondral cysts in the tibial head and femoral condyle, subluxed position), as shown in figure 2. Others forms of imaging are Magnetic Resonance and Imaging (MRI), which helps to detect cartilage defects and bone marrow lesions [42-43], Optical coherence tomography (OCT) which can demonstrate real-time imaging in vivo of human

cartilage at a resolution of micrometers [44] and Scintigraphy which can predict subsequent loss of joint space in patients with established OA of the knee joint [45] etc.

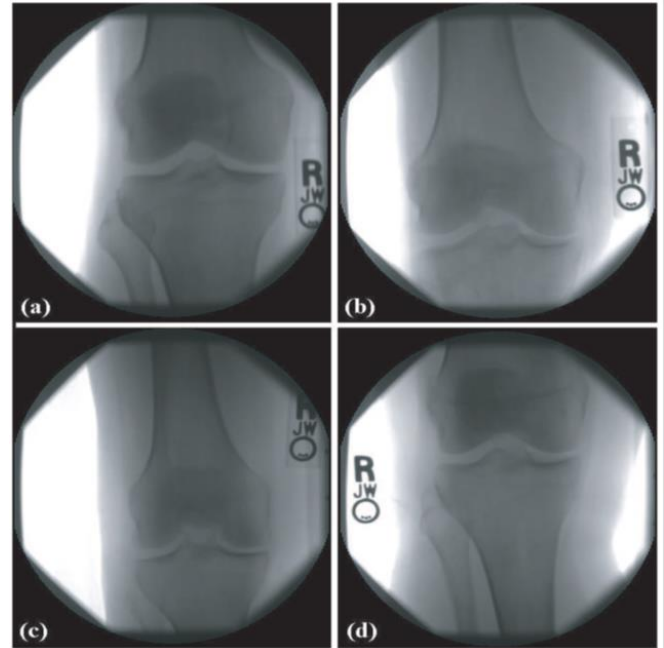


Figure 2. X-ray images of four different Kellgren and Lawrence (KL) grades: a. 0 (normal), b. 1 (doubtful), c. 2 (minimal), d. 3(moderate) [136].

## 3. Management of Knee Osteoarthritis

Osteoarthritis (OA) is not a curable disease at present, as the mechanism by which it arises and progresses remains incompletely understood. Therefore, the goal of treatment is to alleviate the signs and symptoms of the disease and, if possible, to slow its progression. The therapeutic spectrum ranges from general measures to physiotherapy, orthopaedic aids and orthosis, pharmacotherapy, and finally surgery and rehabilitation. The goals of treatment, as stated in many of the guidelines are: pain relief, improve quality of life, improve mobility, improve walking and delay progression of osteoarthritis.

### 3.1. General measures

Some general measures for reducing chances of OA occurrence are patient education, lifestyle adjustment, and, when indicated, weight loss. Chodosh et al., 2005, in a meta-analysis, found that general measures have no appreciable effect on pain and function in knee osteoarthritis [46]. A further meta-analysis of 16 controlled trials yielded the finding that individual exercise and self-management had a

moderate, but clinically significant psychological effect and made a positive contribution to the patients' emotional well-being [47]. In one study, R. Christensen et al., 2005, found out that, 8 weeks of Low Energy Diet (3.4 MJ/day) was found to be advantageous because of the rapidity of weight loss and a more significant loss of body fat [48]. In some cases, elderly patients diagnosed with knee OA are apprehensive about exercising. In one study, it has been found that, provided trauma is avoided, moderate exercise does not lead to acceleration of knee osteoarthritis, whether or not there is evidence of pre-existing disease. It is likely that exercise interventions are underused in the management of established knee OA symptoms [49-50]. Usage of cane can diminish pain, improve function and some aspects of quality of life in patients diagnosed with knee OA [51].

### **3.2. Orthopaedic Aids and Orthosis**

Brouwer RW et al., 2005, conducted a study to evaluate the effect of a brace intended to reduce load in patients with medial or lateral compartmental osteoarthritis and concurrent varus or valgus alignment, respectively. They found out that a brace intended to reduce load shows small effects in patients with unicompartamental osteoarthritis. However, many patients do not adhere in the long run to this kind of conservative treatment [52].

### **3.3. Pharmacotherapy**

One of the procedures to be followed for management of knee OA is pharmacotherapy. In this procedure, usage of medicines or drugs is employed. It is generally used to relieve the patient from pain and inflammation. The following classes of medications are currently used to treat osteoarthritis of the knee: analgesics/anti-inflammatory agents, glucocorticoids, opioids, symptomatic, slow-acting drugs for osteoarthritis (SYSADOA) and anti-cytokines [53]. Research studies have showed that though Cochrane database contains a review of 16 randomized trials, yet, despite the large number of studies the efficacy and safety of these drugs cannot yet be judged conclusively [54]. When signs of inflammation arise, intraarticular glucocorticoid injections can rapidly eliminate a joint effusion. The most suitable type of glucocorticoid for injection has been found to be one with a long half-life, in crystalloid solution, with a small crystal size e.g. triamcinolone acetonide or hexacetonide, at a dose of 10 mg or 40 mg, respectively. A number of studies have shown that intra-articular corticosteroids (IAS)

injections are effective than hyaluronic acid (HA), placebo or lavage [55-57]. However, in some cases septic arthritis has emerged as a serious potential complication from repeated intra-articular injections [58]. Towheed et al., 2005, found that Slow Acting Drugs for OA slow the radiological progression of knee osteoarthritis [59]. It was shown that either high or low molecular weight use of HA was effective in improving WOMAC pain and function scores than using IAS or intra-articular placebo (IAP). Hence, the American Medical Society for Sports medicine (AMSSM) recommends the use of HA for the appropriate patients suffering from knee OA [60-61]. Osteoarthritis Research Society International (OARSI) members recommended the use of 25 different modalities. The eight recommendations covering pharmacological modalities of treatment includes acetaminophen, cyclooxygenase-2 (COX-2) non-selective and selective oral nonsteroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs and capsaicin, intraarticular injections of corticosteroids and hyaluronates, glucosamine and/or chondroitin sulphate [62] for symptom relief; glucosamine sulphate, chondroitin sulphate and diacerein for possible structure-modifying effects and the use of opioid analgesics for the treatment of refractory pain. OARSI recommendations for the management of hip and knee OA, states that overall there was no statistically significant difference between non-pharmacological therapies and pharmacological therapies. However, optimal management of patients with OA hip or knee requires a combination of nonpharmacological and pharmacological modalities of therapy [63]. In most cases, OA patients find usage of NSAIDS more effective than acetaminophen. However in one study, researchers have found that the efficacy of ACET, 1000 mg four times a day, on average, was found effective than that of either an analgesic or an anti-concluding that adequate relief of osteoarthritic pain could be achieved in some cases with an analgesic [64-65]. On a debate whether older patients with chronic knee pain should be advised to use topical or oral non-steroidal anti-inflammatory drugs, researchers concluded that, both have same effectiveness, but usage of oral NSAIDS could have gastrointestinal (GI) side effects, hence topical use is preferred by elderly patients with knee OA [66]. ACR has recommended a set of 'strong' and 'conditional' recommendations for use of non-pharmacological and pharmacological therapies, for patients suffering from knee OA. Non-pharmacological modalities strongly recommended for the management of knee OA were aerobic, aquatic, and/or resistance

exercises as well as weight loss for overweight patients. Non-pharmacologic modalities conditionally recommended for knee OA included medial wedge insoles for valgus knee OA, subtalar strapped lateral insoles for varus knee OA, medially directed patellar taping, manual therapy, walking aids, thermal agents, tai chi, self-management programs, and psychosocial interventions. Pharmacologic modalities conditionally recommended for the initial management of patients with knee OA included acetaminophen, oral and topical NSAIDs, tramadol, and intra-articular corticosteroid injections; intra-articular hyaluronate injections, duloxetine, and opioids were conditionally recommended in patients who had an inadequate response to initial therapy. Opioid analgesics were strongly recommended in patients who were either not willing to undergo or had contraindications for total joint arthroplasty after having failed medical therapy [67].

### **3.4. Surgery**

Five surgical modalities that are recommended by OARSI are; total joint replacements, unicompartmental knee replacement, osteotomy and joint preserving surgical procedures; joint lavage [68] and arthroscopic debridement in knee OA, and joint fusion as a salvage procedure when joint replacement had failed. A study conducted by Sylvia et al., 2012, showed that patients diagnosed with non-traumatic degenerative meniscal tear when treated with combination of arthroscopy and exercise or exercise alone, both showed significant clinical improvement from the baseline to the follow ups at 24 and 60 months. However later, one third of the patients in the exercise alone group started showing symptoms and thus had to undergo arthroscopy treatment. The findings indicate that arthroscopic surgery followed by exercise therapy was not superior to the same exercise therapy alone for this type of patients [69]. On one study to find out the efficacy of arthroscopic surgery for the treatment of osteoarthritis of the knee, the researchers found out that Arthroscopic surgery for osteoarthritis of the knee provides no additional benefit to optimized physical and medical therapy [70]. The goal of bone stimulating techniques is to open the subchondral cartilage and thereby bring pluripotential stem cells to the joint surface, where they are then supposed to form fiber bundles under the influence of mechanical and biological forces. Studies have not revealed any significant differences between the various methods that are used [71]. In Autologous

chondrocyte transplantation cartilage cells are taken from the joint, enzymatically isolated and cultured *ex vivo*, and then put back into the joint at the site of the cartilage defect, which is prepared before the cultured cells are added [72]. Long term results are not yet available to document the survival of implanted cartilage cells [73]. In Autologous osteochondral transplantation (OCT), mosaicplasty, cylinders of cartilage and bone are taken from a part of the joint that is not affected, and then inserted into the cartilage defect with press-fit technology. In principle, OCT can be performed through an arthroscope, unless the defect is too large [74]. The reported results of OCT are, in general, very promising [75]. Corrective osteotomy, either tibial osteotomy or femoral osteotomy is carried out to relieve pain in osteoarthritic knee which has either varus or valgus deformity [76]. As shown by Petterson, 2006, total knee replacement is one of the most sought after option in cases of end stage arthritis. Total knee replacement by modern technologies promises improvement lasting 15 years or longer. However these operations are very expensive, highly dependent on technical skills and the kind of implant materials employed [77].

### **3.5. Physiotherapeutic Measures**

Physiotherapy for knee osteoarthritis includes exercise therapy as well as electrotherapy including ultrasound application, Transcutaneous Electrical Nerve Stimulation (TENS), muscle stimulation, Pulsed electrical stimulation (PES) etc. Ultrasound (US) refers to mechanical vibrations which are similar to sound waves but of a higher frequency. The frequency employed for physiotherapeutic purposes is in the range from 0.5 to 5 MHz. Piezoelectrical transducers are used to achieve the high frequency ultrasound energy needed for imaging and therapy. These are suitably cut crystals (quartz, barium titanate or lead zirconate titanate) which change shape under the influence of an electric charge. The other essential parts of therapeutic ultrasound generator are a circuit to produce oscillating voltages to drive the transducer and a controlling unit which can turn the oscillator on and off to give a pulsed output. The principle therapeutic uses of ultrasound include promoting the healing of chronic ulcers, healing of acute soft tissue injuries, relief of both neurogenic and chronic pain, improvement of scar tissue etc [78]. Table 1 shows some recent study of US therapy for management of knee OA.

Table 1. Recent study of US therapy for management of knee OA.

Year	Author	Research/Work	Achievement/Outcome	Limitations
1995	Arne Nyholm Gam et al [95]	A meta-analysis of 293 papers published since 1950 to assess the evidence of effect of US in the treatment of musculoskeletal disorders.	Pain relief could not be achieved by ultrasound treatment hence, they concluded that the use of ultrasound in treatment of musculoskeletal disorders is based on empirical experience	Study is lacking firm evidence from well-designed controlled studies
1999	Danielle A.W.M. van der Windt et al [96]	Study to evaluate the effectiveness of US therapy in the treatment of musculoskeletal disorders.	No statistical significant outcome in favor of US therapy	Little evidence to support the use of US therapy in the treatment of musculoskeletal disorders
2005	Judith Falconer et al [97]	An RCT to determine the effectiveness of US (plus exercise) in relieving stiffness and pain on 69 patients diagnosed with knee OA and chronic knee contracture.	Study showed that both groups significantly improved in active ROM, pain, and gait velocity, and maintained improvement for at least 2 months.	Benefits of exercise program may have led to improvement in range of motion.
2007	Rita A Wong et al [98]	Survey study on 457 physical therapists (orthopedic certified specialists from the Northeast/Mid-Atlantic regions of the United States).	The respondents indicated that they were likely to use US for patient treatment. Thus Ultrasound continues to be a popular adjunctive modality in orthopedic physical therapy.	These findings may help researchers prioritize needs for future research on the clinical effectiveness of US
2008	Cetin N et al [99]	Study to understand the effectiveness of application of US and hot packs prior to isokinetic exercises on patients with bilateral knee OA	Improvement in isokinetic performance as well as physical function seen in treatment groups.	None reported
2008	Levent Özgönenel et al [100]	A randomized double blind clinical trial on 67 patients to determine the effectiveness of US therapy in knee OA	Statistically significant improvement was seen in the experimental group as compared to the placebo group.	None reported
2008	Grojamtvedt et al [101]	Systematic reviews published between 2000 and 2007 on physical therapy interventions for patients with knee OA	Besides exercises, weight reduction, acupuncture, TENS and low level laser therapy, the quality of evidence is low in other interventions incorporated in the treatment of knee OA.	None reported
2008	John Z Srbely et al [102]	A Pubmed search of the literature was performed from 1985 to 2008 and retrieved a total of 313 publications. A total of 17 articles met the researchers search criteria and hence was considered.	Ultrasound proven to therapeutically beneficial, safe and effective for the management of knee OA	Lack of consistency in current literature. Strict methodologies and meticulous reporting of output parameters and application techniques mandate in future studies. Conduct of isolated studies on US alone by excluding adjunctive modalities in their methodology.
2010	F Tascioglu et al [103]	A study to understand the effectiveness of either pulsed US, continuous US or sham US on 90 patients with idiopathic knee OA aged 54 – 70 years.	pulsed ultrasound therapy was proven to be safe and effective form of treatment modality	Long term efficacy of ultrasound therapy for knee OA requires further investigation.
2010	A. Loyola-Sánchez et al [104]	A systematic review of US therapy on knee OA	US could be efficacious for decreasing pain and may improve physical function in patients with knee OA	Low quality of evidence. More clinical trials are mandate.
2010	Rutjes AWS et al [105]	Study on effectiveness of US therapy on knee or hip OA when compared to sham treatment or no treatment.	Therapeutic ultrasound may be beneficial for patients with osteoarthritis of the knee	Methodological quality and the quality of reporting was poor and a high degree of heterogeneity among the trials was revealed for knee function
2013	Mirsad Muftic et al [106]	Prospective study on 68 patients to determine the effectiveness of continuous US to chronic musculoskeletal pain.	Chronic pain caused by degenerative changes could be alleviated by application of continuous ultrasound.	None reported

Conclusions drawn from the table showed that besides a few studies where no significant changes were observed, other studies showed significant improvement and was found to be beneficial as it was safe and improvement in physical functions in patients were observed with reduction in pain.

Transcutaneous Electrical Nerve Stimulation (TENS) is the application of low frequency current in the form of pulsed rectangular current through surface electrodes. TENS is usually employed for pain relief. TENS is mostly applied as short pulses of around 50micro seconds at 40-150 Hertz, called as conventional TENS, and is a high frequency, low intensity stimulation. These low intensity short pulses will selectively stimulate the large low threshold A Beta fibres and produce pain inhibition by pain gate mechanism, as proposed by Melzac and Wall, 1965 [79]-80]. This conventional mode is the most usual method for self-treatment. The recommended duration

and timing of such treatment varies from 30-60 minutes sessions, once or twice a day as stated by Klein and Pariser, 1987 [81].

Acupuncture like TENS or high intensity, low frequency stimulation, is commonly used. Pulses of around 0.2 milli seconds at about 2 Hertz are given at intensities so that a visible contraction can be seen. This kind of stimulation stimulates the small diameter A delta and C fibres causing release of endogenous opioids. It is mostly applied to acupuncture points hence relieving pain. It is applied for 20-30 minutes per session.

Table 2 shows an overview of some recent study on TENS therapy on knee OA. There have been a few contradictory results. Though there have been inconclusive results, many results concluded that it was effective only for a short term duration, and that too mostly pain relief.

Table 2. Recent study on TENS therapy for management of knee OA.

Year	Author	Research/Work	Achievement/Outcome	Limitations
2001	Osiri et al [107]	Systemic review of TENS on knee osteoarthritis	Conventional TENS and acupuncture-like TENS effective over placebo	The studies were heterogeneous with different study designs and outcomes used
2003	Kathleen A. Sluka and Deirdre Walsh [108]	Study of clinical effectiveness of TENS.	Though TENS is a non-invasive modality that is easy to apply, clinical efficacy remains equivocal	Sufficient numbers of high quality, randomized, controlled clinical trials needs to be done
2003	Gladys L. Y. Cheing et al [109]	Study to examine the optimal stimulation duration of TENS for relieving OA knee pain and the duration of post-stimulation analgesia	40 mins is the optimal treatment duration of TENS, in terms of both the magnitude of pain reduction and the duration of post-stimulation analgesia for knee OA	28 patients received either 20 mins, 40 mins, 60 mins of TENS or 60 mins of placebo TENS 5 days a week for 2 weeks
2004	Pearl P. W. Law et al [110]	Study on the improvement of physical performance of people with knee OA using TENS	Improvement observed till about 10 days, insignificant beyond it	A larger study with the assessment of other functional outcomes may be required
2007	Kazunori Itoh et al [111]	Study tests whether a combined treatment of acupuncture and TENS is more effective than acupuncture or TENS alone for treating knee osteoarthritis (OA).	The study showed that TENS gave short relief from pain while acupuncture gave a longer relief and the combination of both gave a better result than control group, only acupuncture or only TENS treatments.	Initially 32 patients were taken for the purpose, but on completion, only 24 remained.
2007	Jan M Bjordal et al [112]	Assessment of the short-term pain relief of the physical agents for knee osteoarthritis	2-4 week treatment regime seemed to offer clinically relevant short-term pain relief	No. of trials taken were 11
2009	Anne W.S. Rutjes et al [113]	Comparison of TENS with sham or no specific intervention in terms of effects on pain and withdrawals due to adverse events in patients with knee osteoarthritis	The study was inconclusive. It could not be confirmed that TENS was effective for pain relief	Small trials of questionable quality. Appropriately designed trails of adequate power were warranted
2012	Wright A. [114]	A study to explore the evidence for using TENS to relieve pain	Literature available provides conflicting evidence.	Inherent problems with trail designs,
2015	Carol G.T. Vance et al [115]	Critical review of the latest basic science and clinical evidence for TENS	High frequency and low frequency TENS have been shown to provide analgesia specifically when applied at a strong, non-painful intensity and high frequency TENS may be more effective for people taking opioids.	Further investigation is warranted to ensure optimal use. Investigation in the area of TENS tolerance is necessary

Electrical stimulation has been used to increase strength [82] and endurance of muscle, improve range of motion, neuromuscular re-education, pain management, reducing oedema, and as an aid in the healing of bone fractures and pressure sores. Electrical stimulation excites the motor nerve going to muscle and not muscle itself. Therefore, high frequency stimulation (>70 Hz) may cause neuromuscular junction failure and muscle will rapidly fatigue. The optimum frequency is similar to the range of normal motor unit discharge frequencies generated during voluntary activity, 20-50 Hz. Lower frequencies cause an unfused muscle contraction. With optimum electrical stimulation, the

cutaneous sensory nerves gets stimulated first, followed by motor nerve stimulation and finally the stimulation of small diameter pain fibres. The sequence of stimulation of these three types of nerve fibers is affected in the same order with any form of stimulating pulse. Neuromuscular electrical stimulation (NMES), used interchangeably with electrical stimulation (ES), is typically provided at higher frequencies (20-50 Hz) to produce muscle tetany and contraction that can be used for functional purposes. Some recent studies on NMES therapy for knee OA management have been shown in table 3.

Table 3. Recent study on NMES therapy for management of knee OA.

Year	Author	Research/Work	Achievement/Outcome	Limitations
1992	David A. Lake [116]	An overview of the effects of NMES and its application on sports injuries	NMES can improve functional performance in a variety of tasks. NMES has been shown to be effective in preventing the decrease in muscle strength, muscle mass and the oxidative capacity of thigh muscles	Unclear whether the selective strengthening is due to local changes in muscle or to a change in the relative magnitude of recruitment of the different muscles
2005	John P. Porcari et al [117]	To study the effects of self administered NMES on the abdominal wall to check changes in strength, endurance, selected anthropometric measures and subject's perceived shape	The study found that NMES significantly increased the isometric strength and dynamic endurance of the abdominal musculature.	Studies may be needed to compare the benefits of using NMES to those performing abdominal curls
2010	Palmieri-Smith et al [118]	Study to determine whether NMES is capable of improving quadriceps muscle strength and activation in women with mild and moderate knee OA	Improvement was not realised.	Women were enrolled based on radiographic evidence of OA, not symptomatic. Also assessor and patients were not blinded to group assignment
2011	Julien Gondin et al [119]	To provide an overview on the benefits and limitations of NMES training program in healthy individuals and in recreational and competitive athletes regarding muscle performance	Short term NMES training appears as an attractive tool for increasing muscle performance. It imposes a specific muscle stress leading to the recruitment of motor units different from those activated throughout voluntary actions	Future studies should focus on the chronic effects of NMES. Also it is needed to better understand the influence of reduced NMES training volume
2012	Bruce-Brand et al [120]	Comparison of NMES, resistance training (RT) and standard care in subjects with moderate to severe knee OA	NMES program significantly improves functional performance in patients with moderate to severe OA. Significant intra-group increase in quadriceps CSA	Dose-response studies with longer follow-up are required to establish the optimum frequency and intensity on NMES training
2012	Mônica de Oliveira Melo et al [121]	Identification of evidence in favour of the use of NMES on quadriceps muscle strengthening in elderly with knee OA	Best result analysis showed moderate evidence in favour of NMES alone or combined with exercise for isometric quadriceps strengthening in elderly with OA	Methodological quality and poor description of the measurement methods
2013	Marco Aurélio Vaz et al [122]	Identifying the association of knee OA with quadriceps muscle architecture and strength and quantifying the effects of a NMES training program on these parameters	Knee OA patients have decreased strength, muscle thickness and fascicle length compared to age and sex matched controls. NMES training offset the changes of quadriceps structure and function, reduces joint pain and stiffness and functional limitation	How NMES reduces muscle inhibition is not clear. The possibility that after NMES training, strength gains observed may partly be associated with an improvement in activation capacity of the quadriceps, needs to be further investigated
2013	Aline Mizusaki Imoto et al [123]	The study investigated the effect of 8 weeks of NMES + Ex (Exercise) on pain and functional improvement in patients with knee OA compared to Ex alone	The addition of NMES to Ex did not improve the outcomes assessed in knee OA patients	100 no. of patients were taken into consideration (86 women and 14 men) with age ranging from 50 to 75 years



Results obtained from the table showed no improvement in two cases whereas in almost all the cases, significant increase in muscle strength was observed, hence increase in functional performance in patients.

One electrotherapy treatment technique, namely the pulsed electrical stimulation (PES), has been employed to decrease pain and improve function in knee OA. High Voltage PES has shown to retard edema

formation in an experiment done on golden hamsters [83], and in some cases have caused healing of dermal ulcers [84]. However, there are not much supported literature available showing the use of PES in the management of OA. Some recent studies on PES therapy used for the management of knee OA have been shown in table 4.

Table 4. Recent study on PES therapy for management of knee OA.

Year	Author	Research/Work	Achievement/Outcome	Limitations
1995	Thomas M Zizic et al [124]	Prospective, randomized, placebo controlled double blind study to test the effectiveness of PES device (Bionicare Stimulator, Model BIO-1000™ ) on patients with knee OA	Intermittent PES therapy provided significant short term improvement in knee pain, function, knee flexion, and duration of morning stiffness in patients with knee OA.	Treatment time was only for four weeks.
2006	Farr J et al [125]	Prospective cohort study on 288 patients to see the effectiveness of PES on knee pain n other symptoms.	This study showed that use of PES device can reduce knee OA symptoms in patients who had failed non surgical treatment.	None reported
2007	D. Garland et al [126]	A 3-month, double-blind, placebo-controlled trial, using either an active (BIO 1000™ BioniCare Medical Technologies Inc ) or placebo device at home on patients with knee OA	Improvement in symptoms and functions in knee OA without any serious side effects.	None reported
2009	Robyn E Fary et al [127]	Case study on three subjects with knee OA to see the effectiveness of PES device(BIO 1000™, BioniCare Technologies)	Improvement on all outcomes were seen on two patients , but not so significant improvement was seen on one patient	Longer randomized controlled studies are needed to understand the effectiveness of Pulsed electrical stimulation.
2011	Robyn E. Fary et al [128]	A double-blind, randomized, placebo-controlled, repeated-measures trial , in 70 patients diagnosed with knee OA of the knee who were randomized to either PES or placebo group.	No significant improvement in the experimental group as compared to the placebo group.	Less literature available
2013	A. Negm et al [129]	To understand the effectiveness of low frequency (<100Hz) subsensory stimulation produced either by using Pulsed electromagnetic field(PEMF) or PES on knee pain and physical function of patients suffering from knee OA	Low frequency stimulation was effective in improving physical function but not pain intensity.	Inconclusive results due to less number of literatures available. More studies are mandate to confirm the findings of this systematic review.
1995	Thomas M Zizic et al [124]	Prospective, randomized, placebo controlled double blind study to test the effectiveness of PES device (Bionicare Stimulator, Model BIO-1000™ ) on patients with knee OA	Intermittent PES therapy provided significant short term improvement in knee pain, function, knee flexion, and duration of morning stiffness in patients with knee OA.	Treatment time was only for four weeks.
2006	Farr J et al [125]	Prospective cohort study on 288 patients to see the effectiveness of PES on knee pain n other symptoms.	This study showed that use of PES device can reduce knee OA symptoms in patients who had failed non surgical treatment.	None reported

From table 4, it can be seen that PES is a very recent method of physiotherapeutic intervention, and hence limited research works were found on it. The literature survey conducted with a few research works showed that the study was either of short duration, no improvement shown or number of subjects was less. A few studies did show some improvements regarding OA symptoms. Hence further research needs to be done in this area.

Application of PES affects the cartilaginous tissue, not all electric field or stimuli affect the cartilage. The effect on the cartilage depends on many factors, namely field strength, frequency, wave-form, time and duration of application etc.

Experiments performed with PES showed capacitively combined electric field increased glycosaminoglycan synthesis and chondrocyte cell proliferation in calf hyaline cartilage pellets and time-varying electrical fields could heal total thickness cartilage lesions with hyaline cartilage in a rabbit model of osteoarthritis. In another experiment, it was seen that electrical stimulation when added to background NSAIDs or analgesics enhanced pain reduction and increased function. Thus, in vitro, animal histological and human data exist to support further trials of time-varying electrical stimulation in human osteoarthritis [145].

#### **4. EMG studies on OA knee**

Electromyography (EMG) is an experimental technique concerned with the development, recording and analysis of myoelectric signals [130]. Till date; EMG signals have been used for better understanding and diagnosis of various diseases [141-143], evaluation of different exercises [144], understanding of muscle function [134], neuromuscular pattern [139], and estimation of muscle forces [131]. In one such study conducted by David G. Lloyd et al, 2003, an EMG driven musculoskeletal model of the human knee was employed to predict knee moments in different dynamic contractile conditions [132]. EMG study has also been employed to provide knowledge about the dominant force producing muscle during a particular test procedure in the lower extremity [133]. Ozlem O. Yilmaz et al, 2010, have shown that there is no significant superiority of EMG-biofeedback-assisted strengthening exercise program to strengthening exercise program without EMG-biofeedback, however there was improvements in parameters such as muscle

strength, pain and function in both the groups after the treatment [137].

Disturbances in normal load distribution and altered muscle activity have been associated with knee OA which can cause further deterioration of the knee joint. Tibor Hortobágyi et al., 2005, found that there is increased hamstring muscle activation than the quadriceps group [138], while performing routine daily tasks in subjects with knee OA. Hence, it has been observed that patients with knee OA have higher antagonist muscle activity [140] as compared with the control subjects.

#### **5. Conclusion**

Knee OA is considered to be the fourth highest cause of disability in women and is responsible for the deterioration of quality of life and functional capacity [85]. A plethora of studies have investigated several aspects related to muscle function, such as aerobic capacity [86], muscle strength [87] as well as other clinical aspects such as pain [88], Range of Motion [89], stiffness [90], and WOMAC Index [91] in patients suffering from knee OA. However there are scant Electromyogram (EMG) studies for those diagnosed with moderate and severe OA [92]-[94]. This review has certain limitations. Since only English language articles were included, it is possible that this review is not a complete representation of the available evidence. The review was limited to published articles and thus may have missed those that were not submitted or accepted for publication, presenting a possible publication bias. We are conducting an in house study employing EMG and motion studies to understand the muscle activities, kinematics and dynamics around knee joints of those patients suffering from moderate to severe knee OA. The study shall be age and gender controlled study. Simultaneous study of ground reaction forces on the affected limb shall be conducted to understand the loading on knee joint, while the subject performs routine daily tasks. We aim to utilize these results in the development of a pulsed electrical knee stimulator for relief of knee symptoms.

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