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"A STUDY ON EFFECTIVENESS OF VISCO-SUPPLEMENTATION IN OSTEOARTHRITIS KNEE"

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ABSTRACT

"A STUDY ON EFFECTIVENESS OF VISCO-SUPPLEMENTATION IN OSTEOARTHRITIS KNEE."

Background:

Osteoarthritis (OA) is a degenerative disease of synovial joints, recently it is also termed as osteoarthrosis.[1] It is among 10 leading causes of disability worldwide. Etiology is multifactorial and divided into local and systemic factors that include local trauma, obesity, synovitis, low grade inflammation and diabetes.[4] A community based programme showed the prevalence of knee OA in urban population was 5.5%, where as in rural population of India it was 3.9%. Higher-Molecular Weight Hyaluronic Acid has a better increase in fluid retention with in the joint and stronger anti-inflammatory effect.

Objectives of the study:

To assess the efficacy of intra articular HA in primary osteoarthritis of knee joint based on clinical outcome with visual analogue score (VAS) and The Western Ontario and McMaster Universities Osteoarthritis index (WOMAC score) and to determine the safety of Intra Articular Hyaluronic Acid in primary osteoarthritis of knee joint.

Material and method:

A Single Group Prospective Interventional Study conducted from November 2017 –May 2019 in R L Jalappa Hospital which is affiliated to Sri Devaraj Urs Medical College, constituent college of Sri Devaraj Urs Academy of Higher Education and Research , Tamaka, Kolar will be enrolled for the study. A total of 36 patients with grade I and II of kellegren Lawrence radiological grading were included and given hyaluronic acid injection and assessed by WOMAC and VAS scores.

Results:

Of the 36 cases, there are 8 male and 28 female patients while 4 cases fall under Grade 1 and 22 cases fall under Grade 2 osteoarthritis. In our study right side knee is more commonly affected than left side knee. After 6 months post injection the WOMAC scores were decreased from their pre injection values with less than 30 over 12 patients in that 5 were grade I and 7 were grade II only 2 patients. At 6 month post injection the patient improved was 15 with a score 0-5 some patient were still in range of 6-10.

Conclusions:

The study concluded that the mean VAS and WOMAC score pain, stiffness and functional ability improved in all the study patients by the end of 6 months follow up. This study observes that intra-articular injection Hyaluronic acid is a reliable, productive, efficient and safe mode of treatment of grade I and II osteoarthritis knee, which also delays surgical intervention.

Key words:

Osteoarthritis, Hyaluronic acid, WOMAC, VAS, Kellegren Lawrence grade, Intra articular Hyaluronic acid injection

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DR SAKTHIKESAVAN S

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Glossary	Abbreviations
OA	Osteoarthritis
HA	Hyaluronic acid
HMW	High molecular weight
i.e,	That is
TF	Tibiofemoral
PF	Patellofemoral
WOMAC	The Western Ontario and McMaster Universities Osteo arthritis Index
VAS	Visual analogue scale
KL	Kellegren Lawrence
RCT	Randomized control trial
IL	Interleukin
PRP	Platelet rich plasma
ACL	Anterior cruciate ligament
PCL	Posterior cruciate ligament
MCL	Medical collateral ligament
LCL	Lateral collateral ligament
UKA	Unicompartmental knee arthroplasty

TKA	Total knee arthroplasty
mg/ml	Milligram / milliliter
TGF	Transforming growth factor
VEGF	Vascular endothelial growth factor
NSAID	Non steroidal anti inflammatory drugs
TA	Triamcelone acetate
CS	Corticoid/ corticosteroid
BMI	Body mass index
MMP	Matrix metallo proteins
ECM	Extra cellular matrix
AP	Antero posterior
PG	Prostaglandins
ACR	American College of Rhematology
MA	Methylprednisolone acetate
AAOS	American Academy of Orthopaedic Surgeons

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease of synovial joints, recently it is also termed as osteoarthrosis.[1]

It is a progressive degenerative condition in which it affects most parts of synovium, ligaments around the joint, meniscus and bones in subchondral region along with loss in the articular cartilage.[2]

It is more common joint disease with most commonly disabling nature than rheumatoid arthritis.[3] It is among 10 leading causes of disability worldwide. Etiology is multifactorial and divided into local and systemic factors that include local trauma, obesity, synovitis, low grade inflammation and diabetes.[4]

KNEE JOINT:

Knee joint is the largest synovial joint composed of distal femur, tibia and patella, meniscus, ligaments and synovial membrane. The synovial membrane gives lubrication and nutrients to avascular cartilage.[5]

ANATOMY:

The lower limb buds appear initially at 4 weeks post fertilization and skeletal elements of lower limb will begin to chondrify from proximal to distal sequence at 5 weeks after fertilization.

The bony structures articulating at knee joint such as femur and tibia has clear cut cartilaginous forms by 8 post ovulation weeks. The patella chondrifies during this time and tendons, cruciate ligament, collateral ligaments and both menisci are clearly differentiated.[6]

Ossification in the upper epiphysis of tibia and lower epiphysis of femur by 13th week and ossification of patella starts by 14th week of gestation.[7]

JOINT STRUCTURE:

The knee joint is heavily loaded and largest joint in the human.[8]The structure of knee joint can be divided into two parts i.e. the tibiofemoral (TF) joint and the patellofemoral (PF) joint. TF joint is between tibia and femur and PF joint is between patella and femur.TF joint will transmit the weight of body from the femur to the tibia

that provides a hinge-like, sagittal plane joint rotation along with some small degree of tibial axial rotation. The PF joint with quadriceps helps in momentum of the body while walking.

The ligaments which are around the knee joint plays an important role during normal day- to-day and recreational activities, also to restrain knee motion during multiple degrees of freedom. These ligaments surrounding knee plays an important role by transmitting the weight through the knee joint, therefore the load will be centering in the joint to minimize the amount of wear and tear on the articular cartilage.[9]

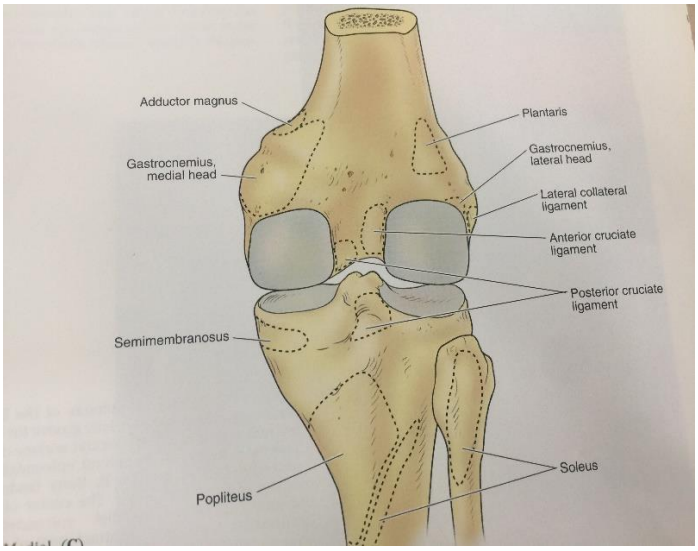


Fig.1 Anterior aspect of knee

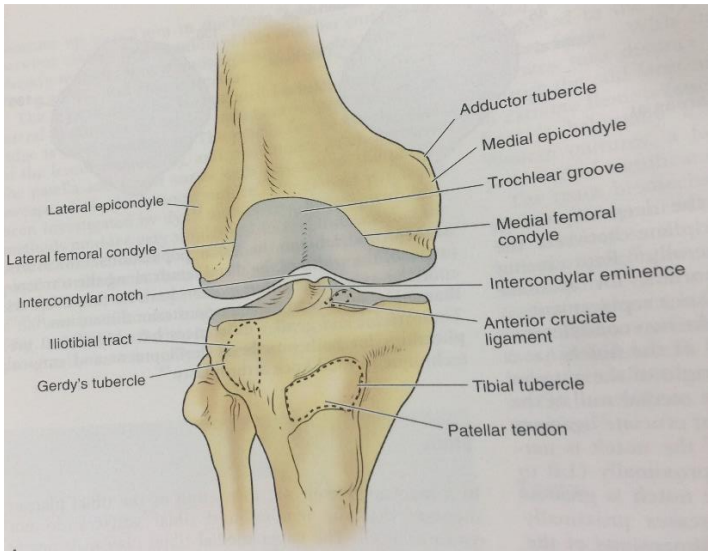


Fig 2 Posterior aspect of knee

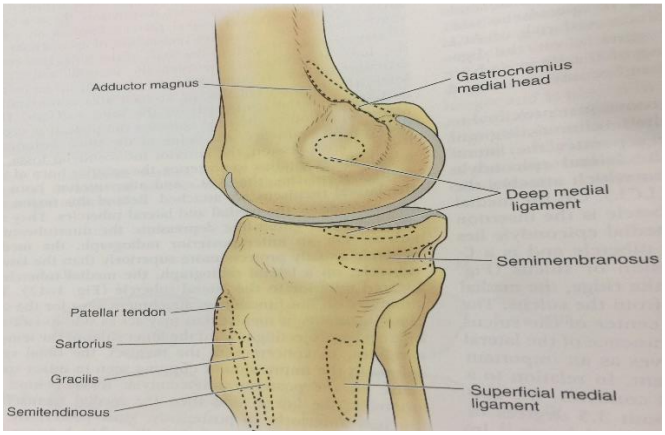


Fig. 3 Medial aspect of knee

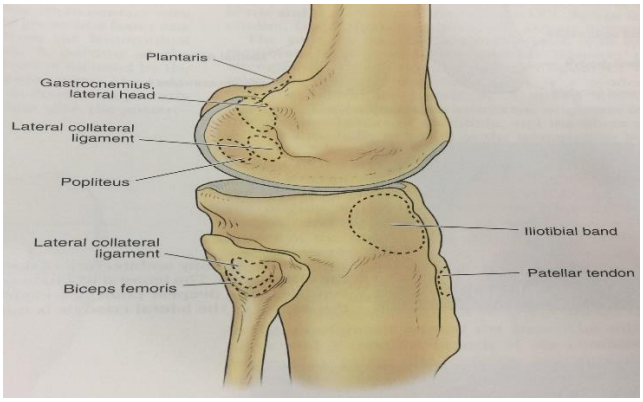


Fig. 4 Lateral aspect of knee

ARTICULAR CARTILAGE:

The bony surfaces of knee joint such as femur, tibia and patella are covered by thin articular cartilage layer which represents the weight bearing surface in our body. It is a flexible and mechanically compliant connective tissue present at the end of long bones i.e. in articulating joints.[2]Function of articular cartilage is to provide lubricated smooth surface for the articulation between two bony ends. It also transmits the loads with a low frictional co-efficient.[10]Eventhough most factors play a role, the articular cartilage component has its own implication in initiation and progress of disease

Articular cartilage of knee joint which surrounding over the distal part of the femur and the proximal part of the tibia will provide a smooth layer for joint articulation. This cartilage layer plays the significant role in providing damping of joint contact forces and also in the joint lubrication.[11,12]The knee joint capsule secretes the synovial fluid and also encloses the joint space. It also functions as a passive knee stabilizer that limits joint movement and it acts actively through the proprioceptive nerve endings.[13]

STRUCTURES IN AND AROUND THE KNEEE JOINT:

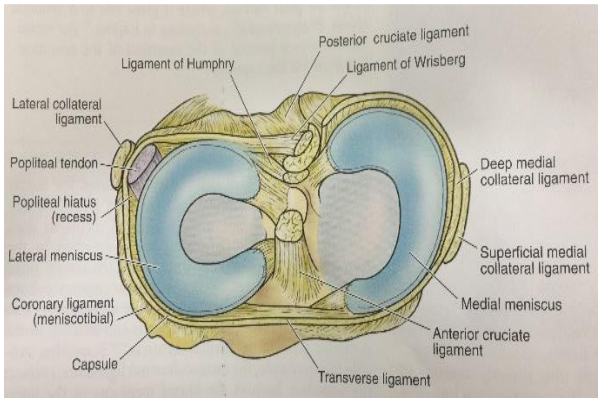


Fig 5 superior aspect of knee joint

The primary function of the patella is increasing the lever arm of the Quadriceps femoris muscle complex.[14]The most frequently injured part in the body is the knee. [15,16]The role of knee joint is to transfer the weight of the body is also loaded by muscles forces around the knee. And at the same time, it generates a flexible movement at the knee.[17]The collagenous structures are the major constituents of the knee joint that provide stability by limiting range of motions in the knee joint and its deformation. [18]

The capsule and ligaments of the knee joint are the most frequently injured soft tissues.[15]In the knee joint, ACL ligament restrains anterior translation [19,20,21]and PCL ligament restrains posterior translation [19] of the tibia relative to the femur.

Functionally, the cruciate ligaments can be divided into two bundles, that is, the ACL has posterolateral and anteromedial bundle. [22]The anteromedial bundle is tighter when the knee is flexed especially in the higher knee flexion angle.The posterolateral bundle becomes taut when the knee is in extension to the full extension position and flexed in lower flexion angle.[23] Whereas the anteromedial bundle becomes taut in the higher knee flexion.

The PCL also contains anterolateral and posteromedial bundle. The anterolateral bundle becomes taut during knee flexion whereas the posteromedial bundle, will be taut during knee extension and deep flexion.[24]

The primary function of LCL as the knee stabilizer during the rotation (varus) loads especially during 0 to 30 degrees flexion. The ligament also resists the rotation of the tibia especially near the knee extension position.[19] as well as to restraint abnormal motion .[25]

The MCL functions as a primary restraint to valgus rotation in the intact knee, especially during knee flexion angles higher than 25 degrees [26]and dominantly at knee flexion angles between 30 and 90 degrees.[27]The posteromedial aspect of the capsule is relaxed and this results in relaxation of the knee capsule during increasing knee flexion and an increasing role of MCL in controlling a valgus rotation.[28] The MCL also serves as a stabilizer against an excessive internal rotation at knee flexion position[22,27] Consequently, the capsules around the knee are involved in controlling the lateral as well as rotational movements in the knee joint both during flexion & extension.

OSTEOARTHRITIS:

OA refers to the clinical syndrome of joint pain with multi factorial etio-pathogenesis which was characterized by the gradual loss of articular cartilage, osteophyte formation, subchondral bone remodeling and inflammation of the joint. Osteoarthritis is a major source of disability owing to pain and loss of function[4].

INCIDENCE:

A study comprising of elderly population in india showed the prevalence of OA knee overall to be 57%, where as in rural areas it was found to be 33% and in urban population to be 60%. [29]

In another study conducted for control of rheumatic diseases which was a community based programme showed the prevalence of knee OA in urban population was 5.5%, where as in rural population of india it was 3.9%.[3]

In Asia, approximately 40 million of the 130 million people with OA will have severe disabling disease by 2030. Prevalence rates in India range from 22 to 39%. [30] In another study the prevalence ranges from 17-60%. Knee osteoarthritis increases with age, about 11% of all women over age 60 years have symptoms due to OA knee. 40% of Indian population above age of 70 years suffer from OA knee. [31]

The OA knee prevalence indefinitely increase with the increase in age as the condition is irreversible. Prevalence are more in men with age <45 years and female >55 years.3 Osteoarthritis has historically been classified as 'primary' if no discernible cause is

evident (e.g. related to age and genetics) and 'secondary' if a triggering factor is apparent (e.g. associated with a history of joint injury, such as those caused by trauma, infection, surgery, mineral deposition, or autoimmune disorders) .[32]

In a study conducted in 2010 global burden of disease OA knee & hip ranked 11 in the global disability. In UK every 3rd person who is 45 years and above were seeking treatment for osteoarthritis.[3]

In Canada, current prevalence is in the range of 1:6 which is predicted to go up to 1:5 by 2031. In Australia OA is the chronic disabling disease causing early retirement. In Asia, approximately 40 million people of the 130 million people with OA knee will have severe disabling disease by 2030.[33]

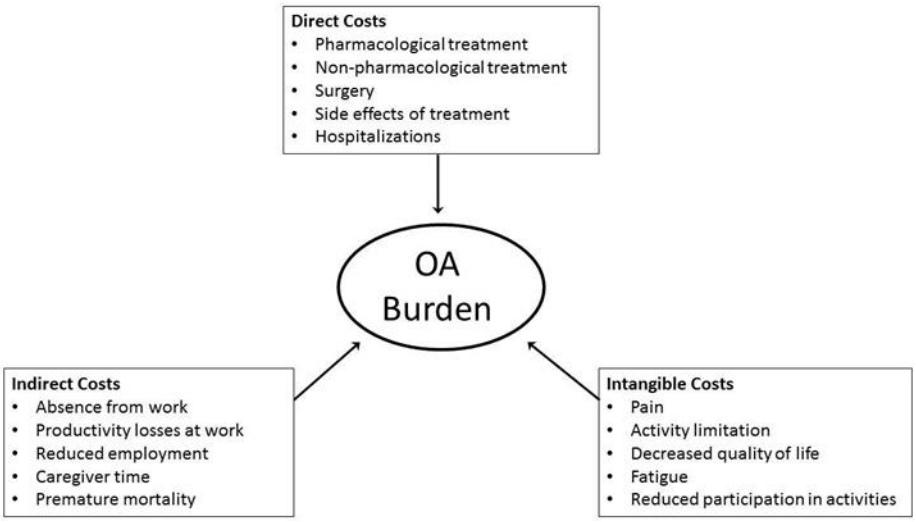


Fig.6 The burden of OA is affected by direct, indirect and intangible costs.[34]

Knee OA, increase with age, about 11% of women over age 60 years have symptoms due to OA knee. 40% of Indian population above age of 70 years suffer from OA knee symptoms. Prevalence are more common in men with age<45 years and females >55 years.

PATHOPHYSIOLOGY:

Lots of debate is going on in role of inflammation in OA knee. Either inflammatory reaction triggers the OA changes (or) instead, inflammation is secondary to OA knee changes.[4]

Synovitis is infiltration of inflammatory cells into synovium is present mostly early stages of OA knee. It is correlated with the severity of the disease. [35]

Many inflammatory mediators- 1) Plasma protiens like CRP- marker for development & progression of OA knee. 2) Prostaglandins like PGE2. 3)Leukotriens like LKB4. 4) Cytokines like TNF, IL-1BETA, IL6. IL15, IL 17, IL18, IL21. 5)Growth factor like TGF-BETA, FGP,VEGF were present in synovial fluid in patients with OA knee. [35,36]

Most of these components induces MMP and hydrolytic enzymes (cyclo-oncogenes?) PGE-cartilage breakdown, which is secondary to PG and collagen destruction. [37]

CYTOKINES AND OSTEOARTHRTIS:

Chondrocyte cells found in cartilage were primarily responsible matrix synthesis and its break down. This is regulated by cytokines and growth factors. In arthritic condition there is disturbance in chondrocyte balance.

Apoptosis (programmed cell death) of chondrocytes (chondroptosis) has also been found to be playing an important role in articular cartilage degeneration and its failure in OA. [38-43]

The common molecular inducers of chondroptosis may include ROS, RNS, cytokines [IL-1β, TNF-α, TNF-related apoptosis inducing ligand, and Fas ligand], and mechanical stress.[42] In an in vitro study, Miwa et al. [44] demonstrated that chondroptosis appears to be due to elevated PGE2 through a cAMP-dependent pathway. In addition

to this inflammatory pathway, mitochondrial dysfunction pathway leading to oxidative stress is another contributing factor to chondroptosis.[45]

Hashimoto et al.[46] and Kim et al.[40] reported that the collagen framework plays a significant role in chondrocyte survival and its maintenance in the cartilage, and upregulation of Fas ligand in matrix depleted specimens suggested that the Fas pathway may have a role in chondroptosis induced by matrix depletion. In another study, Blanco et al.[38] found that IL-1-stimulated chondroptosis occurs due to excess generation of NO. Chondrocyte death is a central feature in OA progression. Chondroptosis is also characterized by increases in caspase-3 and−8, DNA fragmentation, increases in MMPs and ADAMTS,and decreases in aggrecan and type II collagen.

Chondrocyte death and ECM loss appears to be interlinked. Chondroptosis triggers ECM loss and ECM loss will further activate pathways leading to chondrocyte death leading to a vicious cycle.[42]In early and late stages of OA, the key cytokine is IL-1.

The main functions of IL-1 are lymphokine production and cartilage breakdown. It also interferes with the activity of growth factors such as insulin like growth factor, and decreases the synthesis of key matrix components such as aggregan and fibroblast proliferation.[47]

Key regulatory mechanisms involved in regulating and controlling expression of cytokines is done by NF- kb (nuclear factor kappa-light-chain)which is critical in inflammation and immune function. [48]

It is also responsible for expression of IL1b and TNFa.[49]

Elevated level of TGF-b activity has been found in the synovial fluid of OA patients, in addition TGF-b released by tissue damage and inflammation triggers cells to form osteophytes.[50,51]

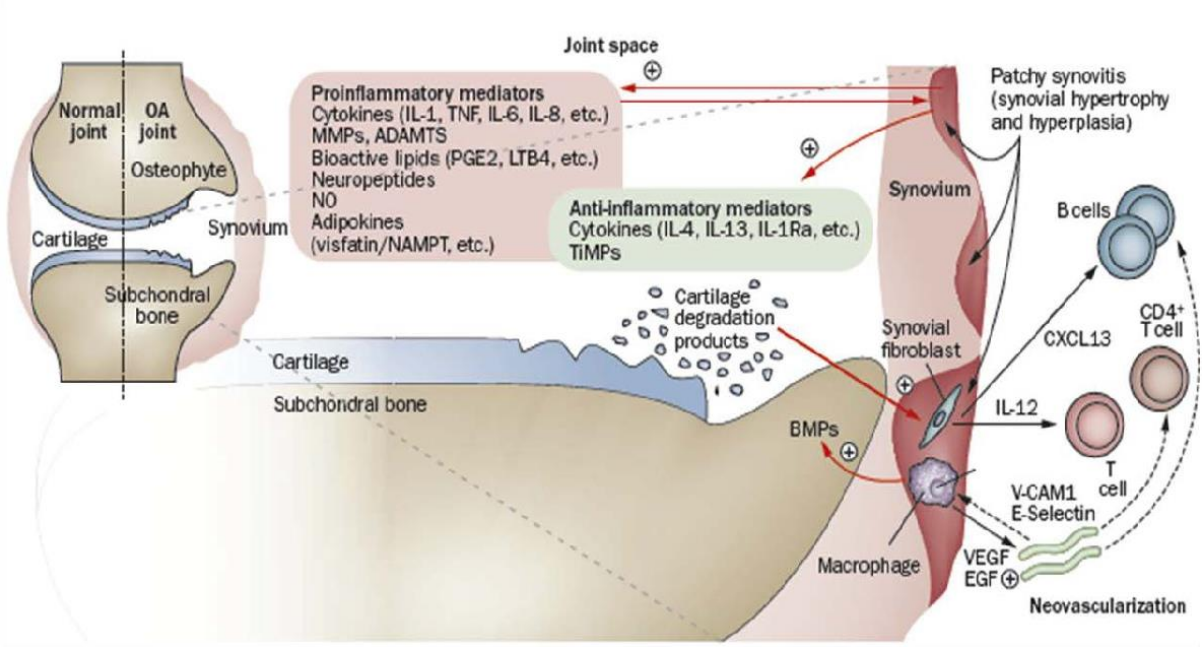


Fig 7: Pathophysiology of OA [37]

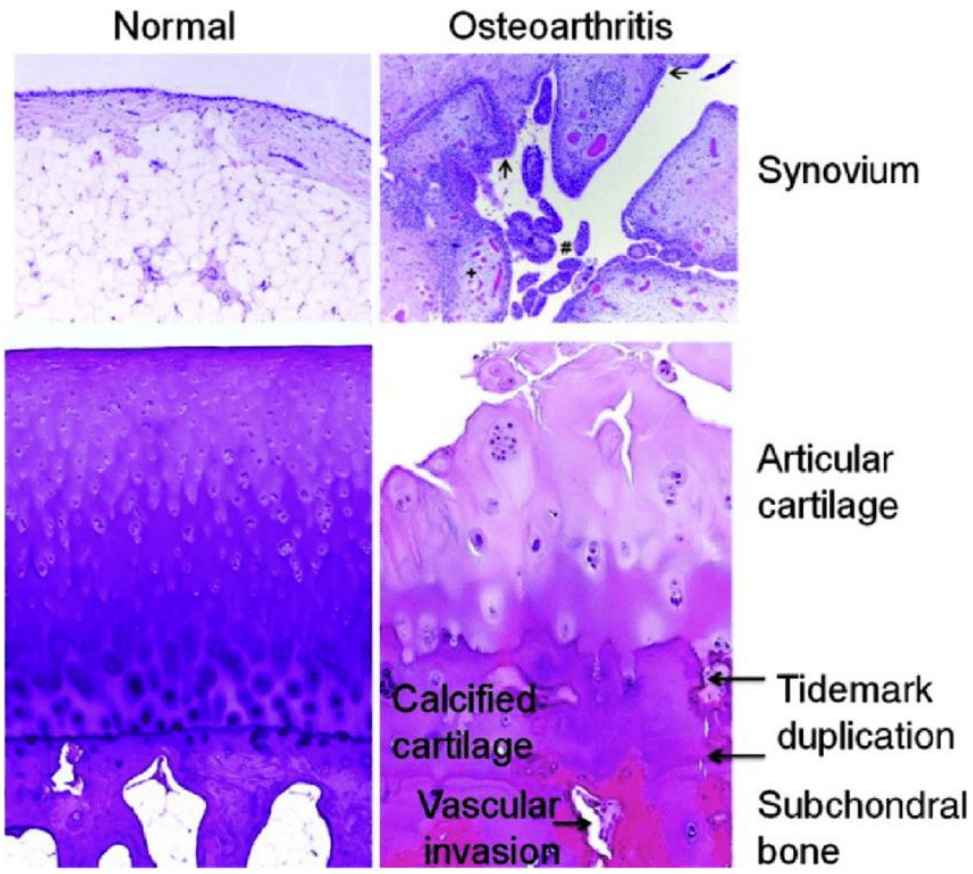


Fig 8.Histological features of OA. The normal synovium has a thin (1e2 cells thick) lining layer and a vascularized, loose connective tissue sublining layer. OA synovium demonstrates features of synovial villous hyperplasia (#), lining hyperplasia (arrows), increased vascularity (D), and perivascular mononuclear cell (inflammatory) infiltration. In OA articular cartilage, loss of cells and matrix is accompanied by areas of cell clusters. There is thickening of the calcified zone and duplication of the tidemark, which normally separates the articular cartilage from the underlying calcified cartilage. The subchondral bone is also thickened, and vascular invasion, which can extend through the tidemark and into the base of the articular cartilage, is seen. OA osteoarthritis.

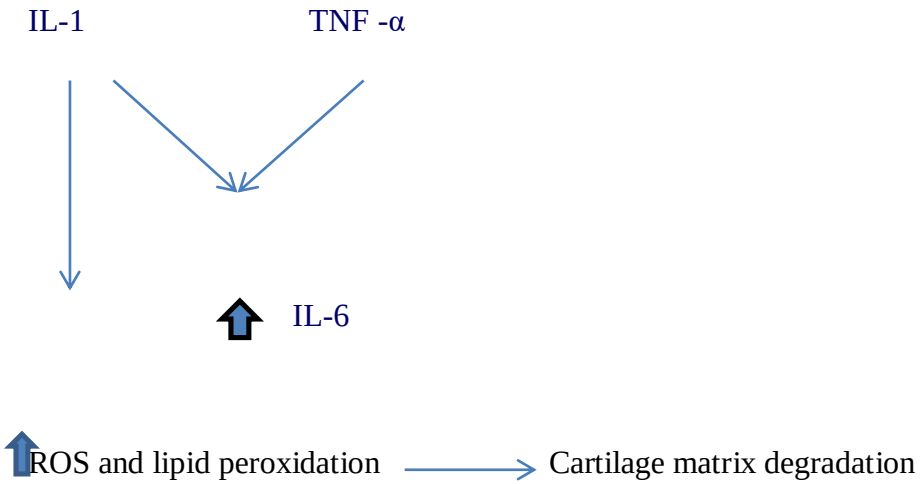


Fig.9 Role of interleukins in degeneration

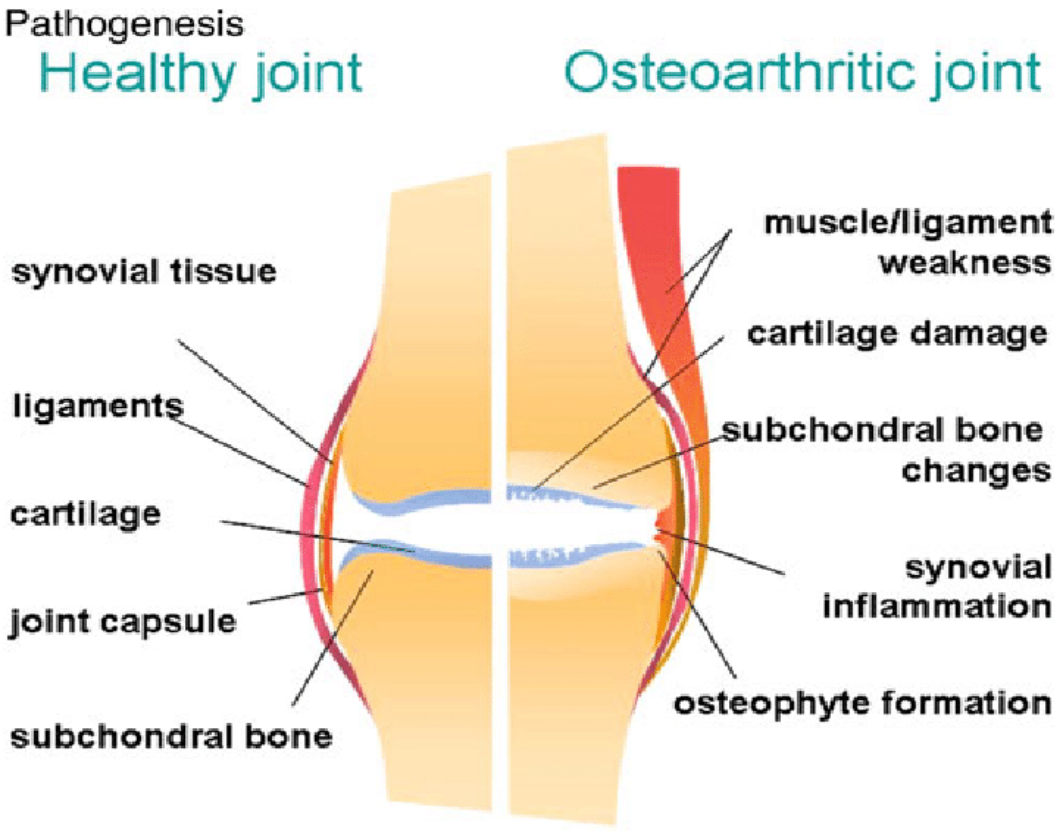


Fig. 10 Changes in oa knee in articular cartilage

CIRCADIAN RHYTHM AND OA KNEE

catabolic cytokines implicated in the pathophysiology of OA can disrupt the circadian clock and theexpression of clock-controlled genes in cartilage via an NFkB dependent pathway. The chondrocyte core clock gene and transcription factor BMAL1 is the key genes that controls cartilageintegrity and its homeostasis. Another study by Dudek and colleagues shows that BMAL1 is disrupted in human OA cartilage and in aged mouse cartilage.

circadian rhythm disruption is a risk factor for the pathogenesis and progression of degenerative joint diseases such as OA.[53] Clock genes are also believed to regulate reactive oxygen species (ROS) homeostasis and oxidative stress responses that suggests the disruption of circadian rhythms may exacerbate inflammation and enhance ROS levels and oxidative stress signaling in OA.[54]

SLEEP DISTURBANCE AND DEPRESSION IN OA:

Sleep disturbance in OA is linked withdisability, pain and depressive symptoms. Their work highlights the link between sleep disturbance, disability and pain in OA. Depression appears to play a strong role in the sleep-pain linkage, particularly when pain is particularly severe.[55]

RISK FACTORS:

The most important OA risk factors are age, gender, genetics, overweight/obesity, joint trauma/sports injuries (and the consequent joint instability and muscle laxity), certain occupations that place repetitive stress on a particular joint , bone deformities, metabolic disease (i.e. diabetes), endocrine disorders and having previously had other rheumatic diseases such as RA and gout.

There is clinical evidence to suggest that the risk for developing OA can be mitigated and reduced by weight management, avoiding obesity/overweight, maintaining high levels of mobility and avoiding sedentary lifestyles.

Systemic risk factors for OA

1. AGE:

   Age is one of the very important factor for the development of osteoarthritis; as the age increases, the tensile property of cartilage network in knee articular cartilage is decreased that will result in the accumulation of glycation products which causes mechanical failure.[56]

2. Gender

Women will have a severe disability and pain than men.[57]

Osteoarthritis has high incidence of 68% in women and 58% of men aged 65 and older.[58]

3. Genetics hormones:

Classic study of monozygotic twins aged 48 to 70 years, having identical genes showed 65% influence of genetic factors in developing of osteoarthritis.[59]

Between 39% and 65% of the osteoarthritis cases in the general population can be attributed to genetic factors, women after menopause are more susceptible to knee arthritis because of increasing level of osteocalcin and bone resorption.[60]

osteocalcin, a marker of bone turnover, were in lower quantity in women with knee osteoarthritis.[61]

4. Diet:

Rapid changes in lifestyle and diet by consumption of unrefined carbohydrates and Junk foods leads to increased the rate of chronic diseases.[62]

5.Joint injury and trauma

Articular cartilage usually tolerates loading from daily physical activities, in knee joints injuries and trauma the cartilage will lose its flexibility, also kills the cells and decrease the loading of the subchondral Bone. [63]

6. Obesity

People with high body mass index (BMI) as a measure of relative weight for obesity, has a positive association between obesity and knee OA results in substantial overloading and damage to the knee joint.[64]

7. Occupation

The lifting of heavy loads was found mainly in farmers, fishermen, construction site workers, and general laborers. Walking up stairs was experienced mainly by general laborers; all of these stress activities causes the strong relationship between osteoarthritis and knee injury.[65]

8. Physical activity/Sports

In china women practicing gymnastic or kung fu (traditional Chinese martial arts) regularly were at the risk of Knee injury.[66]

TYPES:

Osteoarthritis has been historically classified as primary if no discernible cause is evident i.e related to age and genetics and secondary if a triggering factor is apparent i.e associated with history of joint injury such as those caused by trauma, infection, surgery, mineral deposition or auto immune disorders.[67]

Most commonly used case definitions are

1.Radiographic OA,

2. Symptomatic OA,

3. Self- reported OA

Radiographic definition is based on pathophysiological findings in X-rays.[68]

Symptomatic OA is considered when both radiographic and joint symptoms such as pain, stiffness & loss of function are related to the pathology.[69]

Self reported OA is in which patient had previous records of OA knee.[70]

PHENOTYPES OF OA KNEE:

There are 4 clinical phenotypes suggested by a study 8th journal these kind of categorization will help in relieving pain and management of different stages of OA knee.

Biomechanical OA: Mechanical stress will be one of the major factors that are involved in the development process of OA knee and its progression. High dynamic load in knee , particularly at the knee adduction moment impulse, were related with maximum loss of volume of medial tibial cartilage.[71] joint load of Medial aspect of knee during walk will especially be enhanced in individuals who are with varus malalignment and also

who had medial meniscal injury. It is noted that there is correlation between the baseline level of cartilage volume with physical activity.[72]

Overweight and obesity has harmful effect on the biomechanics of knee, although the proinflammatory adipokines will partially correlates increased BMI and knee OA.[73] The Surrogates for mechanical stress i.e fat free mass and body weight have been strongly associated with development of OA knee, in many population-based cohort studies, even there is adjustment of metabolic factors .[74]

The linear relationship between change in body weight and change in volume of tibial cartilage has been observed in obese patients at 2.3 years follow-up.[75] Likewise, loss in body weight alsoassociated with proteoglycan content improvement. and also in reduction of cartilage thickness loss of medial articular cartilage over 1 year.[76]Increase in Weight was found to have greater loss in cartilage , whilst loss in weight were associated with the converse in subjects with meniscal tears.[77] Patients who has biomechanical profile will benefit from non-pharmacology therapy such as load-modifying approaches and hyaluronic acid.

Osteoporotic OA: There is marked increase inof OA knee prevalence among women around menopause age. The estrogenic α receptors presence in joint tissues correlates role of estrogen deficiency in OA knee. Estrogens regulate the important cellular events at the level of articular tissues by acting through several molecular mechanisms which is complex at multiple levels.[78]Various studies of OA knee have reported that an elevated remodeling with an impaired subchondral bone structure that will aggravate damage to the cartilage.[79,80]

Epidemiological along with clinical studies have suggested a relationship between decreased estrogen with OA knee .[78] In some animal studies its been proved that, there was structural effects with estrogen therapy and SERMs.[82] There are recent studies showing decline in the 50% of biomarkers levels of cartilage degradation in women who receives estrogen therapy.[83] Recent studies shown, that women who all taking estrogen therapy had significantly very less knee joint arthroplasty,[84] and moreover, this estrogen therapy had reduced almost 40% of the revision arthroplasty of knee and hip.[85]

Together, all these data indicate that the deficiency of estrogen will induce deleterious effect on all the joint tissues, particularly at the level of sub chondral bone where there is high remodeling capacity which may lead to the progression of osteoporotic OA in early post menopause women.[86]Patients of this kind may potentially be responsive to bone active drugs.

Metabolic OA: Beyond the correlation between OA knee and metabolic syndrome including obesity there is increased affliction of hand OA,[87] which is a non weight-bearing joint that suggests the presence of a specific clinical subtype, referred to as metabolic OA. Metabolic factors that includes hypertension, high abdominal circumference, high fat consumption, and diabetes mellitus were associated with early degradation of cartilage measured with T2 relaxation times at the knee in middle-aged people.[88] The knee OA incidence was significantly related with the accumulation of MetS components. The prolonged duration of diabetes mellitus and hypertension was correlating with loss of subchondral bone in knee OA.[89]

Leptin values in human body were found to explain half of the association between knee OA and elevated body weight.[73] longitudinal cartilage thinning were correlated

with Both baseline leptin level and change in its level.[90] Furthermore, baseline leptin levels were also correlating with the presence of osteophytes, effusion and synovitis, also bone marrow lesions, cartilage defects, and meniscal tears which were assessed by MRI in middle-aged women 10 years later.[91] In addition, use of statins was correlated with reduction in incidence of knee OA and its progression.[92]For all these reasons, the term Metabolic OA have been proposed currently as discrete OA phenotype and as a fifth of six component of the Metabolic Syndrome. similarily, diabetes mellitus had been proposed as one of the causative factor for this new OA phenotype. Thus, metabolic OA patient may potentially benefit from the anti-lipidemic drugs and caloric restriction.

Inflammatory OA: OA traditionally has been regarded as a degenerative disease, however it is been well established nowadays that even local pathologies as well as chronic systemic lower grade inflammation are important pathological features of OA. Synovial inflammation will enhances to the pathophysiology of knee OA and also to the symptoms of OA, through an increased local secretion of pro inflammatory cytokines and also mediators of joint tissue damage.[93]

OA inflammation is typically a mild and chronic inflammation, that is mediated by the innate immune system, without a marked systemic acute phase response. In advance stages of OA there is Significant inflammatory changes and fibrotic findings were observed in the synovium, also in early stages.[94]

OA synovitisis characterized by infiltration of macrophages and also by activation of specific immune responses, and also by the presence of an associated anabolic events i.e., osteoblast activation and fibrosis rather than unique catabolic pathways.

OA synovitis shows structural progression,[95] and it varies along with changes in

pain pattern. It also shows different distribution with a patched pattern and more confined to the areas that are adjacent to damaged articular cartilage. A synovitis of patella has only pain that other synovitis.[96]Patients with this inflammatory profile OA knee may respond to methotrexate NSAIDs and biologic therapy.

TREATMENT:

NON-PHARMACOLOGICAL MANAGEMENT:

With increasing in the age of population and with increasing obesity, OA arises as a major public health problem and an important financial burden for the global economy. For the knee OA, various conservative treatment modalities are recommended by clinical guidelines. The non-pharmacological modalities includes patient education regarding self-management, exercises, weight reduction, walking supports (crutches), bracing, shoe and insoles modification, local cooling/heating, acupuncture and electromagnetic therapy.

The primary aim of OA management is to control the noxious signals originating from joints. Likewise, it serves in such a way to improve quality of life. Non-pharmacological therapy was the preferred first line of treatment.

A sedentary lifestyle is detrimental to the knee joint health. Significantly, the mechanical stimuli lack will lead to swift cartilage degeneration due to thinning of cartilage, decreased glycosaminoglycan content, impairment of joint mechanics and flexibility. Light-to-moderate physical activity is highly beneficial in addition to

reduced risk of diabetes, cardiovascular disease, disability, and a sense of wellbeing, and self-efficacy.[97,98]

Exercise routines should be customized to every patient's needs and preferences and long-term adherence should be increased to increase success. There are different exercise modalities have proved a favorable effect on OA knee patients, the exercise regimes should be performed thrice each week. To assess the response, these patient should complete a minimum of 12 sessions.[71, 99.]

Aquatic therapies offer an alternative to patients who are reluctant to start land-based exercises, as these activities are gentler on the joint.. Some patients can tolerate aquatic therapy better and decrease the exacerbation of symptoms. Some physicians use this model as a bridge to land-based modalities once the patient has gained more confidence in movement.[97,98] Weight management plays an important role in management of symptoms, and it has been noted that the benefit of exercise is potentiated by the reduction of weight. Obesity has detrimental molecular and mechanical effects. The cytokines adipokine, IL6, TNF alfa, and C-reactive protein are elevated in obese patients and are known to be associated with alteration of cartilage degeneration. [4, 36]

Treatment as per ACR, OARSI and AAOS recommendations:

Weight control

Land and water based exercise

TENS

Acetaminophen, Oral NSAIDS, intraarticular corticosteroids

These organizations are unanimously against the use of Duloxetine, opioids and intraarticular viscosupplementation

The different exercise modalities recommended for OA knee patients include

1. Aerobic/endurance Exercise modalities

2. Balance/proprioceptive Stretching
3. Resistance/strength training

Cycling has always been a favorite amongst patients as it involves low impact on their joints. Isotonic, isokinetic and dynamic modalities target the quadriceps, hip abductors, hamstrings, and calf muscles. They improve strength and physical function just as aerobic exercises.

This includes Tai Chi, in which movements are gentle and slow to adopt different weight baring postures along with breathing techniques. This helps in improving patient's flexibility and range of motion.[97]With respect to myriad non-pharmacological interventions, patients might benefit from thermal modalities, but there is insufficient evidence to advice TENS or therapeutic ultrasound.[100]

PHARMACOLOGICAL MANAGEMENT:

Pharmacologic therapies can be summarized as Non-Steroidal Anti-Inflammatory Drugs, Opioid analgesics. If orally administered drugs are ineffective, intra articular (IA) injection (corticosteroids, visco-supplements, blood-derived products) is the last non surgical treatment option that could be preferred. In OA knee there will be both qualitative and quantitative decrease in HA content. i.e., chain length is halved from 4-5mD in normal individual to 2-3mD in affected individual.

Since vast majority of OA patients are elderly with multiple comorbidities, one must consider the adverse effects that systemic medications can generate in this population. Cyclooxygenase inhibitors (acetaminophen and NSAIDs) have been the most commonly used medications. But due to the gastrointestinal, renal and cardiac adverse

effects of these medications, their prolonged use has limits. Drug Acetaminophen had been proved to be inferior to NSAIDs.[101]

Topical NSAIDs are known to be safer than systemic NSAIDs, due to comparable efficacy.[101,102] Some studies have depicted them to be of higher superiority than placebo in view of controlling pain during the first week of treatment but failed to prove beneficial after 2 weeks.

Recently, more and more awareness has been raised with respect to the consequences of the prolonged use of opioids. Various studies provide evidence that opioids are not superior to NSAIDs in improving pain or WOMAC scores, and the risks of their use, clearly outweigh the merits. But, if the patient is refractory to other modes of treatment, employing

an opioid is considered, Tramadol is more beneficial in the treatment of worsening OA. This medication has slightly less risk for abuse potential and respiratory depression.[103]

Duloxetine, a serotonin and norepinephrine reuptake inhibitor was approved to prescribe by the US Food and Drug Administration (FDA) in the therapy of diabetic peripheral neuropathy and fibromyalgia. [104,105]

Interventional management:

The delivery of multiple substances via intra-articular (IA) injections have been explored in the past. The concept behind this is that local treatments will have less systemic adverse effects and deposition of the medication inside the joint will have a direct effect. Studies have illustrated that in general IA therapies are way better than NSAIDs and other systemic

pharmacologic treatments, but they also revealed that a percentage of that benefit might be secondary to IA.[106]

Corticoid injections:- Corticoids (CS), derive their immunosuppressive and anti-inflammatory effects by directly acting on nuclear receptors, thus interrupting the inflammatory cascade at multiple levels. They decrease the production and action of IL-1, leukotrienes, prostaglandins, and metalloproteinases.[4,35] Currently, FDA approved Immediate Release (IR) corticosteroids for IA usage are: Methylprednisolone Acetate (MA), Triamcinolone Acetate (TA), Triamcinolone Hexacetonide (TH), Betamethasone Acetate (BA), Betamethasone Sodium Phosphate (BSP), and Dexamethasone. There have been attempts to define which is the best option in the past. Dosages higher than 50 mg of prednisone (equivalent to 40 mg of TA and MA) are linked to a relief of pain extending 12–24 weeks compared to 2-4 weeks of pain relief that has been reported with lower dosages. [107,108]There might be small differences between approved IR corticosteroid preparations with regards to pain relief, but present evidence is equivocal. Yavuz et al stated that a higher degree of relief of pain can be achieved within the first 6 weeks with MA when compared to the various corticosteroids used but all of them provide equivalent analgesia from week six to week twelve.108 Pyne et al recommended that TA acts more swiftly and provides better pain relief for the first 3 weeks than MA, but its resulting effect is not immediate and thus might provide better analgesia after the eighth week.[109]

A recent study by Buyuk et al showed that both MA and TH were equally effective until 24weeks and showed an upsurge in action by second week thus confirming similar findings by Lomonte et al.[110] Various studies have statedquestions regarding IA CS, such as its mode of action, its duration, indications, effect on cartilage structure/intra-

articular space and its negative effects. Some of the studies showed several variabilities in their design, depicting contradictory results and hindering the creation of a strong consensus. This has been reflected in the guidelines of various associations. Other possible variables like the degree of knee tenderness, baseline pain, BMI, gender, and anxiety or depression, have failed to show reliable predictors of response.[111]In contrast, a low degree of radiographic changes on the KL system (0–1) shows a good response as opposed to patients with severe radiographical

changes. Earlier several techniques of Intraarticular injection have been described, including the anterolateral and anteromedial, as well as the mid-lateral and superolateral approaches (performed with the knee extended). Studies agree that using ultrasound guidance with a superolateral approach provides the best chance to inject the CS accurately.

On average the ultrasound provides 96.7% of accuracy, vs 81% with landmarks. Furthermore, proper use of the ultrasound guidance can be reflected in better pain reduction, when compared with other techniques. 112Although complications are quite rare (about 1 in 3000), they still pose a concern in employing this particular therapy.. Facial flushing and transient pot-injection flares are self-limited and can be seen within the first 3 days. A study comparing radiographical changes of repeated, every 3 months injections of 40 mg of TA vs placebo for a 2-year period showed no difference. But a randomized controlled trial conducted recently, using MRI, found evidence of cartilagevolume loss.[113]

Research regarding CS and knee cartilage integrity has also provided significant results, with some studies suggesting that there is no alteration in the structure of cartilage, while others recommend that CS can promote chondrocyte destruction and increase the

necessity for joint replacement. The damage to the cartilage could possibly be reduced by vitamin C supplements.[114]

A minor part of the IA CS is absorbed systemically, with the possibility to produce hypoglycemia and hence, transiently affect the hypothalamic-pituitary-adrenal (HPA) axis in up to 25% of the patients. Cortisol levels may reduce after injection, but they return to baseline after 1–4 weeks.[115]

Non-corticoid interventional therapies

As an alternative to the IA CS, in the recent years, new products and therapies have been used that target different factors other than inflammation. However, some research is required to determine their efficacy, applicability, and safety profile. Viscosupplementation with hyaluronic acid (HA), is a natural glycosaminoglycan which is synthesized by type B synovial cells, chondrocytes, and fibroblasts and later secreted into the synovial fluid. It acts as a shock absorbent and provides a viscous lubricating property and a possible anti-inflammatory functions have also been described.[4,35] In an osteoarthritic knee, concentration of HA decrease significantly and hence formulated a proposal of viscosupplementation of the joint so as to to reinstate the HA benefits. The current evidence regarding efficacy is conflicting and consequently, there is variation regarding recommendations from the societies. The AAOS does not recommend its usage, the ACR has no recommendations about it, and the OARSI has an "uncertain recommendation.[102] A recent European consensus mentioned that HA had a good level of tolerance for low and moderate grade OA. Lastly, this treatment might be more effective in patients with higher levels of knee pain. [116]

Regenerative medicine

With the intention to stop and revert the degeneration, Intra articular injections of autologous conditioned serum , platelet rich plasma (PRP), mesenchymal stem cell were experimented.[4,35] Their mechanism is reduction of inflammatory reactions mediated by cytokines in addition to inducing anabolism and chondrocyte differentiation through stem cells and growth factors present in it. These methods have proven to be quite promising and certain studies mentioned their safety, well tolerated and superior to IA placebo and HA with respect to relief of pain and function .[4,35,117,118] It is a developing field and certainly more research is needed so as to define the optimal retrieval, preparation and storage methods of these products.

HYALURONIC ACID

Hyaluronic acid produced by B cells of synovial membrane is biochemically a high viscosity polysaccharide also classified in glycosaminoglycan group.[119] In physiological conditions HA acts as a salt also named as sodium hyaluronate or hyaluronan.[120] High viscosity solution formed by interlinking high molecular weight molecules. This high viscosity acts as both lubricant as well as shock absorber.[121]

HA on interaction with the CD44 receptors will acts as an important modulator that helps in decreasing pressure due to body weight and promotes the better force distribution.[122]

Uses of hyaluronic acid:

Diminishes prostaglandin production, degradation of type 2 collagen and also had analgesic action by diminishing nociceptor sensitivity and the nerve impulses.[123] It stimulates the proliferation of chondrocytes by this way it increases aggrecan and type 2 collagen production.[124,125]

Exogenous hyaluronic acid is produced from two sources:

• Avian origin: from poultry material (cock crest). This presents allergenic potential due to avian antigens.

• Non-avian origin: Bio-fermentation products using bacteria (Streptococcus zooepidermicus). These have lower allergenic potential.

These substances can be classified into two types:

Hyaluronans: Long-chain molecules of biofermenation or avain origin, with a MW of between 0.5 and 1.8 x 10^6 Da.

Hylan: hyaluronan molecule chemically modified by means of cross-links, with a liquid phase of higher molecular weight (around $6x10^6$ Da), through crosslinking connections between long chains of hyaluronan, and a solid portion (of infinite molecular weight) formed by even greater presence of links.

In relation to molecular weight, although all the hyaluronic acids used in orthopedics can be considered to have high molecular weight, the current products can be classified as: "Low molecular weight", i.e. between 0.5 and 1 x 10^6 Da, "Intermediate molecular weight", i.e. between 1 and 1.8 x 10^6 Da, "High molecular weight", i.e. 6 x 10^6 The molecular weight, concentration and presence of cross-links on the visco suplementation. Sodium hyaluronate has an intra-articular half-life of 13 hours, while the hylan G-F 20 has a half-life of 1.5 days (liquid phase) and 8.8 days (solid phase), probably because of the cross-links. This may explain why the good results are obtained with only one application.[126]

Adverse reaction:

Adverse reaction accounts about 4.2% of the patients presented with effusions,

arthralgia, heat and the joint erythema.[127]In such cases, as occuring in any acute arthritis crisis, the treatment should consist of ice, rest, limb elevation and use of anti-inflammatory medication, if not contraindicated. In need the joint can be punctured.

Hyaluronic acid, a naturally available non-sulfated glycosaminoglycan (GAG) non-protein compound with a distinct physio-chemical properties with repeating b-1,4-D-glucuronic acid and b-1,3-N-acetylglucosamine units.[126,128,129,130] HA is known for its good biocompatibility, excellent viscoelasticity, hygroscopic properties and high moisture retention capacity.[129] HA behaves like a great lubricant, joint structure

stabilizer, shock absorber. Moreover, it is also known for its water balance property and flow resistance regulation properties.[121,122]

HA forms the major component of the extracellular matrix (ECM) and is a major component of synovial fluid, bone marrow and articular cartilage. Hyaluronic acid is required in proliferation of cells, migration, and morphogenesis.131Inside the cavity of the knee joint, HA molecules are predominately synthesized by type B synoviocytes. HA is synthesized by hyaluronan synthase. HA is catabolized by hyaluronidases, with increase in age there is decrease in Hyaluronic acid molecular weight with in the knee cartilage.[132,133,134]

HISTORY:

First proposed by Balazs in 1993 visco-supplementation With intra articular HA injections has emerged as a viable treatment modality for nonoperative care of symptomatic osteoarthritis.122 Hyaluronic Acid , has wide range of usage like in the treatment of osteoarthritis, cosmetic surgery, ophthalmological surgeries and also in healing of wound. The production and recovery of HA, has attained its great importance. Injecting exogenous intra articular HA, there will be restoration of mechanical properties of the articular cartilage and the synovial fluid; and also to achieve certain biological effects.

In OA knee, the cartilage is subjected to mechanical, structural and matrix changes of the articular surface and a decrease in PG monomer size and aggregation.135Aging, oxidative stress and the inflammation acts as a major contributor to the development of OA and its progression. Apoptosis (programmed cell death) of chondrocytes are the cause of failure and articular cartilage degeneration in OA. [43,136]

In late stage Osteoarthritis, the cartilage becomes hypocellular, often accompanied by lacunar emptying, which has been considered as evidence that chondrocyte death is a central feature in OA progression. Chondrocyte death and ECM loss may form a vicious cycle, with the progression of one aggravating the other.

Rheological properties (such as Molecular weight, concentration, and viscoelasticity) of Hyaluronic acid in formulation and route of administration are major determining factors for successful therapy of OA.[130,137]

Intra articular (IA) administration is more efficacious than parenteral or enteral route because it avoids systemic exposure and its potential side effects. Intra articular injection of HA into OA joints could reinstate the Synovial Fluid rheological properties, promote the endogenous production of a higher Molecular Weight HA.

The molecular weight of the Hyaluronic acid appears lower in Osteoarthritis patient Synovial fluid.so IA Hyaluronic acid injections is considered to be a useful option in the treatment of OA knee patients. In SF, Hyaluronic acid is the major chemical component manufactured by synoviocytes, chondrocytes and fibroblasts. Hyaluronic acid has a molecular weight of 4,000,000–10,000,000 Da.160 Normal adult knee has approximately 2mL of SF and 2.5–4.0 mg/mL of hyaluronic acid. . In OA, synovial HA is depolymerized (MW, 2,700–4,500 kDa) and cleared at higher rates (11–12 h) than normal (20 h).[138,139]

In SF, HA is the major chemical component produced by synoviocytes, fibroblasts, and chondrocytes. Native HA has a MW of 4,000,000– 10,000,000 Da, and is present in articular fluid in a concentration of about 0.35 g/100 mL. Within the normal adult knee, there are about 2 mL of synovial fluid, in which the concentration of HA is 2.5–4.0

mg/Ml. In equines, the HA concentration in joints is in the range of 0.33–1.5 mg/mL [140] and MW in the range of 2,000,000–3,000,000 Da.

In a study conducted in 2016 it was concluded that Intraarticular injections using higher-MW or lower-MW improves joint function and reduces stiffness in OA knee. In a study conducted in 2006, the lower-MWHA preparations will achieve higher concentration and will reduce inflammation, however, they present lower elastoviscosity than native HA. Higher-MW HA has a better increase in fluid retention with in the joint and stronger anti-inflammatory effect.[141]

In Osteoarthritis knee there will be cartilage degeneration due to oxidative/nitrosative stress and inflammation. The NO production of the HA group were significantly less than without the HA treatment. These results recommended that there is a inhibition of Nitric Oxide production in meniscus and synovium as part of the therapeutic effect of Hyaluronic acid in OA. [142,143]

Actions of hyaluronic acid:

HA action is by inhibition of the actions of pro-inflammatory mediators and pain producing neuropeptides released by activated synovial cells.

HA specific effects:

1. Antioxidative/Antinitrosative, and anti-inflammatory

HA decreased PGE2 and increased cAMP in Synovial fluid binging about Anti-inflammatory, anti-chondroptosis, and anti-OA.44,144 HA down-regulates aggrecanase-2, cytokines (TNF-a, and IL-8) and iNOS through interaction of CD44 in FLS.145 HA protected mitochondria from oxidative stress, and chondrocytes from

apoptosis. HA reduced IL-1-induced PGE2 and NO concentrations and decreases apoptosis in OA chondrocytes.[146]

2. Analgesics

HA relived joint pain by inhibiting PGE2 production.126,147 HA produces reduction of the sensitivity of mechanosensory ion channels of nociceptive nerve terminals.148 HAdecreased cytokines, leptin in serum and synovial fluid of OA patient. 149In a dose-dependent manner, HA interacts with HA receptors on or surrounding the free nerve endings that detect pain in the joint tissue .[150]

3. Structure of bone and cartilage with functions

HA ameliorated IL-1b-induced expression of genes of matrix degrading enzymes (MMP1), inflammatory mediators (IL6, PTGS2) by chondrocytes and fibroblasts.[151]The production of MMP-13 via CD44 and p38 in chondrocytes/articular cartilage is inhibited by HA.[152] Higher-Molecular weight HA also inhibits cartilage degeneration and loss of chondrocytes. The down regulation of MMP-3 and IL-1b by HA.[153] HA inhibits PPAR-g mRNA being expressed and exerts anti-chondroptosis. [142,153] HA regulates the function and distribution of sulphated GAG. [154] HA suppressed IL-1b-induced-transcriptional activity of type a2(VI) collagen. HA decreased synovial hypertrophy, macrophages, lymphocytes, mast cells, and adipocytes, and increased synovial FLC.[147]

4. Rheological properties of Hyaluronic acid and Synovial Fluid

HA increased viscoelasticity, anti-inflammatory potential, increased proliferation of chondrocytes.[155,156] HA stimulated synoviocytes of high MW HA synthesis, and reduced synovial hyperplasia.[157,158] IA viscosupplementation promoted endogenous

HA production in SF of OA knee. Increased HA concentration and viscoelasticity. [147,159,139,155]

5. Pharmacokinetics of HA

After oral administration of 99mTc-HA, it readily absorbed, distributed and excreted suggesting a rapid uptake of HA. There is Short half-life of the Hyaluronic acid in humans.[160]Hyaluronic acid also distributes to lymphatics suggesting Rapid distribution and elimination of HA.[160,161]

Evidence for disease-modifying activity of HA stems from the complex molecular and cellular effects of the Hyaluronic acid in the ECM of articular cartilage, including interactions between exogenously administered HA and articular cartilage, subchondral bone, matrix PGs, and collagens. IA injections of HA also causes reduction in the progression of cartilage degeneration and inhibit narrowing joint space on X-ray images. [162,163]

TOXICITY AND SAFETY EVALUATION

HA as a physiological component, will not produce adverse reactions even after repeated usage.[141]In various clinical trials, Hyaluronic acid is safe and well-tolerated in Osteoarthritis patients, when given IA.[164,165] After administration, minor side effects can occur, like pain at the injection site (in 1–30% of patients), swelling (in 1–30%), and local skin reactions (in 3–21%).[106] These effects are transient. In rare cases, treated joints may become infected.[166]

CONTRAINDICATIONS:

HA treatment is contraindicated in individuals who are hypersensitive to HA products, woman who are pregnant or nursing, pediatric patients, patients with bacteremia, or patients with infections in or around the target knee.[167]

SURGICAL OPTIONS IN OA KNEE:

Arthroscopic Lavage and Debridement

Arthroscopic lavage and debridement will relieve symptoms by removing inflammatory cytokines that cause synovitis and the debris.[168,169]According to the results of a study which was conducted in 2007,the arthroscopic treatment of OA knee was found to have limited benefit.[170]Maximum benefit of the surgery was seen in patients with initial stages of arthritis as seen by radiography, less severe involvement of articular cartilage, and a young age during surgery.[171] Patients with OA of knee are routinely treated by arthroscopic debridement, it should no longer be done as some patients with symptoms like meniscal tears and loose bodies with locking symptoms may improve.

Techniques to repair cartilage

Focal cartilage defect is the only cartilage damage that is indicated for repair, as it behaves as a precursor of OA. Drilling, microfracture or abrasion are some of the different bone marrow stimulating techniques. Replacement techniques have also been tried like mosaicplasty or osteochondral allograft transplantation and grafting and combined techniques like periosteal flap transplantation, and autologous chondrocyte implantation, autologous matrix induced chondrogenesis.[172]

Bone Marrow Stimulating Techniques

Cartilage repair is enhanced when penetration of the subchondral lamina is done, due to which the pluripotent stem cells from the subchondral bone marrow will further improve the chondrogenesis in the defect area. This technique enhances chondral resurfacing and takes advantage of the healing potential of the body. This is a simple procedure done arthroscopically.[173,174]

Osteochondral Transplantation Techniques

Transplantation of osteochondral grafts can help in in reconsruction of a cartilaginous surface or osteocartilaginous defects. Autologous or allogenic grafts are used. The term used for autologous transfer is "mosaicplasty" or "the osteochondral autologous transfer system.[175,176]

Autologous Chondrocyte Implantation(ACI)

ACI technique whereby cultivated and proliferated autologous chondrocytes are re-implanted underneath a periosteal flap.[177]Techniques of cartilage repair serves as aindication for limited size cartilage lesions especially in younger patients. After these cartilage repair procedures there is a reduction in the symptoms prevalance .[178]

Osteotomies around the Knee

This procedure alters the weight bearing axis of the legs.[179] Leading to unloading from the damaged compartment and transfers the weight load by slightly overcorrecting into a valgus or varus axis. This will reduce pain, slow the degenerative process, and delays the need for joint replacement.[180,181] Different techniques are used to correct load axis in uni-compartmental knee OA. This includes proximal tibial head osteotomies and supracondylar femoral osteotomies.

JointArthroplasty

Regarding the treatment of advanced knee OA, joint arthroplasty is a safe and a cost-effective procedure. It is recommended only in patients for whom other treatment modalities have failed or are contraindicated as this surgery is irreversible. Hence, must be avoided in individuals before 60 years of age.

Unicompartmental Knee Arthroplasty (UKA)

UKAis indicated when only one of the three compartments of the knee: the medial tibio-femoral, lateral tibio-femoral or patella-femoral compartment is afflicted. The commonest UKA replaces the contact surfaces of the medial tibio-femoral compartment with two metallic prosthetic devices and inserts a polyethylene inlay between them.[182,183]

Total Knee Arthroplasty(TKA)

In advanced knee OA, with more than one compartment involvement and failure of conservative treatments, TKA is a highly effective treatment which results in substantial improvement in patient functioning and health-related quality of life. It has been the first-line procedure for end-stage knee OA.

Minimal Invasive Surgery:

In this procedure splitting of the quadriceps tendon is avoided. Access is made possible through a mid-vastus approach, where splitting of vastus is done or a sub-vastus approach. Eversion of the patella is avoided. Skin incision is shortened to a minimum. This will have lesser hospital stay and faster recovery.[184,185]

In 1991 a study that compared methylprednisolone and HA on 40 patients suggests HA had prolonged action than prednisolone. They said that HA would bring the therapeutic breakthrough in the treatment of knee OA. That was a short duration study of only two months, and VAS score was used to measure the outcomes.[186]

A prospective randomized control study with a total of 118 patients conducted in 1993 showed from 2 weeks to 6 months of follow up in the treatment group around 71% had better improvement than the control group. After 6 months the results were excellent in around 53% of study group.[187]

A multi centered double blind study with around 100 control and 95 patients conducted in the year 1993, concluded that there is a significant decrease of lequesne index scores between the control and the treatment group with p value of <0.05 in the same study. After 14 weeks of follow up there was a change in the visual analogue pain scale -27.6 in the treatment group versus -17.8 in the control group[188]

A 1 year double blind placebo control study done in 1994 with a total of 52 patients of which 24 were control and 28 were patients, showed no difference in the pain function and any other activity after one year of follow up.[189]

In 1994, a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy concluded that intraarticular administration of this preparation of 750 kD hyaluronan offers no significant benefit over placebo

during a five week treatment period, but incurs a significantly higher morbidity, and therefore has no place in the routine treatment of osteoarthritis.[190]

In 1995 a randomized control trails of 93 patients were divided into 3 groups such as group 1, will be treated with only NSAIDS, group 2 with only HYLAN and group 3 with both NSAIDS and HYLAN. In this study at around 12 weeks there was a improvement in all the groups from the baseline values but there was no significant difference between the groups. At 26 weeks both the HYLAN groups i.e., group 2 and group 3 had better results than group 1 (NSAIDS alone).[191]

In 1995 a randomized double blinded comparative study conducted to compared the effectiveness of Hyaluronic acid injection given weekly once over 5 weeks and other group treated with steroid at first week followed by 4 placebo injection weekly concluded that hyaluronic acid was better than steroid at 6 months.[192]

In 1996 a retrospective study conducted for about 2 ½ years which included 336 patients with 3 injections of hyaluronic acid. In the study they assessed the patients with pain score on ordinary scale, over all response and change in the activity showed 76% of patient were improved in the first series and 84% of patients were improved in 2nd series.[165]

A multi centered double blinded RCT conducted in Japan in 1996 which included 240 patients to measure the efficacy of HA injection suggested no significant differences in the outcomes for age less than 60 years, but for patients over 60 years who have less demand of activity with severe OA knee showed better improvement with intra articular hyaluronic acid injection.[193]

In 1997 a double blinded randomized control study with a total of 36 patients concluded that there is an improvement in the pain score in the study group when compared with control group even they suggested the quality of life favoured in the treatment group.[162]

A double blinded placebo controlled trial study with 90 patients in 1997 concluded that intra articular hyaluronic acid was better than placebo over a follow up period of 6 months.[194]

In 1998 a multicenter RCT conducted to evaluate the efficacy and safety of Hylan G-F 20 over placebo showed that there is a significant improvement in the VAS scores over a period of 26 weeks in patients with knee pain less than 1 year with low grade OA knee.[195]

A open label prospective study conducted in 1998 with 40 patients who were given 5 injections of hyaluronic acid followed up for a period of 6 months with VAS scores suggested there is a less pain at rest and at load up to one year[196]

In 1998 a double blinded parallel randomized control trial study was done in around 495 patients of which 162 were dropped out who were treated with 5 weekly injections of hyalgan and oral placebo for one group. And for the other group it was saline injections and oral placebo and for other group, it was Naproxen and subcutaneous local anaesthesia. These patients were assessed with VAS score for pain and WOMAC score. This study were followed up for a period of 26 weeks and at the end of 26 weeks, the results was 47.6% pain free in HA group vs 33% in saline and oral placebo group and

in Naproxen group it was 38.9%. It also suggests the WOMAC score was better with HA group than the placebo group and side effects was fewer with HA when compared to Naproxen.[197]

In 1999 a randomized control study which compared 5 weekly injection of hyaluronic acid with normal saline with 100 patients as study population which utilized VAS score and Lequense index as assessing tool suggested that there was improvement in pain score at 5 weeks of injection which was maintained till 6 months post injection.[198]

In 1999 a openly prospective study which studied 73 patients over a period of 1 year given five injections of hyalgan showed an improvement symptom relief of about 68 % of patients at 4 weeks post injection which was maintained over 55% of patients till one year.[199]

A prospective study conducted in 2000 with a total of 61 patients who were given 3 injections of Synvisc and were assed with SF 36 functional score showed a significant improvement in the function during the follow up of 6 months but there is no difference in the general health or vitality.[200]

A double blinded parallel randomized control study done in the year 2000 over 46 patients with a 6 dropped out patients who were given low molecular weight HA with a co intervention of Acetaminophen and exercise suggested HA is superior to placebo during the follow up period of 12 weeks.[201]

In 2001, a randomized control trial was conducted in 226 patients with a follow up period of 27 weeks. In this study the patients were given 3 injections of Orthovisc and a cointervention with Acetaminophen suggested HA is superior to placebo during the follow up period of 7 to 27 weeks who were analysed using WOMAC score.[202]

Another study conducted in 2001, which was a open label, single blinded, parallel randomized control trial with 49 patients given 5 weekly injection of BioHy were assessed using pain, stiffness, function scores, suggested HA has decreased the pain and stiffness upto 20 weeks but it was nonsignificant.[203]

A double blinded, parallel randomized control trial done in 2001 over 49 patients. The patients in the study were given 4 injections of Hyalgan and saline placebo. In this study the patients were assessed over a period of 26 weeks with VAS score for pain suggests HA superior to placebo which has given a positive effect.[204]

In 2001 a retrospective study was done for a period of 10 months which included 70 patients and 100 knees with 3 injections of synvisc who were assessed with pain score showed 2/3rd of the knee had relief from the pain. The study also suggested with more severe osteoarthritis the relief from the pain is decreased and the procedures towards the surgery is increased.[205]

In 2002, a double blinded, parallel randomized control trial over 120 patients, who were divided into 4 groups. Group 1 had HA (3 injections of Suplasyn) and oral placebo. Group 2 HA and Diclofenac with Misoprostol, Group 3 intraarticular placebo with Misoprostol and group 4 with oral and intraarticular placebo. In this study the patients outcome were measured with VAS score and WOMAC index. This study concluded the effect of HA is same as NSAID for pain at rest whereas it was superior to placebo for pain with activity and function. It also concluded the effect of HA improves over time but the effect of NSAID unchanged after 4 weeks.[206]

Another single blinded, parallel randomized control trial conducted in 2002 over 43 patients who were given 5 injections of Hyalart and the control was the opposite knee. These patients were assessed with VAS score for pain and Lequesne functional index over a period of 6 weeks suggested HA has reduced the pain when compared to the baseline values and also improved the peak torque on Lequesne functional index with a P value of < 0.001.[207]

In 2002 an open label, prospective parallel effectiveness trial was conducted over 255 patients for a period of 1 year follow up in this they excluded Grade 4 patients, tense effusion and deformity. These patients are divided into 2 groups in which first group had only appropriate care. Whereas in second group, the patients were given 3 injections of Synvisc and appropriate care. These patients were assessed with WOMAC score. This study concluded the patients who had received HA along with appropriate care reduced the pain in around 38% of this group vs 13% of patients in appropriate care group.[208]

In 2003, a systematic review done for evaluating efficacy and safety of Hylan G-F 20 over placebo, NSAIDs and Sodium hyaluronate. This study included 7 RCTs, 6 case series and 1 cross sectional study. They used pain and functional capacity of knee as a evaluation tool. This review concluded there is an improvement in the pain and the functional capacity of knee following Hylan G-F 20 over a short term.[209]

A prospective randomized clinical trial conducted in 2003 which compared the intra articular steroid with HA injection which was given 3weelky injections which utilized WOMAC score, VAS score, knee society score as an evaluating tool showed that there is a significant improvement in the VAS and WOMAC score but not in Knee society score. It also observed that the women who were treated with both groups noted lower response to treatment when compared to men.[210]

In a multicenter RCT clinical trail conducted in 2004 included 347 patients which was used to evaluate the efficacy of single non animal stabilized HA, came with primary outcome reduction in WOMAC score more than 40% from the baseline at 26 weeks.[211]

In 2004 a Randomized double blinded RCT compared 5 injections of HA with placebo suggested large decrease in pain and stiffness at regular intervals i.e, 6, 10, 14 and 18 weeks.[212]

A systematic review of literature on high molecular weight HA(HMWHA) was done in 2004. In this review they included 5 case series and 13 RCTs where they considered pain as a parameter for calculating outcome measures. This study proven high molecular weight HA is effective in controlling pain in OA knee patients. It also

suggests the action of HMWHA is slower to start but it has longer effects than the other intraarticular steroids.[213]

A systematic review done for comparing the efficacy of intraarticular HA over placebo included 9 RCTs in the year 2005. In this study the patients were evaluated at different intervals such as 1 week, 5-7 weeks, 8-12 weeks and 15-22 weeks with pain as a scoring parameter. This study concluded HA has a modest effect on pain in patients with knee osteoarthritis, 5-7 and 8-10 weeks after the injection but has no effect after 15-22 weeks.[214]

In 2005, A randomized multi centered comparative study between 4 injections of HMW HA with 3 injections of HMW HA and 3 injections of placebo suggested there is improvement in baseline WOMAC score in all the above mentioned groups.[215]

A Cochrane Database systematic review done in the year 2006 included 67 RCTs for assessing the efficacy of HA over placebo in the treatment of OA knee. It used pain and functional capacity of the knee as a assessing parameter. This review suggested viscosupplementation as an effective treatment for osteoarthritis knee because it reduces the pain and also improves the functional capacity of the patient.

In a double blinded RCT conducted in 2006 compared efficacy of intra articular HA with placebo receiving three versus six consecutive injections. The results showed a significant improvement in baseline WOMAC score.[216]

A single blinded randomized control trial was done over 660 patients was conducted in 2007. These patients were divided into 2 groups of which first group will get Hylan and the other group will get HA.These patients were assessed using WOMAC score and it suggested no evidence of differences between HA and Hylan.[217]

A prospective, randomized, double blinded clinical study of HA, steroid, and placebo was conducted in 2008. They found that the both steroid and placebo groups showed significant pain relief for ten weeks and its effect disappeared by 12 weeks. While patients of HA group continue to have pain relief until 26 weeks after that, it was not statistically significant.[218]

In 2008, a randomized control trial over 392 patients with an intervention of intraarticular Hylan G-F 20, sodium hyaluronate. The patients were evaluated with WOMAC score at the interval of 6 weeks, 3 months, 6 months and 12 months. This study concluded both the treatments provided pain reduction but the clinical effectiveness and the patients satisfaction were better with Hylan G-F 20.[219]

A prospective double blinded RCT done over 60 patients conducted in 2009 for determining effects of Intra articular HA on proprioception, pain, isokinetic muscle force and functional conditions. Suggested HA is better than placebo in terms of improvements in VAS and WOMAC score.[220]

In a multicentered RCT in 2010 compared the efficacy and safety of single injection of Hylan G-F20 versus placebo. It was observed that there is decrease in pain score but not WOMAC.[221]

In 2011, a double blinded, randomized control trial which assessed the pain and functional capacity of 306 patients over a period of 40 months. These patients were given HA and placebo. This study concluded the repetition of IAHA in cycles improved the symptoms in OA knee for a period of 1 year post injection.[222]

A study used steroid and HA injections in the OA of shoulder and found similar results as of knee OA. The effect of steroid decreased after 1month, but HA remains up to 6 months.[223]

A systematic review and metanalysis was done in 2012 that included 89 studies for evaluating effectiveness of viscosupplementation in OA knee. In this study, they compared HA or its derivatives and the placebo. Here, they assessed the patients with pan and functional capacity. This study given a negative result that its administration to be discouraged because of greater local adverse reactions.[224]

A prospective study conducted in 2013, over the activity of HA on the opioid receptor and beside other action described previously it has analgesic activity through this opioid receptor increases pain threshold.[225]

A systematic review done in 2013 included 14 studies which compared HA, placebo, sodium hyaluronate. In this study they used WOMAC as an assessment parameter. This study suggested the hyaluronic acid is not recommended for the patients with symptomatic OA knee.[226]

A metanalysis of 29 RCTs was done in 2013 in US which assessed the safety and effectiveness of US approved intraarticular HA with pain and functional capacity at 4-13 weeks and 14-26 weeks. It concluded that intraarticular HA is a safe and effective treatment for symptomatic OA knee.[227]

A systematic meta-analysis review in 2015, comparing the treatment of knee OA with intra-articular HA versus NSAIDs, IA-corticosteroids, IA-platelet rich plasma (PRP), or IA-placebo to determine which meta-analyses provide the best current evidence and identify potential causes of discordance. They included 14 meta-analysis with total 20,049 patients and found the highest level of evidence suggests that IA-HA is a viable option for knee OA. Compression between HA and PRP, PRP shows more robust result than HA. The study, shows pain and function improvement was significant up to 26 weeks.[228]

In a randomized study done in 2016, which included 140 cases were used to compare IA-HA with IA-steroid assessed the outcome with Western Ontario and McMaster University Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and the visual analog pain scale observed superior results was seen in HA group than the steroid.[229]

A comparative, randomized study conducted in 2017, demonstrated that both the THA and HA are safe and effective in relieving OA pain temporarily and are effective palliative agents and are not curative therapy. Steroid given IA can give pain relief for about 12 weeks while HA provides significant pain relief until six months after the injection.[230]

A randomized control trial done in working age oa knee patients suggested that intra-articular injections with HMW-HA added to usual care is effective in patients in the working age. It results in more responders to therapy and improvement in pain, function and Patient Global Assessment.[231]

A metaanalysis done in 2019 revealed that mono injections produce results similar to multi-injections of IA HA in terms of pain relief in the treatment of knee osteoarthritis[232]

6.3 OBJECTIVES OF THE STUDY

1. To assess the efficacy of intra articular HA in primary osteoarthritis of knee joint based on clinical outcome with visual analogue score (VAS) and The Western Ontario and McMaster Universities Osteoarthritis index (WOMAC score).

2. To determine the safety of IA HA in primary osteoarthritis of knee joint

MATERIAL AND METHOD:

Study design : Single Group Prospective Interventional Study

Study period : November 2017 –May2019

Source of data:

OA Knee patients reported to Out Patient Department ,department of orthopaedics attached to R L Jalappa Hospital which is affiliated to Sri Devaraj Urs Medical College , constituent college of Sri Devaraj Urs Academy of Higher Education and Research , Tamaka, Kolar will be enrolled for the study.

Sample size is estimated based on the reduction of WOMAC score from baseline to 52 week in a study by,[240] observed an average variance of 14.02 to detect the difference of 20% reduction in WOMACscore from baseline to 1 year with 80% power and 95% confidence interval. The calculated sample size is 24 expecting 50% drop out during the follow up period of 6 months the sample size is estimated as 36 sample.

INCLUSION CRITERIA

- Age: 40-80 years

- Gender: Both Male and Female.

- OA knee patients with Kellegren and Lawrence Radiographic grade I-II, and who were not satisfied by other methods of treatment for past 3 months

EXCLUSION CRITERIA

- A clinically apparent tense effusion of the target knee.
- Ligamentous laxity or meniscal instability.
- Concomitant inflammatory disease (rheumatoid arthritis) or other condition that affects the joints.
- Any trauma history to knee
- Any previous surgeries to knee

METHOD OF COLLECTION OF DATA

- Informed written consent will be obtained from patients who are willing to participate in the study and undergo procedure/ treatment.

- Collection of data from 36 OA knee patients within the age group of 40-80 years of both sexes.

- Under aseptic precautions patient in supine position knee in slight flexion a superolateral patellar approach is used to inject single shot prefilled 3ml of HA high molecular weight (>6000kda)intra articularly.
- A short term follow up of 6 months with VAS score and WOMAC score.
- Follow Up Visits:-

  Functional outcome will be evaluated using VAS and WOMAC scores during follow up period at 1, 3and 6 months.

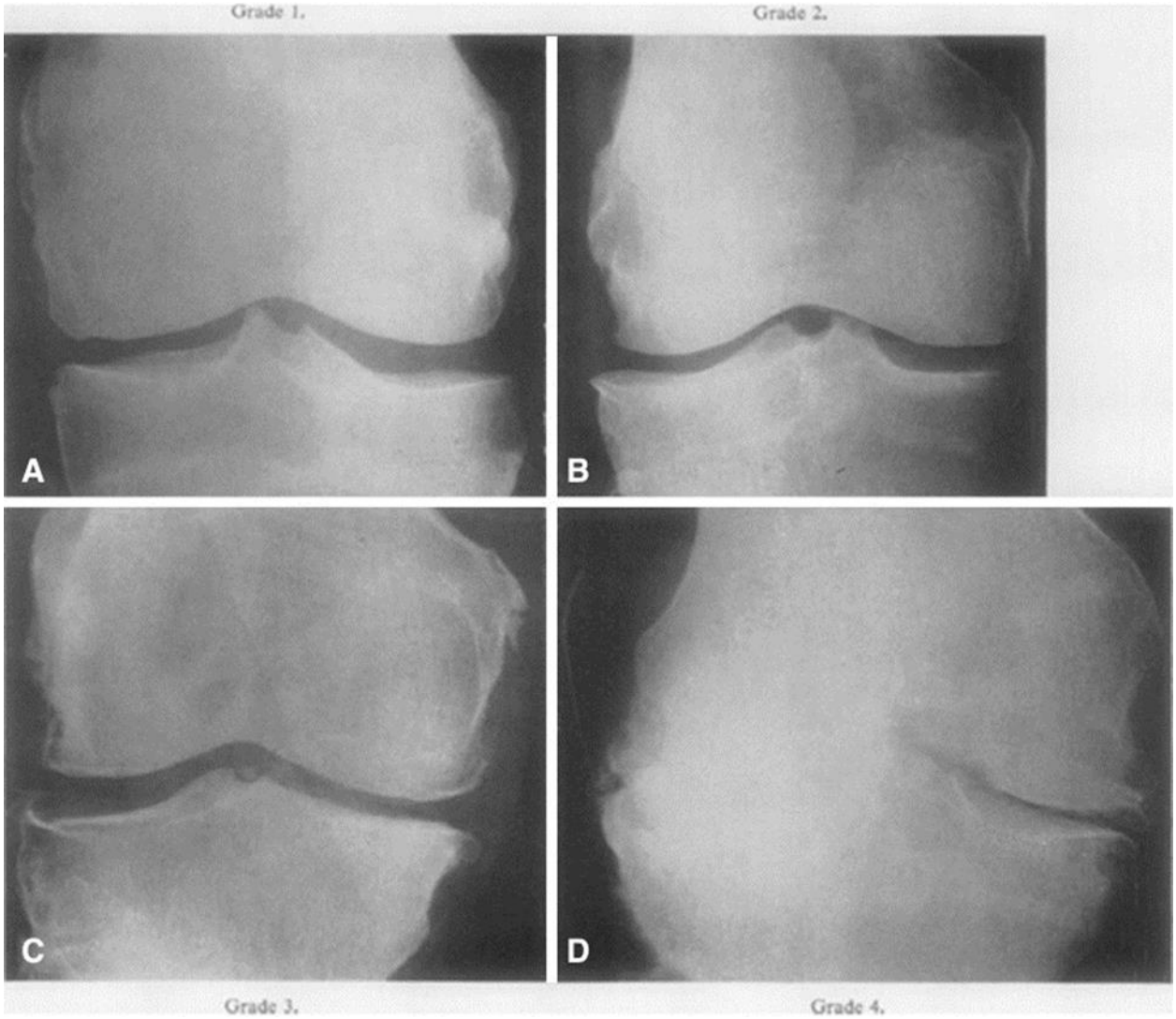
DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS?

Yes, the study require X ray of bilateral knee AP view and lateral view in standing position. After injections patients are started on quadriceps strengthening exercises.

No repeat injections needed as, it is the study of effectiveness of single shot intraarticular hyaluronic acid injection.

Statistical analysis:

Data was analysed using SPSS version 22 software. Calculation are analysed using the Repeated ANOVA test .WOMAC AND VAS scores of all 36 patients before injection and post 1, 3, 6 months injection were obtained are measured for mean and standard deviation. A probability value (p value)<0.005 will be considered statistically significant



AnteroPosterior x rays of knee presented in the original Kellgren-Lawrence article [19]. "(A) Representative knee radiograph of KL classification Grade 1, which demonstrates doubtful joint space narrowing with possible osteophyte formation. (B) Representative knee radiograph of KL classification Grade 2, which demonstrates possible joint space narrowing with definite osteophyte formation. (C) Representative knee radiograph of KL classification Grade 3, which demonstrates definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends. (D) Representative knee radiograph of KL classification Grade 4, which demonstrates large osteophyte formation, severe joint space narrowing with marked sclerosis with definite deformity of bone ends".

CASE ILLUSTRATION:

Fig 11 clinical picture of painted knee

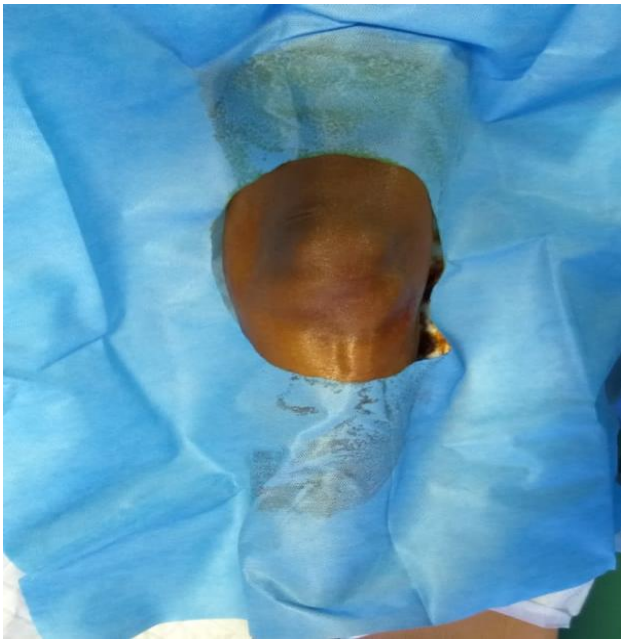


Fig 12 clinical picture of draped knee

Fig 13 clinical picture of aspetic injection tray

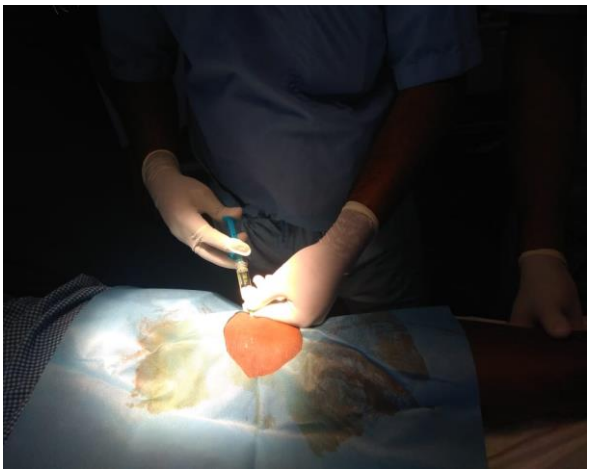


Fig 14 clinical picture of placement of injection

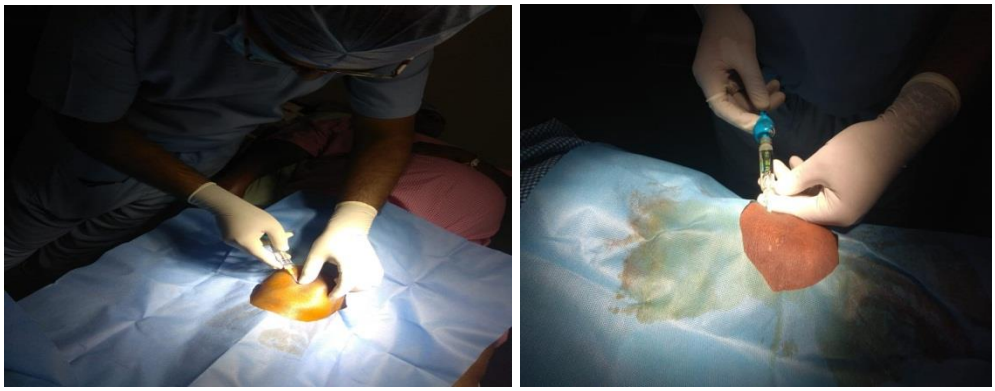


Fig 15 clinical picture of injecting hyaluronic acid

Fig 16 post injection compression bandage application

CASE I

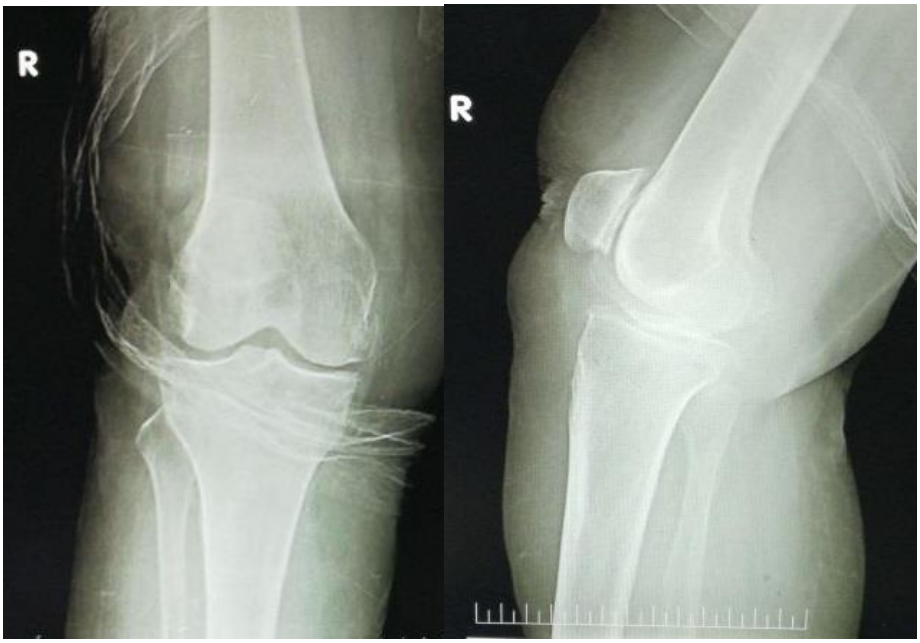


Fig 17. X rays of patient no 1

CASE II

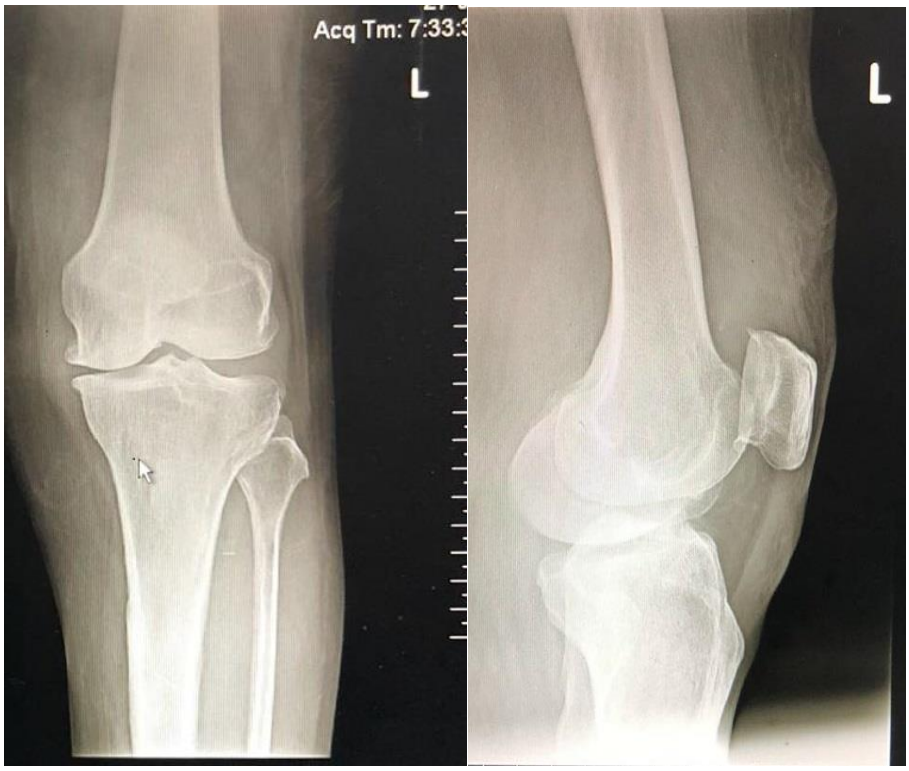


Fig 18. X rays of patient no 2

Case III

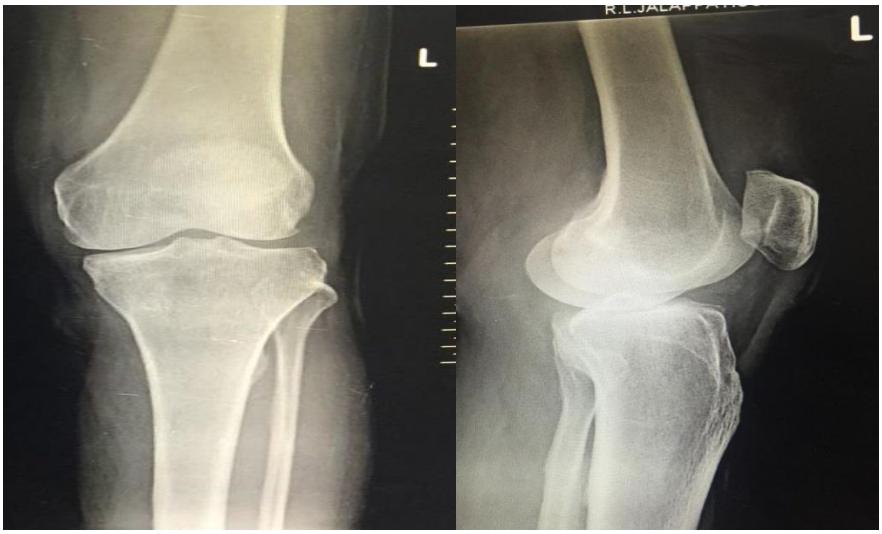


Fig 19. X rays of patient no 3

Case IV:

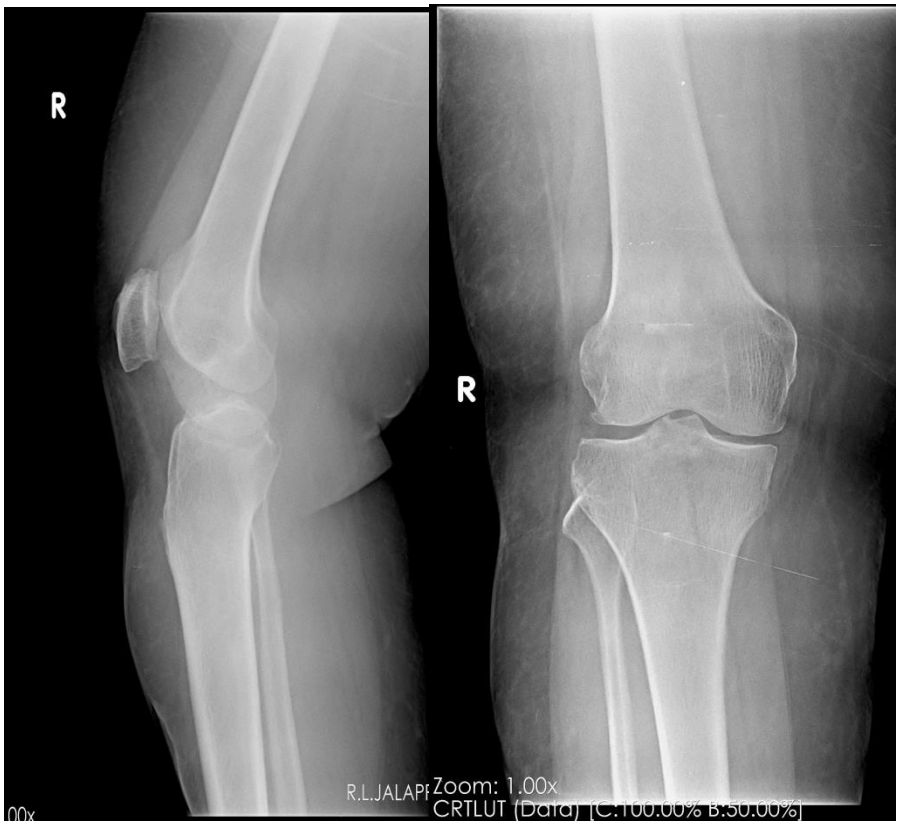


Fig 20. X rays of patient no 4

OBSERVATIONS AND RESULTS

AGE DISTRIBUTION

AGE	GRADE I	GRADE II
40-49	7	6
50-59	7	6
60-69	0	8
70-80	0	2

Table no :1 Shows age distribution

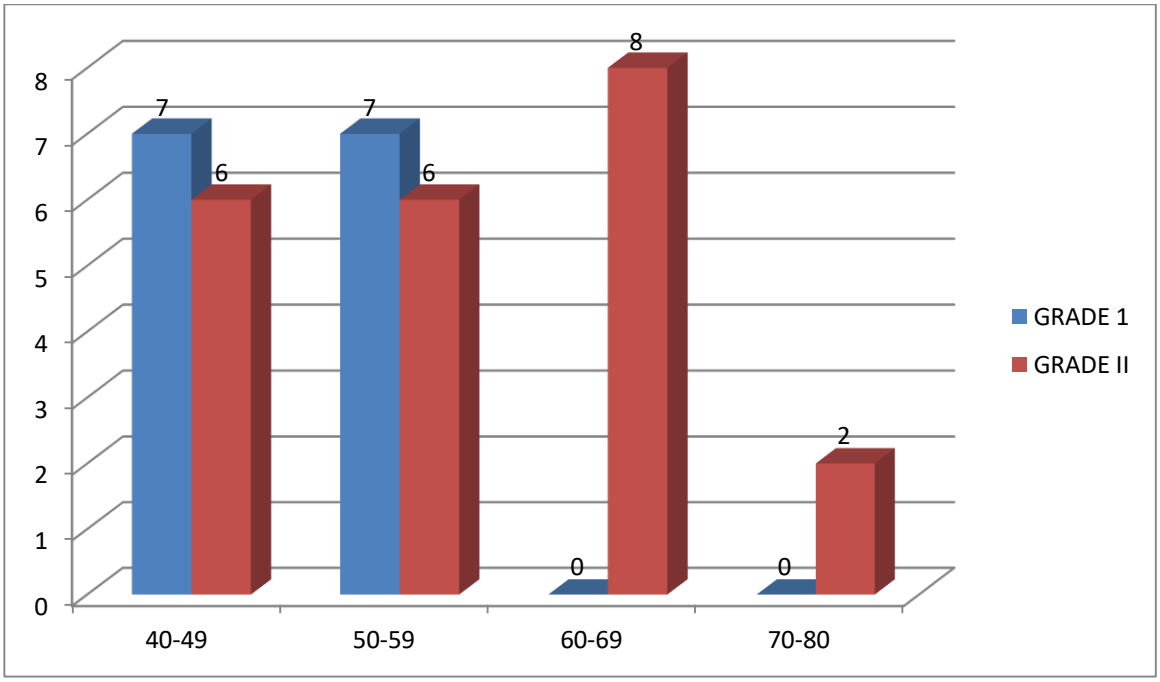


Fig 21. Bar chart showcases the age wise distribution of cases that fall under Grade I and Grade II

Most of the patient are in grade II and in age between there is equal distribution in both the grades of OA knee as the age increases there ia increasing the incidence of grade II oa knee. Only 2 pateints were in the range of 70-80 years .Of the 36 cases, 14 cases fall under Grade 1 and 22 cases fall under Grade 2 osteoarthritis.

GENDER DISTRIBUTION

GENDER	Grade I	GRADE II
MALE	3	5
FEMALE	11	17

Table no :2 Shows grade distribution in different genders

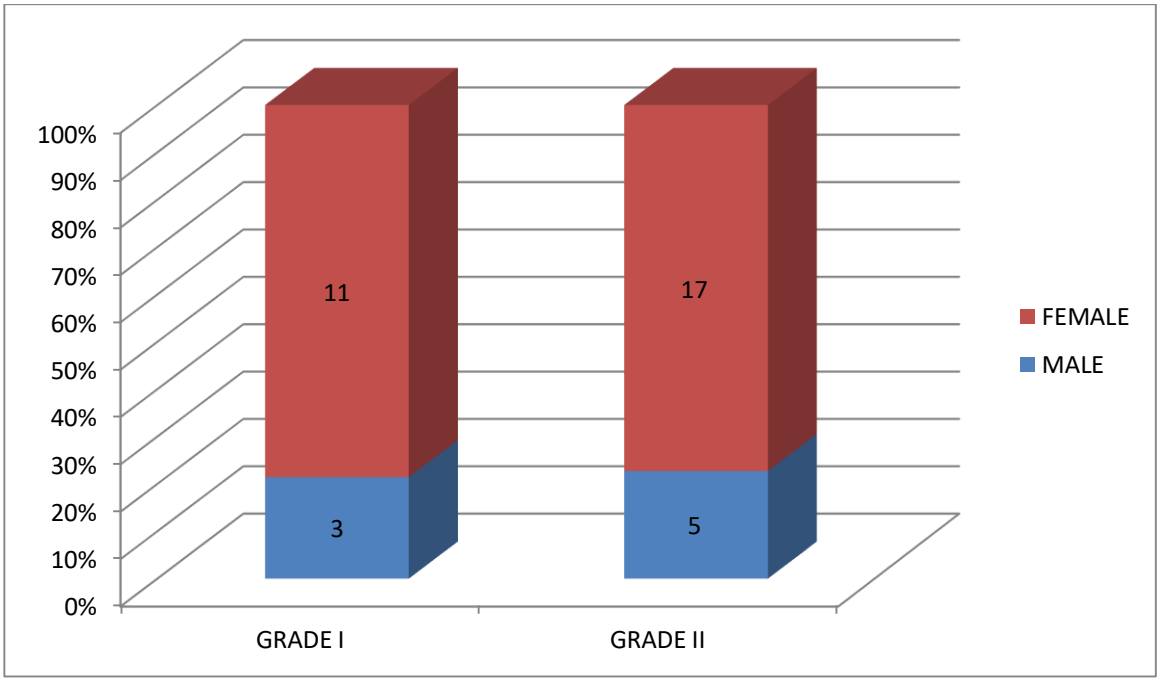


Fig 22.The bar diagram illustrates the gender distribution under Grade 1 and Grade 2 Osteoarthritis.

In a total of 36 patient there are 8 male and 28 female patients. Out of total 8 males 5 patients are in grade II and only 3 males are in grade I. out of 28 females more patient lies in grade II i.e., 17 and 11 patients belong to grade I OA knee.

SIDE DISTRIBUTION

SIDE	NO. OF PATIENTS	PERCENTAGE
RIGHT	20	55.56%
LEFT	16	44.44%

Table no: 3 Shows side distribution

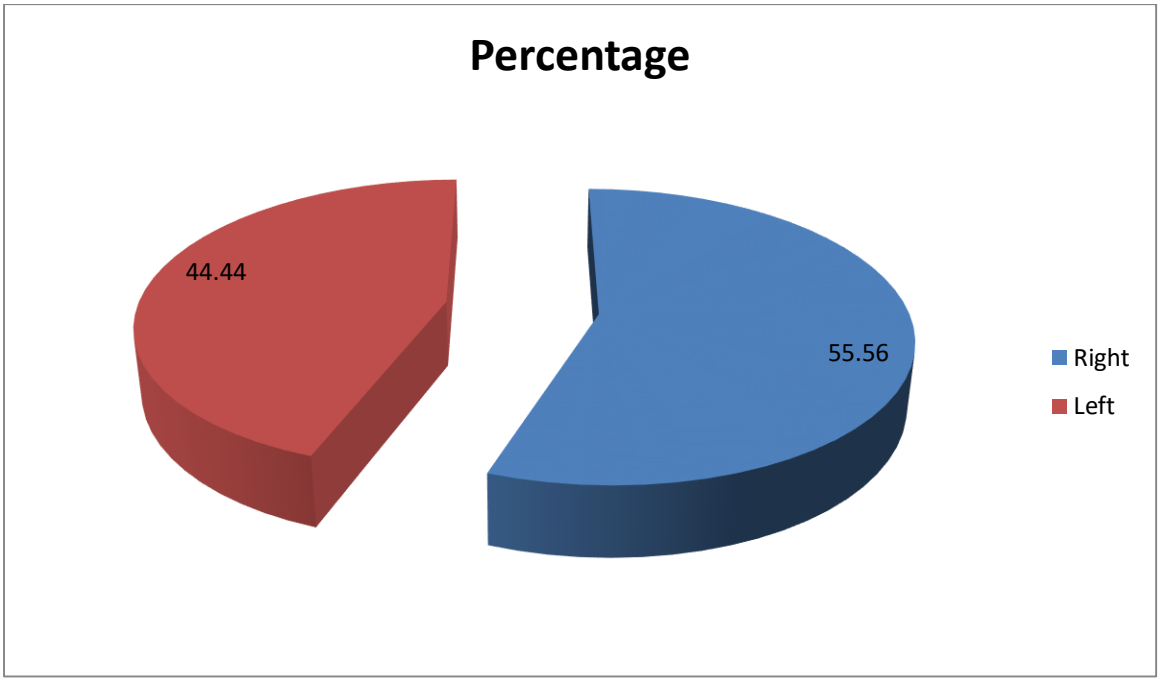


Fig 23. The pie chart depicts the distribution of Right and Left Osteoarthritis.

In a total of 36 patients in our study right side disease is more common than left side as depicited in table and pie chart i.e., 20 patients (55.56%), While 16 patients (44.44 %) had left side affection

WOMAC SCORE DISTRIBUTION PRE INJECTION

WOMAC SCORE	GRADE I	GRADE II
60-69	1	1
70-79	8	5
80-89	5	16

Table no: 4 Shows WOMAC score pre injection in both grade patients

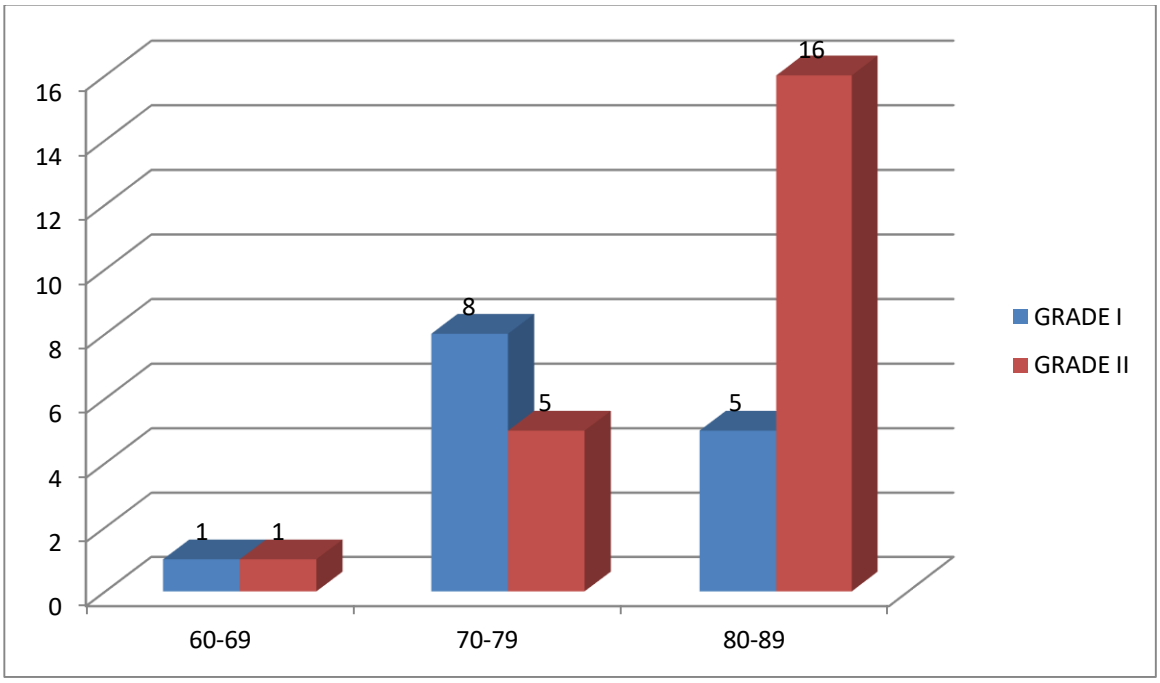


Fig 24 The bar graph represents the WOMAC SCORE of patients Grade 1 OA and Grade 2 OA knee patients pre injection

Before injection most of the patients i.e., 21 has increased womac score between 80-89 in this 21 patients most of them were in grade II i.e., 16 where as only 5 patients were in grade I OA knee. Out of 36 patients only 2 were below 69 score and 13 patients are having score of 70-79.in this patient with score between 70-79 more belong to grade I i.e., 8 and only 5 belongs to Grade II. In 2 patients who were below 69 score had equal distribution in both the grade of OA knee.

WOMAC SCORE DISTRIBUTION 1 MONTH POST INJECTION

WOMAC SCORE	GRADE I	GRADE II
<55	2	2
56-65	9	8
66-75	2	10
>75	1	2

Table no: 5 Shows WOMAC score post injection 1 month in both grade patients

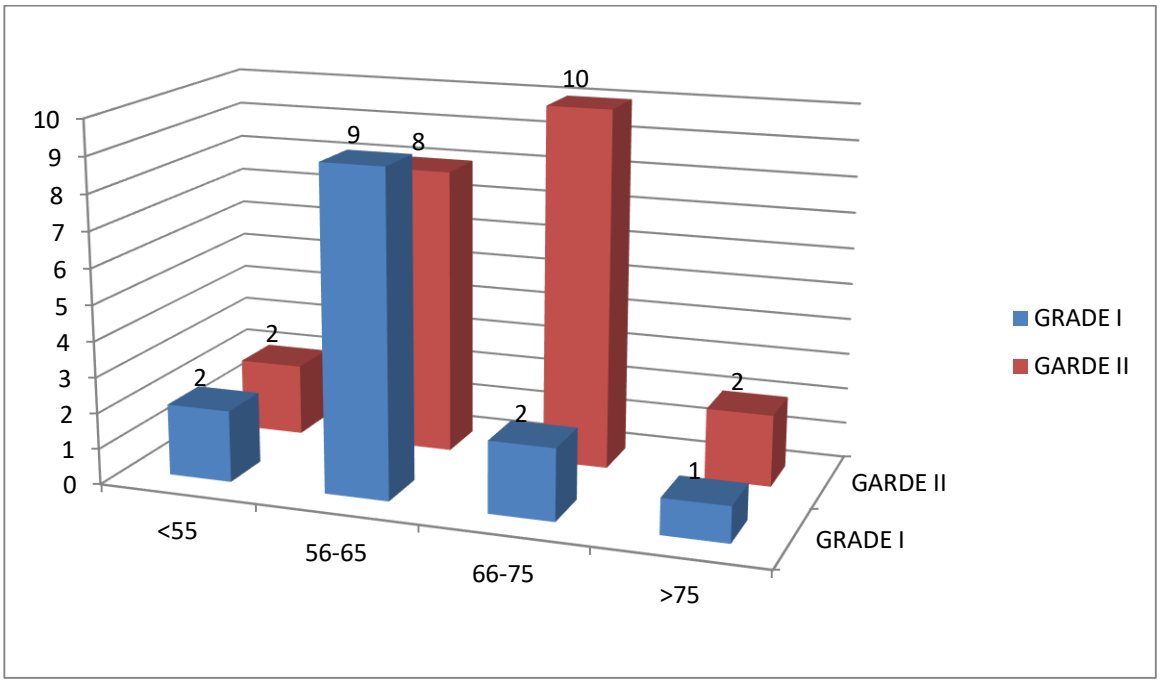


Fig 25. The bar diagram shows cases the WOMAC score distribution in different grades of patient with OA knee 1 month after hyaluronic acid injection.

After 1 month post injection the womac score was declined with maximum patients in the score range 55-75 whereas still 3 patients had score more than 75.only 4 patients improved with score less than 55. Grade I patients responded well with intra articular injection but more percentage of grade II patients also shown improvement by decrease in the scores.

WOMAC SCORE DISTRIBUTION 3 MONTHS POST INJECTION

WOMAC SCORE	GRADE I	GRADE II
30-39	4	3
40-49	2	7
50-59	5	7
60-69	3	5

Table no: 6 Shows WOMAC score post injection 3 months in both grade patients

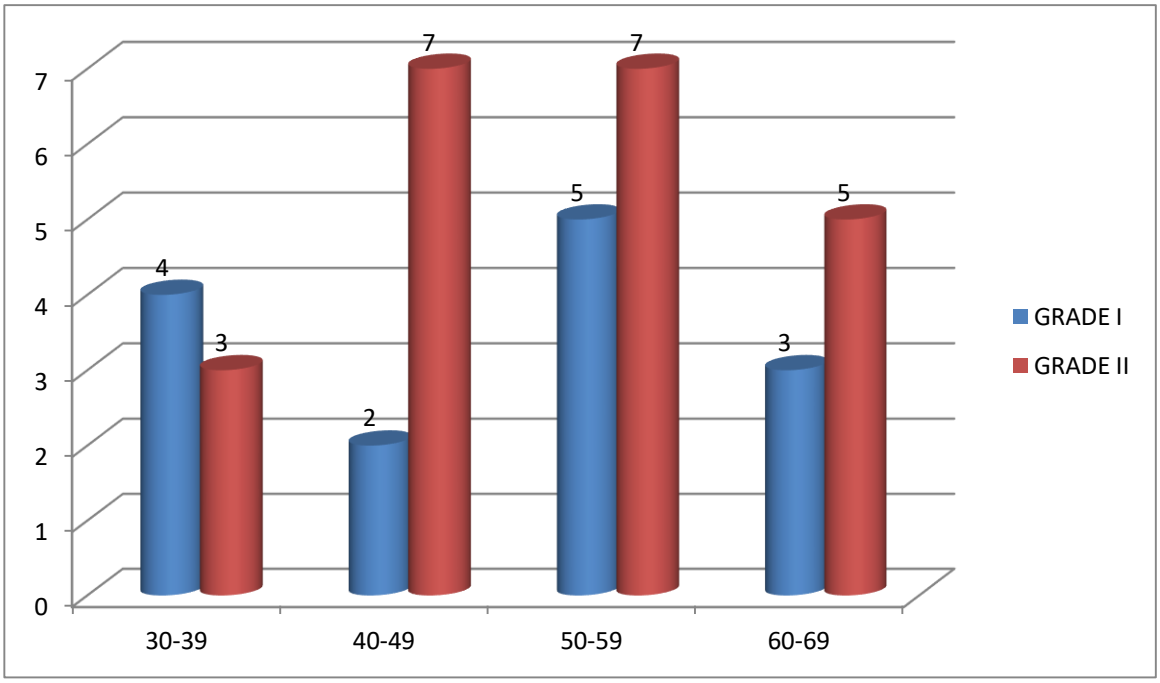


Fig 26. The graph depicts the OA knee grading of patients 3 months after hyaluronic acid injection.

At three months post injection there is rapid decline in the WOMAC scores i.e maximum score is within 60-69. Around 7 patients i.e., 4 patients of grade I and 3 patients of grade II well responded with the score in the range of 30-39. Around 9 patients are in arrange of 40-49 and 12 patients in the range of 50-59.

WOMAC SCORE DISTRIBUTION 6 MONTHS POST INJECTION

WOMAC SCORE	GRADE I	GRADE II
<30	5	7
31-45	6	9
46-60	2	5
>60	1	1

Table no: 7 Shows WOMAC score post injection 6 months in both grade patients

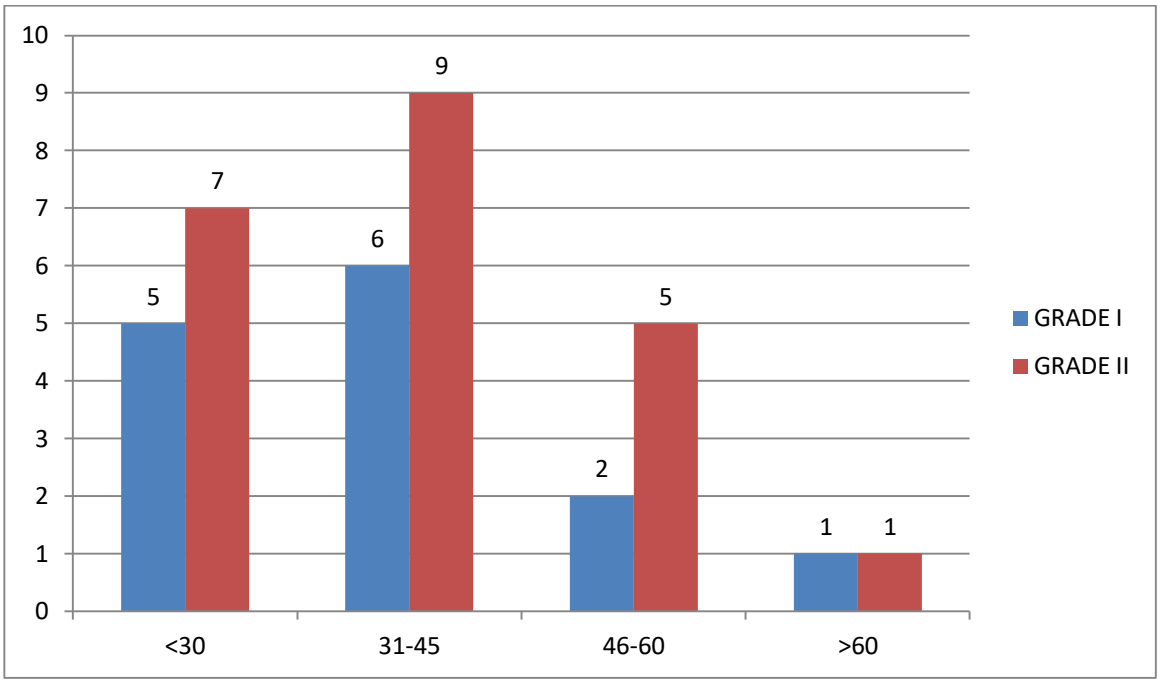


Fig 27.The bar diagram depicts WOMAC of OA knee patients in different grades at 6 months after the injection of Hyaluronic acid

After 6 months post injection the WOMAC scores were decreased from their pre injection values with less than 30 over 12 patients in that 5 were grade I and 7 were grade II only 2 patients of both grade I and grade II had high scores of more than 60. Out of 36 most of them in the scores between the range of 31- 45 i.e., 15. It shows that

around 6 months almost 27 patients had scores below 45 which shows that there is improvement of WOMAC scores in most of the patients in both the grades.

VAS scores pre injection:

VAS SCORE	GRADE I	GRADE II
8	9	6
9	3	2
10	2	14

Table no: 8 Shows VAS score pre injection in both grade patients

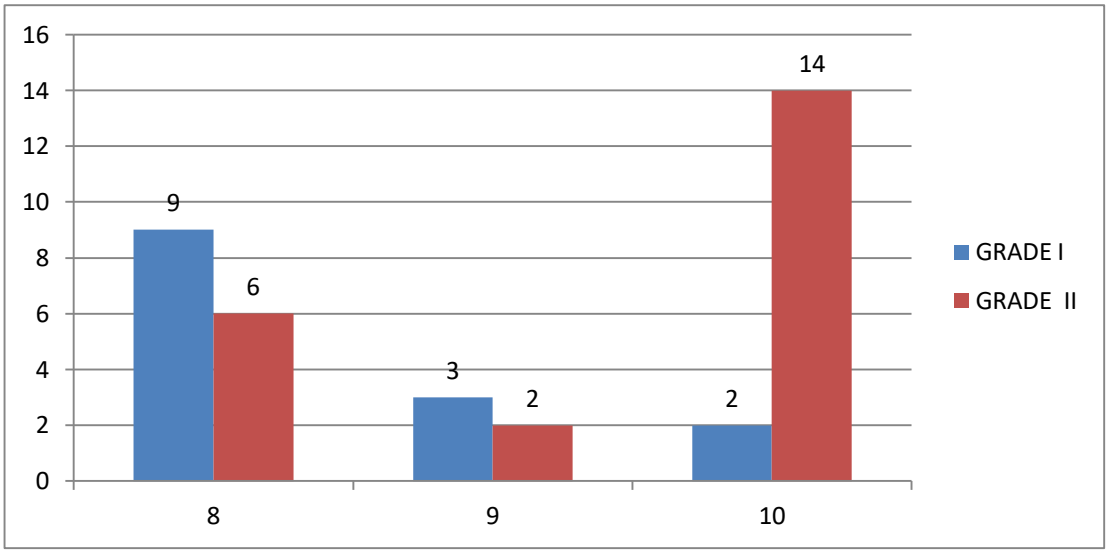


Fig 28. This graph show cases the VAS score of the samples prior to the injection of Hyaluronic acid.

All the 36 patients before injection had a pain score i.e., VAS between 8-10 in that around 14 of grade II patient had maximum score of about 10 and 6 had minimum score of 8. In grade I only 2 patient had maximum scores i.e., 10 and most of the patient of grade I i.e., 9 had score of 8.

GRADE I OA KNEE PATIENT VAS SCORE POST INJECTION FOLLOW UPS

VAS SCORE	1 MONTH	3 MONTHS	6 MONTHS
0-5	3	12	14
6-10	11	2	0

Table no: 9 Shows VAS score post injection 1,3,6 months in grade I patients.

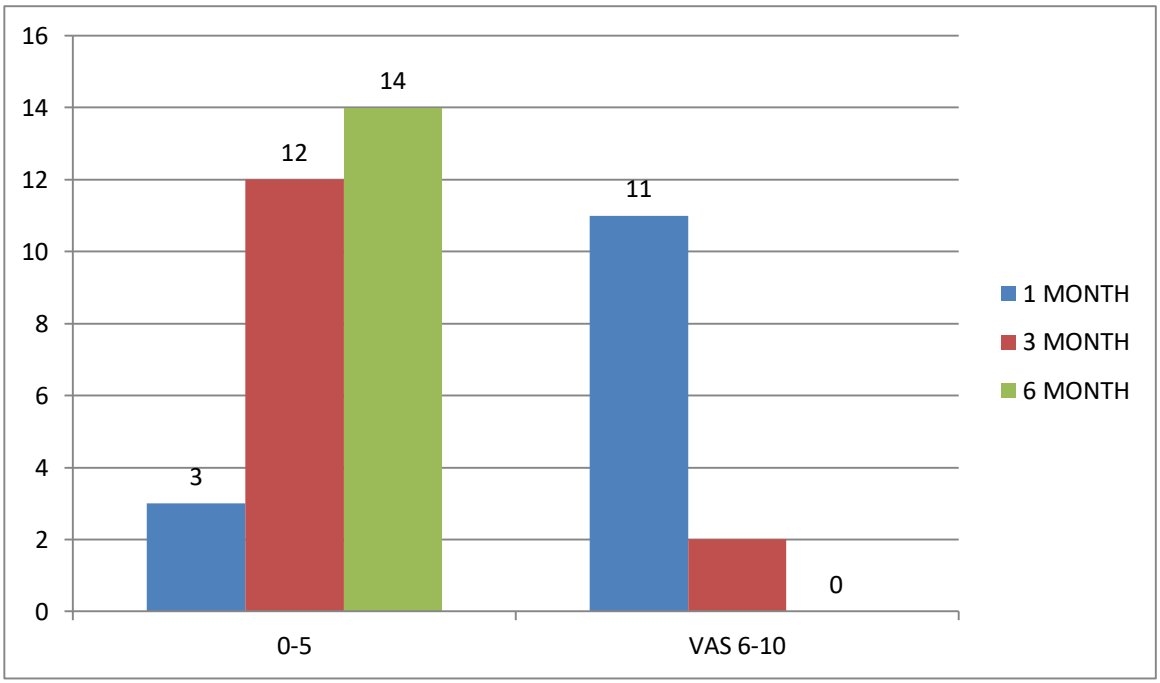


Fig 29.This graph represents the VAS score of Grade 1 OAE cases 1, 3 and 6 months after the injection of Hyaluronic acid.

After intra articular injection most of the patient of grade I had pain score below 5 over the follow up months at first month 3 patients and 3 month 12 patient. At last follow up 6 months all of the patient had decreased score below 5.

GRADE II OA KNEE PATIENT VAS SCORE POST INJECTION FOLLOW UPS

VAS SCORE	1 MONTH	3 MONTHS	6 MONTHS
0-5	2	11	15
6-10	20	11	7

Table no: 10 Shows VAS score post injection 1, 3, 6 months in grade II patients.

In grade II OA knee patient the VAS scores were in the range of 6-10 for 20 patients and only 2 patients at I month post injection. At 3 months it was decreased to a range of 6-10 for 11 patients and in a range of 0-5 for 11 patients. where as at 6 month post injection the patient improved was 15 with a score 0-5 some patient were still in range of 6-10.

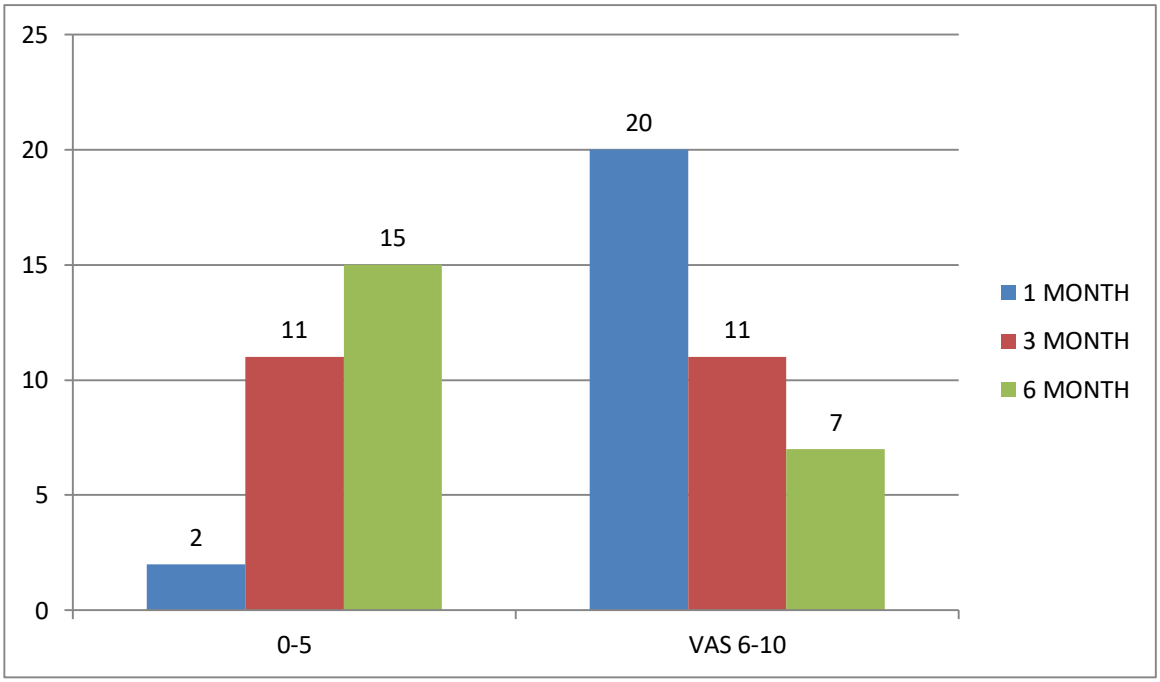


Fig 30. This graph represents the VAS score of cases affected by Grade 2 OAE knee, during their follow up 1, 3 and 6 months after the injection of Hyaluronic acid.

GRADE DISTRIBUTION

GRADE	NO. OF PATIENTS	PERCENTAGE
I	14	38.89%
II	22	61.11%

Table no: 11 Shows grade distribution and its percentage

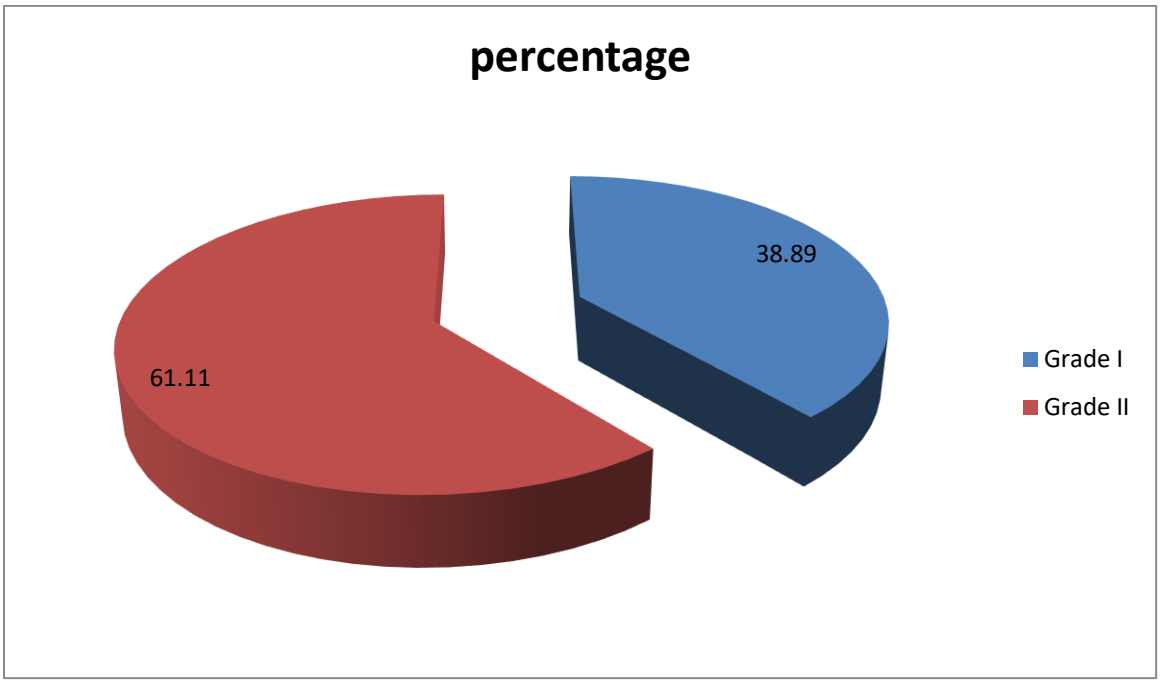


Fig 31. The given pie chart depicts the OAE grade distribution of cases. 38.89% are affected by Grade 1 OA whereas, 61.11% are affected by Grade 2 OA knee.

Out of this 36 patients most of the patient i.e., 22 belong to grade II i.e., 61.11% and the remaining14 patients with 38.89% were belongs to grade I.

PAIN MEAN DISTRIBUTION

Table no: 12 Shows mean pain scores in all patients pre and post injection.

	PRE INJECTION	1 MONTH POST INJECTION	3 MONTHS POST INJECTION	6 MONTHS POST INJECTION
MEAN	17.7	14.5	11.14	7.65
STANDARD DEVIATION	2.158	1.828	2.167	2.739
MINIMUM	8	10	6	3
MAXIMUM	20	19	15	13

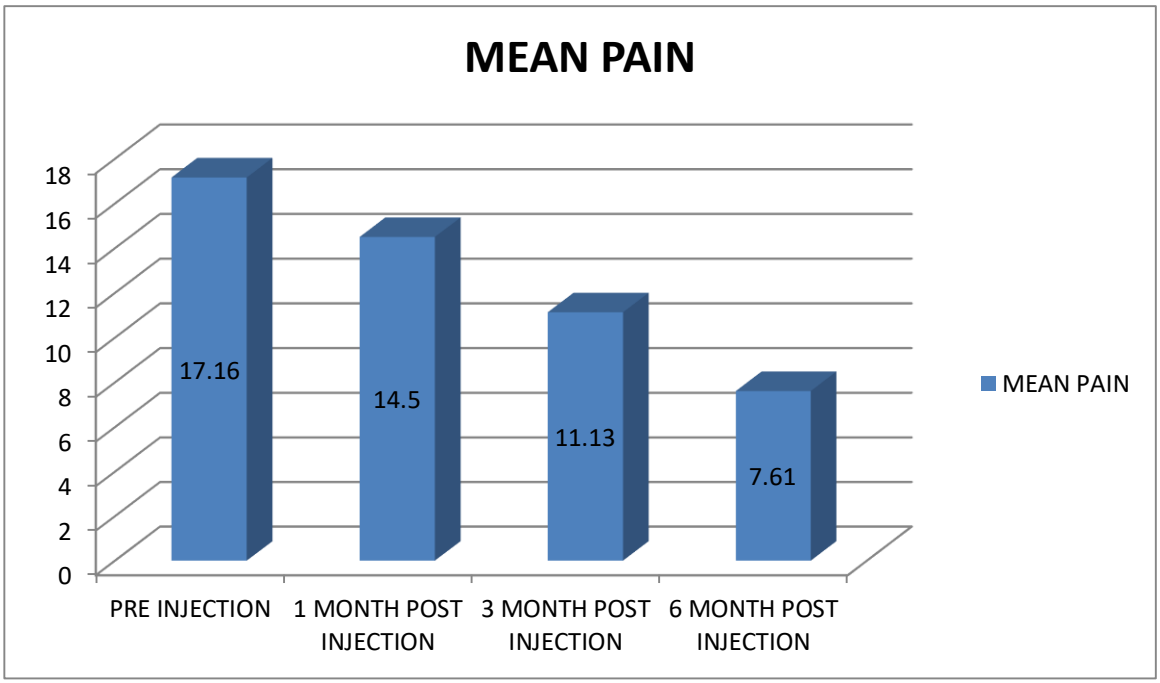


Fig 32.The bar graph showcases the mean distribution of pain in all the samples before and after they were administered Hyaluronic acid.

Pain score in WOMAC had a maximum score of 20 with minimum score 0. In this our patients had a mean score of 17.16 pre injection and following injection it has decreased to 14.5 at 1 month follow up. At 3rd month follow up mean scores was decreased to 11.13 and at 6 months it was less than half of the total score i.e., 7.6.

The total pain score is 20 but in our study of 36 patients there is minimum and maximum scores at pre injection was 8-20 in which mean score was 17.7, after injection the mean pain score decreased to 14.5, 11.4, 7.65 post injection 1st month, 3months, 6 months respectively.

MEAN STIFFNESS DISTRIBUTION

	PRE INJECTION	1 MONTH POST INJECTION	3 MONTHS POST INJECTION	6 MONTHS POST INJECTION
MEAN	6.17	5.08	4.00	2.67
STANDARD DEVIATION	0.971	0.806	1.121	1.265
MINIMUM	4	4	2	1
MAXIMUM	8	7	6	6

Table no: 13 Shows mean stiffness scores in all patients pre and post injection

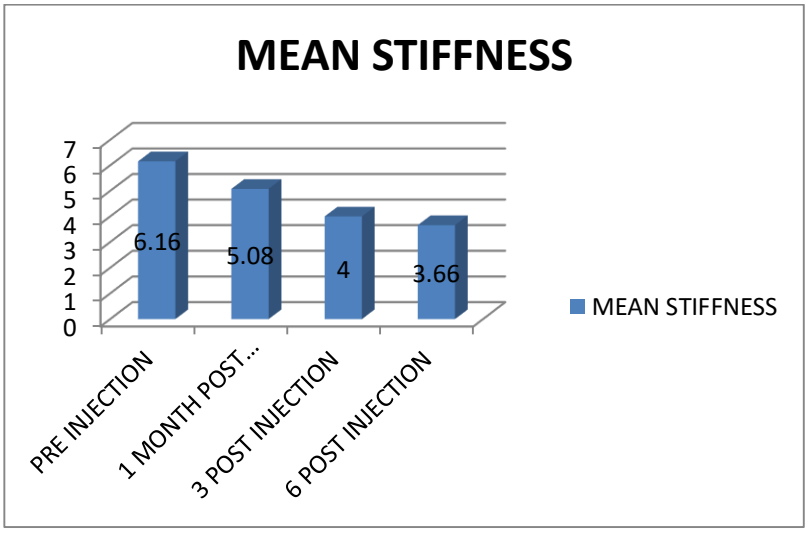


Fig 33.This graph depicts the mean stiffness distribution of cases before and after they were given Hyaluronic acid injection.

In womac there is stiffness score which is in range of 0-8. The mean stiffness score at pre injection was 6.16 which was decreased further to 5.08, but at 3rd month follow up

it was decreased to 4 and at 6 month to 3.66. Which showed progressive decrease in scores over a period of time.

PHYSICAL FUNCTION DISTRIBUTION

	PRE INJECTION	1 MONTH POST INJECTION	3 MONTHS POST INJECTION	6 MONTHS POST INJECTION
MEAN	56.42	45.86	35.31	25.56
STANDARD DEVIATION	4.511	6.343	7.906	9.782
MINIMUM	45	34	22	9
MAXIMUM	64	64	51	48

Table no: 14 Shows mean physical function scores in all patients pre and post injection.

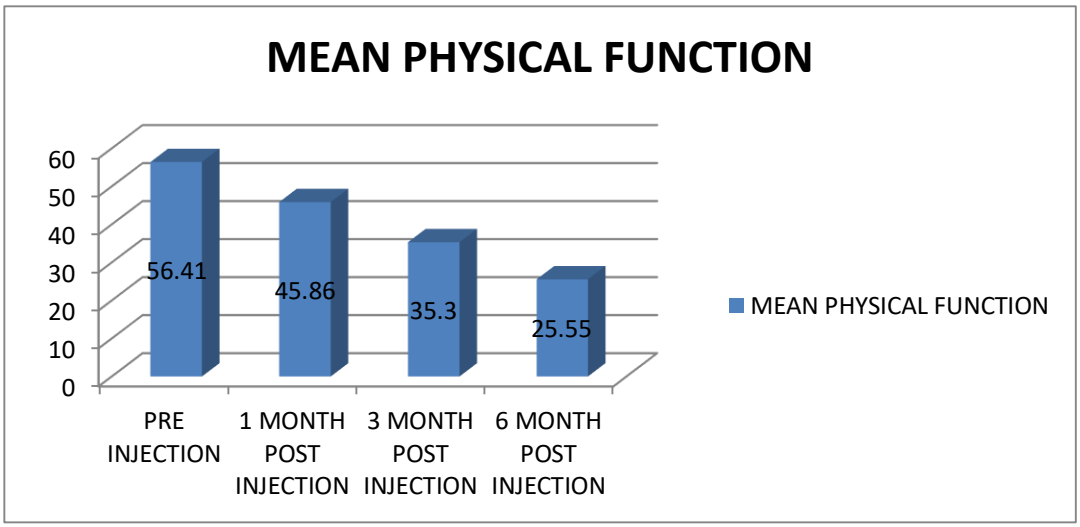


Fig 31. The given bar graph represents the mean physical function of the samples before and after the administration of Hyaluronic acid.

In WOMAC score physical function score are in a range of 0- 68. The mean pre injection score is 56.41 which was decreased to 45.86 at 1 month and post 3 month injection the scores was 35.30 and at 6 months follow up it was 25.55

MEAN WOMAC SCORE

	PRE INJECTION	1 MONTH POST INJECTION	3 MONTHS POST INJECTION	6 MONTHS POST INJECTION
MEAN	81.14	65.14	50.19	35.81
STANDARD DEVIATION	6.437	7.208	10.504	13.44
MINIMUM	60	49	32	13
MAXIMUM	89	79	69	64

Table no: 15 Shows mean total WOMAC scores in all patients pre and post injection

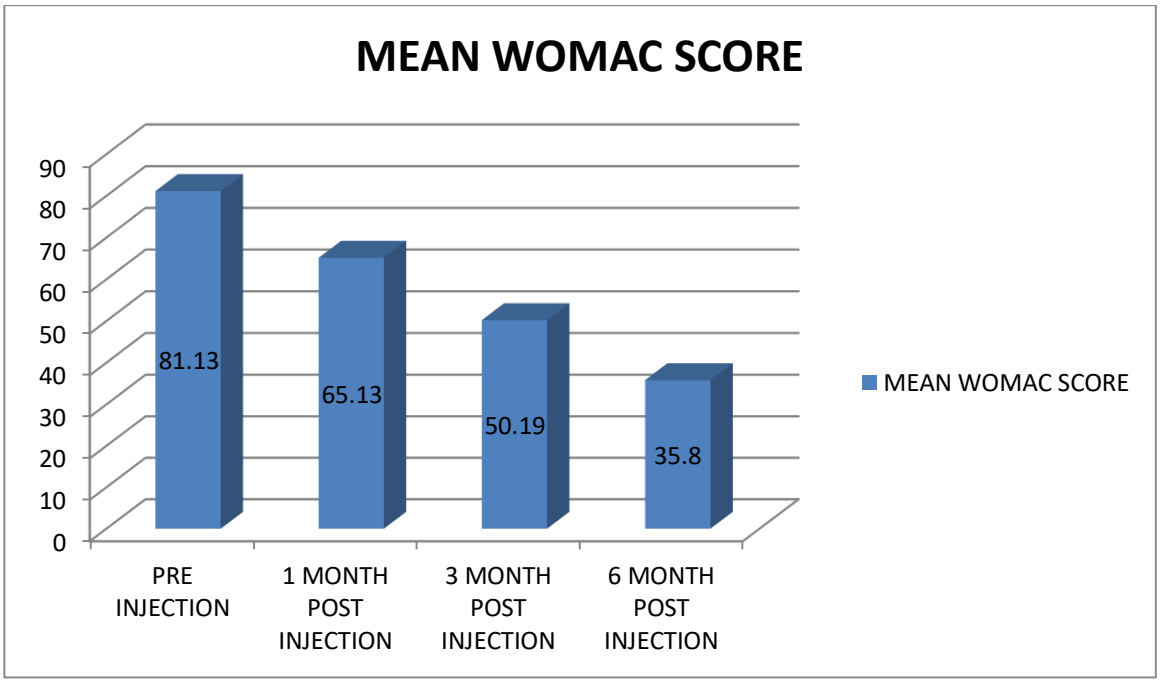


Fig 35. The graph illustrates the mean WOMAC score of sample cases before and after Hyaluronic acid injection.

The total WOMAC score is 96. In our study the mean score at pre injection was 81.13 and at 1st month follow up it was 65.13, it was progressively decreased during 3 and 6 months follow up to 50.19 and 35.80 respectively.

VAS SCORE DISTRIBUTION

	PRE INJECTION	1 MONTH POST INJECTION	3 MONTHS POST INJECTION	6 MONTHS POST INJECTION
Mean	9.03	6.75	4.58	2.61
Standard deviation	0.941	1.317	1.1697	2.155
Minimum	8	3	1	0
Maximum	10	10	8	6

Table no: 16. Shows mean VAS scores in all patients pre and post injection

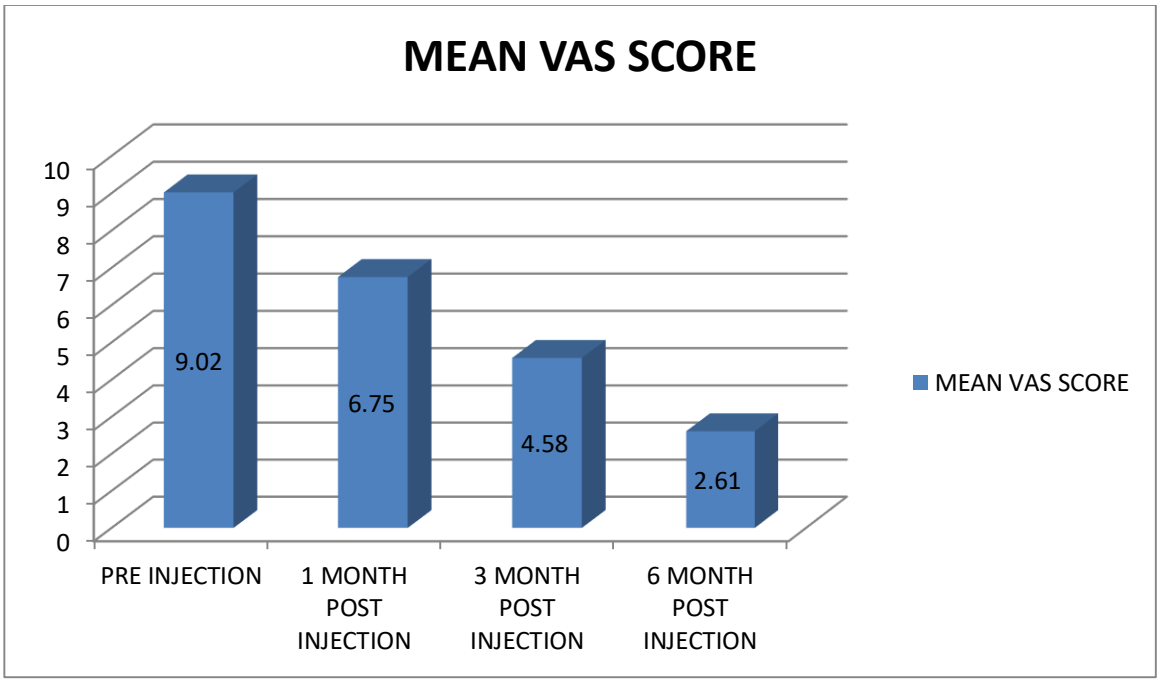


Fig 36. This bar graph demonstrates the mean VAS score of sample cases before and after the injection of Hyaluronic acid.

The VAS acore ranges from 0-10. In our study the mean VAS score at pre injection was 9.02, post 1 month it was 6.75 at 3rd month it improved to 4.58. at around 6 month it was decreased to 2.6

BMI DISTRIBUTION:

BMI RANGE	GRADE I	GRADE II
<25	6	5
25-30	4	10
30-35	3	4
>35	1	3

Table no: 17 Shows BMI distribution in both the grades.

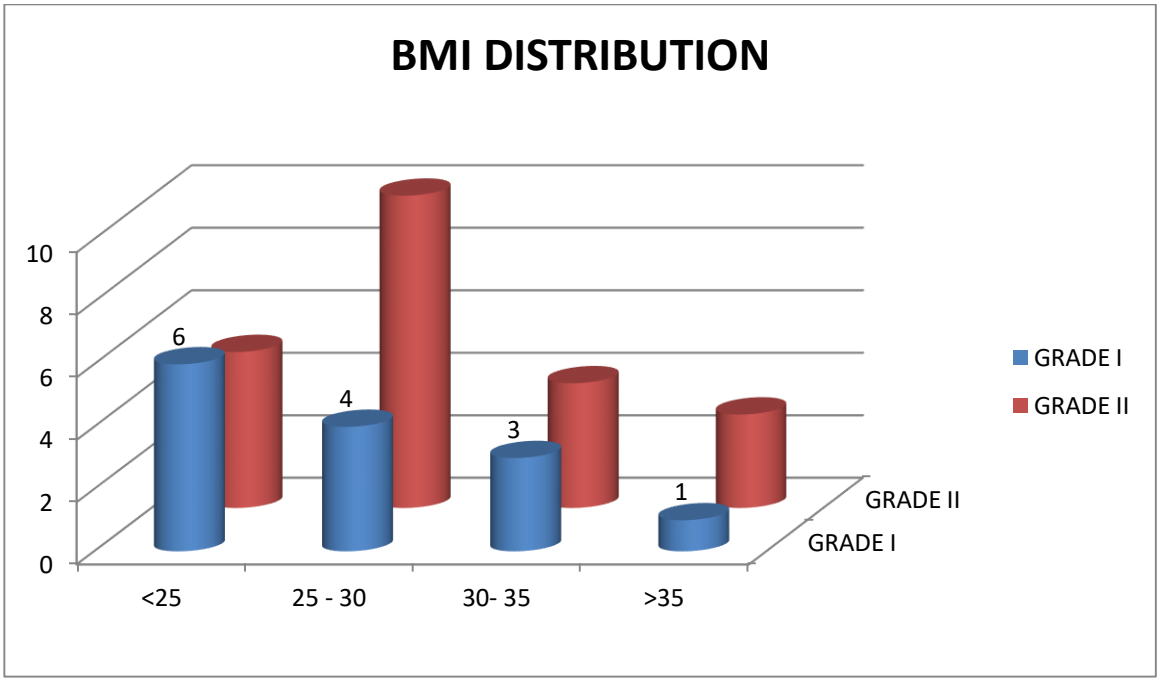


Fig 37 The graph illustrates the BMI distribution of cases into the grades of Osteoarthritis of knee. 14 cases are affected by Grade 1 OA knee and 22 cases by Grade 2 OA knee.

BMI (Body Mass Index) is a factor for OA knee as from previous studies. We also had patients with increased BMI that in both grades where 4 patients in grade I and 10 patients were overweight and 3 patients in grade I and 4 patients were in grade II. 1 patient of grade I and 3 patient of grade II were morbidly obese.

CO MORBIDITIES OA KNEE PATIENT

CO MORBIDITES	Diabetes Mellitus	Hypertension	Post Hysterectomy
GRADE I	2	1	4
GRADE II	8	3	2

Table no: 18 Shows comorbities in both the grades.

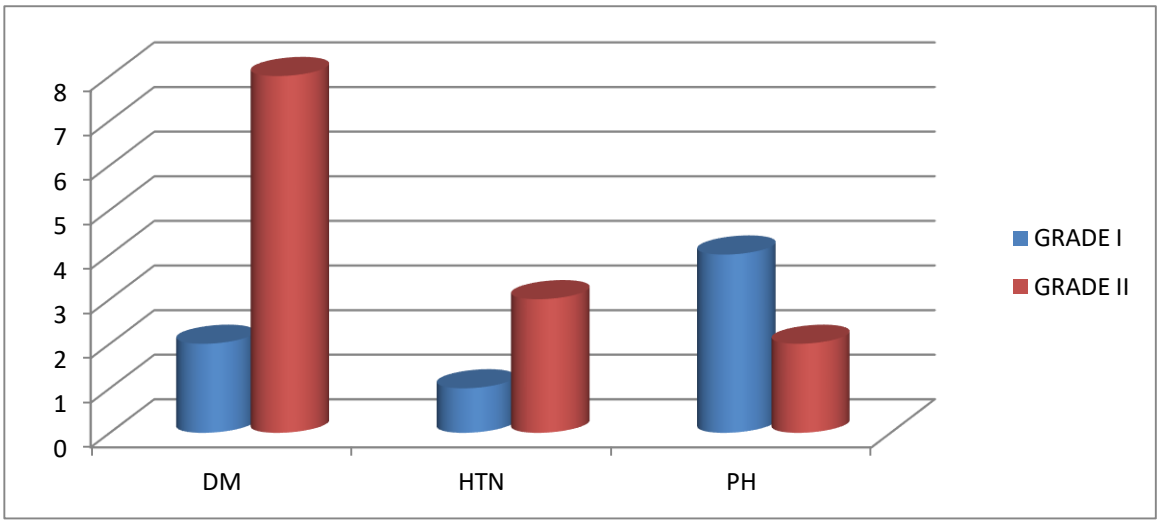


Fig 38. This graph depicts the relation between comorbidities namely, Diabetes mellitus, Hypertension and Post hysterectomy and Grade 1 and 2 OA knee

In this 36 patients only 2 patients in grade I in had Diabetes mellitus as associated co morbity but in patient in grade II were 8 patients this shows that diabetes mellitus is one of the trigerring factor for OA knee that leads to more cartilage damage and increases the damage with glycation end products. As our patients who had grade I disease had undergone hysterectomy for various reasons, their age were less than 50 years that shows that there is correlation between OA knees with estrogen. Only 4 patients were had associated hypertension as their co morbities.

Multivariate test result for VAS score :

Pre injection VAS score comparison	1 month post injection	3 months post injection	6 months post injection
Mean difference	2.278*	4.444*	6.417*
Standard error	.206	.283	.353
Significant	.001	.001	.001

Table no.19 multivariate analysis with VAS score

As per statistical analysis which was done by Wilks' Lambda multivariate test for VAS scores it shows significant difference between pre injection scores and post injection one month and with one month to third month values and even with 6 month value and pre injection values

Multivariate test for WOMAC score:

WOMAC Pre injection	1 month post injection	3 months post injection	6 months post injection
Mean difference	16.000*	30.944*	45.333*
Standard error	1.165	1.767	2.532
Significant	.001	.001	.001

Table no 20.multivariate analysis with WOMAC score

As per statistical analysis which was done by Wilks' Lambda multivariate test for WOMAC scores it shows significant difference between pre injection scores and post injection one month values and with one month to third month values and even with 6 month value and pre injection values. P value <0.001 shows it is significant decrease in the score.

DISCUSSION:

Osteoarthritis is a progressive degenerative condition of the synovium of knee joint with variable local and systemic factors that contribute to the disease. In our study we analysed around 36 patients who are meeting our inclusion criteria after excluding the patients under exclusion criteria who were assessed with WOMAC and VAS scores at pre injection, one month, three months and six months post injection.

	Our Study	Pal S Et Al[238]	Askari A Et Al[229]	Varun Gbs[30]	Pal Cp Et Al[239]	Das S[236]	Sancheti P Et Al[237]	Jesalpura Bh Et Al[234]	Sudheer U Et Al[233]	Bowman EN[235]
MEAN AGE	53.33+/-9.451	57.6+/-9.8	58.5+/-8.3	43.13	57.4+/-9.05	59.83+/-10.73	55.6+/-11.1		58+/-12	61
MALE	22.22%	27.7%		60%	42%	46.7%	36.1%	35%	48%	27.5%
FEMALE	77.78%	72.3%		40%	58%	53.3%	63.9%	65%	52%	72.5%
GRADE 1	38.89	5.1%		63%	48.3%		35%			38%
GRADE 2	61.11	38.3%		40%	51.7%		31%			36%
RIGHT SIDE	55.56	55.8				36.7%	15.8%		59%	
LEFT SIDE	44.44	44.2				20%	18.2%		41%	
BMI	27.83	27.7=/-4.4					25.6+/-3.5		25+/-4	33.2
NORMAL	11	26.9%		30%	25.4%					
OVERWEIGHT	14	50.6%		27%	47%					
OBESE	7	22.5%		43%	25%					
MORBID OBESE	4				2.6%					
WOMAC (PRE)	81.14+/-6.437				71.9	58.83+/-9.29				
WOMAC 1	65.14+/-7.208				59.02	40.93+/-10.27				
WOMAC 3	50.19+/-10.504				33.2	26.97+/-7.68				

Table no 21 shows comparision of variable with different studies.

WOMAC 6	35.81+/-13.4				28.2	28.43+/-11.4				
PAIN 0	17.17+/-2.158								10.82+/-3.77	
STIFNESS 0	6.17+/-0.971								4.34+/-1.95	
PHYSICAL FUNCTION 0	56.42+/-4.519								36.78+/-12.79	
PAIN 1	14.5+/-1.828		13.9+/-4.37						3.62+/-2.95	
STIFFNESS 1	5.08+/-0.806		4.71+/-2.9						2.03+/-0.82	
PHYSICAL FUNCTION 1	45.86+/-6.343		35.9+/-12.8						17.1+/-10.75	
PAIN 3	11.14+/-2.167		13.11+/-4.24							
STIFFNESS 3	4+/-1.121		4.29+/-2.88							
PHYSICAL FUNCTION 3	35.31+/-7.906		33.54+/-12.69							
VAS (PRE)	9.03+/-0.941			5.03+/-0.61					6.6	6.1
VAS 1	6.75+/-1.317	6.63+/-2.03		3.4+/-0.93						4.4
VAS 3	4.58+/-1.697	6.7+/-2.01		3.16+/-0.91					4.1	
VAS 6	2.61+/-2.155								5.9	

AGE INCIDENCE:

The mean age and standard deviation in our study including both males and females is 57.4 +/- 9.45. It was comparable with other studies such as Pal S et al, with a mean and standard deviation of 57.6 +/- 9.8 and Askari A et al with a mean and standard deviation of 58.5 +/- 8.3. Pal CP et al with a mean and standard deviation of 57.4 +/- 9.05. Another study by Das S with mean and standard deviation of 59.83 +/- 10.73, Sancheti P et al with mean and standard deviation of 55.6 +/ 11.01 and also with other study by Sudheer U, Jaya Prakash C with mean and standard deviation of 58 +/- 12.

SEX INCIDENCE:

The sex incidence in our study is male 22.22% and female 77.78% which was comparable with other studies. Pal S et al showed a sex incidence of male 27.7% and female 72.3%, Varun GBS in his study gave a sex incidence of 60% male and 40% female. Pal CP et al with a sex incidence of 42.0% male and 58.0% female. Das S had a percentage of 46.7% male and 53.3% female. Sancheti P, had an incidence of 36.1% male and 63.9% female. Gesalpura BH et al had an incidence of 35% male and 65% female. Sudheer U had an incidence of 48% male and 52% female. Bowman EN with an incidence of 27.5% male and 72.5% female.

GRADE DISTRIBUTION

In our study most of the patients were belonging to Grade 2, i.e. 22(61.11%) and 14 patients (38.89) belong to Grade 1 of Kellegren Lawrence grading of OA knee, which was comparable with other studies by Varun GBS et al in which 63% belong to Grade 1 and 40% belong to Grade 2, Pal CP et al 48.3% Grade 1 and 51.7% Grade 2.

SIDE DISTRIBUTION:

In this prospective study, we had 55.56% of patients who were affected by right sided OA knee and around 44.4% had more symptoms on the left side which was comparable with other studies by Pal S et al showing a right sided laterality around 55.8% and left side is 44.2%, Sudheer E et al concluded 59% of patients had right sided symptoms and 41% had left sided symptoms.

BMI DISTRIBUTION:

The normal BMI is between 18.5 to 24.9. 11(30.5%) of our patients had a normal BMI, of which, 6 belonged to Grade 1 and 5 belonged to Grade 2. 14 (38.89%) of our patients are overweight with a BMI range of 25 to 30. Obese patients were 7 (19.4%) and morbid obese patients constituted 4(11.11%). This is comparable with other studies done by Pal CP et al which shows normal BMI for 25.4% over weight patients were 47%. Obese patients were 25%, morbid obesity 2.6%. Other two studies by Pal S et al had 26.9% patients with normal BMI and 50.56% were overweight and remaining 22.5% were obese. It is also comparable with other studies done with Varun GBS et al who had 30% of normal BMI patients, 27% over weight and 43% were obese. The mean BMI in our

study is 27.83 which were comparable with other studies done by Pal S et al, Sancheti P et al, Sudheer U et al, Bowman EN with mean BMI of 27.7, 25.6, 25, and 33.2, respectively.

WOMAC SCORE:

The mean WOMAC score in our study pre injection was 81.14 which is comparable with other studies by Pal CP et al and Das S et al with a mean of 71.9, 58.83 respectively. Post 1 month injection, it was 65.14 in our study comparable with the other studies 59.02, 40.93. At 3 months post injection, it was 50.19, 33.2, and 26.97 in consecutive studies. At 6 months post injection, the scores were 35.81 and with other studies it was 28.2 and 28.43.

WOMAC PAIN SCORE:

In our study the mean pain score before injection was 17.7 which improved to 17.5 1 month post injection which was comparable to a study done by Sudheer U et al who has a mean score of 10.82 prior to injection and 3.62 post injection. The pain score at 1 month post injection was 13.9 in a study done by Askari at al. At 3 months post injection the pain score was not satisfactorily decreased, i.e 13.11. But in our study the pain score was 11.14 which was satisfactory.

WOMAC STIFFNESS SCORE:

The mean stiffness score in our study prior to injection was 6.17, 1 month post injection was 5.08 which was comparable with the study done by Sudheer U et al, with a mean

stiffness score of 4.34, 2.03, at preinjection and 1 month post injection respectively. The mean stiffness score at 3 months post injection was 4 which was comparable with a study done by Askari A et al with a mean stiffness score post 3 months after injection was 4.29.

WOMAC PHYSICAL FUNCTION SCORE:

The mean physical function score in our study preinjection was 56.42 which was comparable to a study done by Sudheer U eta al which was 36.78. At 1 month post injection, the mean score was 45.86 whereas it was 17.1 by a study done by Sudheer et al. The mean physical function score at 3 months post injection was 35.31 which was comparable to another study by Askari A et al with a mean score of 33.54.

VAS SCORE:

The mean VAS SCORE in our study prior to injection was 9.03 which was comparable to other studies by Varun GBS et al, Sudheer U et al, and Bowman et al with the mean values of 5.03, 6.6, and 6.1, respectively. The mean score at 1 month post injection in our study was 6.75 as opposed to other studies, namely, Pal S et al, Varun GBS et al and Bowman showing scores of 6.63, 3.4, and 4.4 respectively. Likewise, the mean score in our study at 3 months after injection showed 4.58 when compared to studies by Pal S et al, Varun GBS and Bowman et al which showed 6.7, 3.16, and 4.1. In addition to this, the mean VAS score of our study at 6 months showed 2.61 when compared to a study by Bowman EN showing 5.9.

CONCLUSION

- In this study of 36 patients treated with intra articular injection of Hyaluronic acid injection for Kellegren Lawrence grade I and II osteoarthritis knee patients, following conclusions were drawn.

- Elderly Females were more commonly affected with osteoarthritis knee with increased incidence in the age group of 4th to 6th decade.
- Osteoarthritis knee affects right side knee more than the left side knee.
- Both Elderly and younger Females was found to be significantly associated with Diabetes Mellitus, post-menopausal and post hysterectomy status
- The functional outcome of the grade II OA Knee was similar compared to grade I OA Knee patients.
- The mean active and passive abduction, flexion, internal and external rotations have significantly improved following the procedure at the end of follow up.
- The pain significantly reduced in all of the patients when assessed with visual analogue score at the end of 6 months follow up.
- All the patients were found to have improved daily activity of living like walking, standing, stair climbing, rising from sitting and bed last but not least in heavy domestic works.
- The mean WOMAC score suggested that functional ability improved in all the study patients by the end of 6 months follow up.
- Pain at the injection site was self-limiting and resolved without any medication.
- This injection has slow onset of action but effect stays for 6 months
- The best improvement in their range of movements was observed in flexion

- In grade I and II osteoarthritis knee, intra-articular hyaluronic acid injection is found to be beneficial in the patients who were treated previously with analgesics alone or with exercises alone.
- This study observes that intra-articular injection Hyaluronic acid is a reliable, productive, efficient and safe mode of treatment of grade I and II osteoarthritis knee, which also delays surgical intervention.

LIMITATION:

- Though it is a prospective study, the study was done for a shorter duration of time and with limited sample size.
- This injection is little costlier than other intra articular preparations.
- The intra-articular injection of the Hyaluronic acid injection was given based on the clinical and radiological examination which is also a limitation of this study as better imaging modalities could be used to confirm the intra articular injection.
- Long term follow up needed with M.R.I to assess the regeneration of cartilage.

BIBLIOGRAPHY:

1. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr Cartil 2013; 21:16–21.
2. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect 1998; 47:487–504.
3. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73:1323–30.
4. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid,hyaluronic acid, platelet rich plasma) for the knee osteoarthritis.World J Orthop. 2014; 5(3):351–361.
5. Baker-LePain JC, Lane NE. Relationship between joint shape and the development of osteoarthritis. Curr Opin Rheumatol 2010; 22:538–43.
6. Gardner E, O'Rahilly R. The early development of the knee joint in staged Human embryos. J Anat .1968;102:291-93
7. Merida- Valasco JA, et al. Development of the human knee joint. Anat Rec. 1997; 248:26-78.
8. Potočnik, B., Zazula, D., Cigale, B., Heric, D., Cibula, E., Tomažič, T., 2008. A patient-specific knee joint computer model using MRI data and 'in-vivo' compressive load from the optical force measuring system. Journal of Computing and Information Technology – CIT 16: 209-222.
9. Peña, E., Calvo, B., Martínez, M.A., Doblaré, M., 2006. Influence of the tunnel angle in ACL reconstructions on the biomechanics of the knee joint. Clinical Biomechanics 21, 508–516.

10. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. Sports Health 2009; 1:461–8.
11. Mow, V.C., Ratcliffe, A., Poole, A.R., 1992. Cartilage and diarthrodial joints as paradigms for hierarchical materials and structures. Biomaterials 13: 67–97.
12. Kumar, P., Oka, M., Toguchida, J., Kobayashi, M., Uchida, E., Nakamura, T. et al., 2001. Role of uppermost superficial surface layer of articular cartilage in the lubrication mechanism of joints. Journal of Anatomy 199(Pt 3): 241-250.
13. Ralphs, J. R., Benjamin, M., 1994. The Joint capsule: structure, composition, ageing and disease (Review). Journal of Anatomy 184, 503-509.
14. Kaufer, H., 1971. Mechanical function of the patella. The Journal of Bone and Joint Surgery 53-A (8): 1551-1560.
15. Beynnon, B.D., Amis, A.A., 1998. In vitro testing protocols for the cruciate ligaments and ligament reconstructions. Knee Surg Sports Traumatol Arthrosc 6: S70-S76.
16. Ryder, S.H., Johnson, R.J., Beynnon, B.D., Ettlinger, C.F., 1997. Prevention of ACL injuries. J Sport Rehabilitation 6: 80-96.
17. Heesterbeek, P., 2010. Mind the gaps! Clinical and technical aspects of PCL-retaining total knee replacement with the balanced gap technique. Thesis-Introduction: 9-31. 20.
18. Hoffman, A.H., Grigg, P., 1984. A method for measuring strains in soft tissue. Journal Biomechanics 17 No. 10: 795-800.

19. Sanchez, A.R. 2nd, Sugalski, M.T., La Prade, R.F., 2006. Anatomy and biomechanics of the lateral side of the knee. Sports Medicine and Anthroscopy Review 14(1): 2-11.
20. Woo, S., L-Y., Wu, C., Dede, O., Vercillo, F., Noorani., S.,2006. Biomechanics and anterior cruciate AAligament reconstruction. Journal of Orthopaedic Surgery and Research 1:2.
21. Dargel, J., Gotter, M., Mader, K., Pennig, D., Koebke, J., Schmidt-Wietoff, R., 2007. Biomechanics of the anterior cruciate ligament and implications for surgical reconstruction. Strategies in Trauma and Limb Recontruction 2(1): 1-12.
22. Brantigan, O.C., Voshell, A.F., 1941. The mechanics of the ligament and menisci of the knee joint. The Journal of Bone & Joint Surgery 23:44-66
23. Luites, J.W.H., Wymenga, A.B., Blankevoort, L, Kooloos, J.M.G., Verdonschot, N. Development of a femoral template for computer-assisted tunnel placement in anatomical double-bundle ACL reconstruction, 2011. Journal of the International Society for Computer Aided Surgery 16(1):11–21.
24. Amis, A.A., Gupte, C.M., Bull, A.M.J., Edwards, A., 2006. Anatomy of the posterior cruciate ligament and the menisco femoral ligaments. Knee Surgery Sports Traumatology Arthroscopy 14: 257-263
25. Otake, N., Chen, H., Yao, X., Shoumura, S., 2007. Morphologic study of the lateral and medial collateral ligaments of the human knee. Okajimas Folia Anat., Japan, 83(4): 115-122.
26. Feeley, B.T., Muller, M.S., Allen, A.A., Granchi, C.C., Pearle, A.D., 2009. Biomechanical comparison of medial collateral ligament

reconstructions using computer-assisted navigation. The American Journal of Sports Medicine 37(6): 1123-1130.

27. Robinson, J.R., Bull, A.M., Thomas, R.R., Amis, A.A., 2006. The role of the medial collateral ligament and posteromedial capsule in controlling knee laxity. The American Journal of Sports Medicine 34(11): 1815-1823.
28. Azar, F.M., 2006. Evaluation and treatment of chronic medial collateral ligament injuries of the knee. Sports Medicine and Anthroscopy Review 14(2): 84-90.
29. Varun GBS, Muralidhar N, Kumar VV, Talwar V.Evaluation of effectiveness and safety of intraarticular injection of sodium hyaluronate in the treatment of patients with painful knee osteoarthritis, Int.J.Orthop.Sci. 2016; 2:162-65.
30. Radha MS, Gangadhar MR, Prevalence of knee osteoarthritis patient in mysore city, karanataka: Res J Recent Sci.2015; 6:3316-20.
31. Hussain S, Rather H, Qayoom A, Efficacy, Tolerability and Adverse Events of Single-Shot Intra- Articular Hyaluronic Acid Injection in Knee Osteoarthritis. J Trauma Treat.2015; 4:1-5.
32. March LM, Bachmeier CJ. Economics of osteoarthritis: a global perspective. Baillieres Clin Rheumatol 1997;11:817-34
33. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol. 2014 Jul;10(7):437–41
34. Richards MM, Maxwell JS, Weng L, Angelos MG, Golzarian J. Intraarticular treatment of knee osteoarthritis: from anti-inflammatories

to products of regenerative medicine. Phys Sportsmed. 2016; 44(2):101–108.

35. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016; 12(10):580–592.
36. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol.2010; 6(11):625–635.
37. Blanco JF, Ochs RL, Schwarz H, Lotz M. Chondrocyte apoptosis induced by nitric oxide. Am J Pathol. (1995) 146:75–85.
38. Adams CS, Horton WE Jr. Chondrocyte apoptosis increases with age in the articular cartilage of adult animals. Anat Rec. (1998) 250:418–25.
39. Kim HA, Suh DI, Song YW. Relationship between chondrocyte apoptosis and matrix depletion in human articular cartilage. J Rheumatol. (2001) 28:2038–45.
40. Kim HA, Blanco FJ. Cell death and apoptosis in osteoarthritic cartilage. Curr Drug Targets. (2007) 8:333–45.
41. Hwang HS, Kim HA. Chondrocyte apoptosis in the pathogenesis of osteoarthritis. Int J Mol Sci. (2015) 16:26035–54.
42. Charlier E, Relic B, Deroyer C, Malaise O, Neuville S, Collee J, et al. Insights on molecular mechanisms of chondrocytes death in osteoarthritis. Int J Mol Sci. (2016) 17:2146.
43. Miwa M, Saura R, Hirata S, Hayashi Y, Mizuno K, Itoh H. Induction of apoptosis in bovine articular chondrocyte by prostaglandin E2 through cAMP-dependent pathway. Osteoarthr Cartil. (2000) 8:17–24.

44. Grishko V, Xu M, Ho R, Xu M, Ho R, Mates a, et al. Effects of hyaluronic acid on mitochondrial function and mitochondria-driven apoptosis following oxidative stress in human chondrocytes. J Biol Chem. (2009) 284:9132–9.

45. Hashimoto S, Setareh M, Ochs RL, Lotz M. Fas/Fas ligand expression and induction of apoptosis in chondrocytes. Arthr Rheumatol. (1997) 40:1749– 55.

46. Dinarello CA. Biologic basis for interleukin-1 in disease. Blood. 1996; 87(6):2095e2147.

47. Hayden MS, Ghosh S. Shared principles in NF-kB signaling.Cell. 2008; 132(3):344e362.

48. Lin W, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. Journal of Clinical Investigation. 2007; 117(5):1175.

49. Schlaak J, et al. Different cytokine profiles in the synovial fluid of patients with osteoarthritis, rheumatoid arthritis and seronegative spondylarthropathies. Clinical and Experimental Rheumatology. 1996; 14(2):155.

50. Van der Kraan PM, et al. Age-dependent alteration of TGFb signalling in osteoarthritis. Cell and Tissue Research. 2012; 347(1):257e265.

51. Mobasheri A, Batt M. An update on the pathophysiology of osteoarthritis. Ann Phys Rehabil Med. 2016 Dec 1; 59(5):333–9.

52. Guo B, Yang N, Borysiewicz E, Dudek M, Williams JL, Li J, et al. Catabolic cytokines disrupt the circadian clock and the expression of

clock-controlled genes in cartilage via an NFkB-dependent pathway. Osteoarthr Cartil 2015; 23:1981–8.

53. Lepetsos P, Papavassiliou AG. ROS/oxidative stress signaling in osteoarthritis. Biochim Biophys Acta 2016; 1862:576–91.
54. Parmelee PA, Tighe CA, Dautovich ND. Sleep disturbance in osteoarthritis:linkages with pain, disability, and depressive symptoms. Arthritis Care Res (Hoboken) 2015; 67:358–65.
55. Verzijl N, et al. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: a possiblemechanism through which age is a risk factor for osteoarthritis. Arthritis Rheumatism. 2002; 46(1):114e123.
56. Keefe FJ, et al. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000; 87(3):325e334.
57. Cicuttini F, Spector T. Osteoarthritis in the aged Epidemiological issues and optimal management. Drugs & Aging. 1995; 6(5):409.
58. Spector TD, MacGregor AJ. Risk factors for osteoarthritis:genetics. Osteoarthritis and Cartilage. 2004; 12:39e44.
59. Hunter D, et al. Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. Journal of Bone and Mineral Research. 2001;16(2):371e378.
60. Hirsch R, et al. Osteoarthritis: new insights. Ann Intern Med. 2000;133:635e646.

61. Nishida C, et al. The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases:process, product and policy implications. Public Health Nutrition. 2004;7:245e250.
62. Buckwalter JA, Brown TD. Joint injury, repair, and remodeling roles in post-traumatic osteoarthritis. Clinical Orthopaedics and Related Research. 2004;423:7e16.
63. Toivanen AT, et al. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritisda population-based study with a follow-up of 22 years. Rheumatology. 2010;49(2):308e314.
64. Manninen P, et al. Physical workload and the risk of severe knee osteoarthritis. Scandinavian Journal of Work, Environment & Health; 2002:25e32.
65. Ja¨rvholm B, et al. Age, bodyweight, smoking habits and the risk of severe osteoarthritis in the hip and knee in me.European Journal of Epidemiology. 2005;20(6):537e542.
66. Hussain S, Rather H, Qayoom A, Efficacy, tolerability and adverse effects of single shot intra articular hyaluronic acid injection in knee osteoarthritis. J Trauma Treat. 2015; 4:1-5.
67. Woolf A, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81:56.
68. Kopec JA, Rahman MM, Berthelot JM, Le Petit C, Aghajanian J, Sayre EC, et al. Descriptive epidemiology of osteoarthritis in British Columbia, Canada. J Rheumatol 2007 Feb;34(2):386e93.

69. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;55.

70. Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011;70:1770–4.

71. Teichtahl AJ, Wang Y, Heritier S, Wluka AE, Strauss BJ, Proietto J, et al. The interaction between physical activity and amount of baseline knee cartilage. Rheumatology 2016;55:1277-84.

72. Fowler-Brown A, Kim DH, Shi L, Marcantonio E, Wee CC, Shmerling RH, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol 2015;67:169-75.

73. Mork PJ, Holtermann A, Nilsen TI. Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: longitudinal data from the Norwegian HUNT Study. J Epidemiol Community Health 2012;66:678-83.

74. Teichtahl AJ, Wluka AE, Tanamas SK, Wang Y, Strauss BJ, Proietto J, et al. Weight change and change in tibial cartilage volume and symptoms in obese adults. Ann Rheum Dis 2015;74:1024-9.

75. Anandacoomarasamy A, Leibman S, Smith G, Caterson I, Giuffre B, Fransen M, et al. Weight loss in obese people has structure-modifying

effects on medial but not on lateral knee articular cartilage. Ann Rheum Dis 2012;71:26-32.

76. Teichtahl AJ, Wluka AE, Wang Y, Strauss BJ, Proietto J, Dixon JB, et al. The longitudinal relationship between changes in body weight and changes in medial tibial cartilage, and pain among community-based adults with and without meniscal tears. Ann Rheum Dis 2014;73:1652-58.
77. Roman-Blas JA, Castañeda S, Largo R, Herrero-Beaumont G. Osteoarthritis associated with estrogen deficiency. Arthritis Res Ther 2009;11:241.
78. Bellido M, Lugo L, Roman-Blas JA, Castañeda S, Caeiro JR, Dapia S, et al. Subchondral bone microstructural damage by increased remodelling aggravates experimental osteoarthritis preceded by osteoporosis. Arthritis Res Ther 2010;12:R152.
79. Sniekers YH, Weinans H, van Osch GJ, van Leeuwen JP. Oestrogen is important for maintenance of cartilage and subchondral bone in a murine model of knee osteoarthritis. Arthritis Res Ther 2010;12:R182.
80. Riancho JA, García-Ibarbia C, Gravani A, Raine EV, Rodríguez-Fontenla C, Soto-Hermida A, et al. Common variations in estrogen-related genes are associated with severe large-joint osteoarthritis: a multicenter genetic and functional study. Osteoarthritis and Cartilage 2010;18:927–33.
81. Lugo L, Villalvilla A, Largo R, Herrero-Beaumont G, Roman-Blas JA. Selective estrogen receptor modulators (SERMs): new alternatives for osteoarthritis? Maturitas 2014; 77:380-4.

82. Karsdal MA, Bay-Jensen AC, Henriksen K, Christiansen C. The pathogenesis of osteoarthritis involves bone, cartilage and synovial inflammation: may estrogen be a magic bullet? Menopause Int 2012;18:139-46.

83. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hipand knee joint replacement in the Women's Health Initiative. Arthritis Rheum 2006;54:3194–204.

84. Prieto-Alhambra D, Javaid MK, Judge A, Maskell J, Cooper C, Arden NK; on behalf of the COASt Study Group. Hormone replacement therapy and mid-term implant survivalfollowing knee or hip arthroplasty for osteoarthritis: a population-based cohort study. Ann Rheum Dis 2015;74:557-63.

85. Herrero-Beaumont G, Roman-Blas JA. Osteoarthritis: Osteoporotic OA: a reasonable target for bone-acting agents. Nat Rev Rheumatol 2013;9:448-50.

86. Marshall M, Peat G, Nicholls E, van der Windt D, Myers H, Dziedzic K. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical characteristics at baseline and 3-years. Osteoarthritis Cartilage 2013;21:1674-84.

87. Jungmann PM, Kraus MS, Alizai H, Nardo L, Baum T, Nevitt MC, et al. Association of metabolic risk factors with cartilage degradation assessed by T2 relaxation time at the knee: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2013;65:1942-50.

88. Wen CY, Chen Y, Tang HL, Yan CH, Lu WW, Chiu KY. Bone loss at subchondral plate in knee osteoarthritis patients with hypertension and type 2 diabetes mellitus. Osteoarthritis Cartilage 2013;21:1716-23.
89. Stannus OP, Cao Y, Antony B, Blizzard L, Cicuttini F, Jones G, et al. Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. Ann Rheum Dis 2015;74:82-8.
90. Karvonen-Gutierrez CA, Harlow SD, Jacobson J, Mancuso P, Jiang Y. The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women. Ann Rheum Dis 2014;73:883-9.
91. Clockaerts S, Van Osch GJ, Bastiaansen-Jenniskens YM, Verhaar JA, Van Glabbeek F, Van Meurs JB, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. Ann Rheum Dis 2012;71:642-47.
92. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone 2012;51:249-57.
93. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6:625-35.
94. Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis –results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis and Cartilage 2005;13:361-67.

95. de Lange-Brokaar BJ, Ioan-Facsinay A, Yusuf E, Visser AW, Kroon HM, van Osch GJ, et al. Association of pain in knee osteoarthritis with distinct patterns of synovitis. Arthritis Rheumatol. 2015;67:733-40.
96. Esser S, Bailey A. Effects of exercise and physical activity on knee osteoarthritis. Curr Pain Headache Rep. 2011;15(6):423–430.
97. Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: asystematic review and meta-analysis of randomized controlled trials. Clin Rehabil. 2013;27(12):1059–1071.
98. Beckwée D, Vaes P, Cnudde M, Swinnen E, Bautmans I. Osteoarthritis of the knee: why does exercise work? A qualitative study of the literature. Ageing Res Rev. 2013;12(1):226–236.
99. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum. 2014;43(6):701–712.
100. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ. 2004;329(7461):324
101. Mcalindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363–388

102. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis: a systematic review and metaanalysis. J Rheumatol. 2007;34(3):543–555.
103. Wang ZY, Shi SY, Li SJ, et al. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. Pain Med. 2015;16(7):1373–1385.
104. Citrome L, Weiss-Citrome A. A systematic review of duloxetine for osteoarthritic pain: what is the number needed to treat, number needed to harm, and likelihood to
105. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, Mcalindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162(1):46–54.
106. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev. 2006;2(2):CD005328.
107. Yavuz U, Sökücü S, Albayrak A, Oztürk K. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. Rheumatol Int. 2012;32(11):3391–3396.
108. Pyne D, Ioannou Y, Mootoo R, Bhanji A. Intra-articular steroids in knee osteoarthritis: a comparative study of triamcinolone hexacetonide and methylprednisolone acetate. Clin Rheumatol. 2004;23(2):116–120.
109. Lomonte AB, de Morais MG, de Carvalho LO, Zerbini CA. Efficacy of Triamcinolone Hexacetonide versus Methylprednisolone Acetate

Intraarticular Injections in Knee Osteoarthritis: A Randomized, Doubleblinded, 24-week Study. J Rheumatol. 2015;42(9):1677–1684.

110. Pendleton A, Millar A, O'Kane D, Wright GD, Taggart AJ. Can sonography be used to predict the response to intra-articular corticosteroid injection in primary osteoarthritis of the knee? Scand J Rheumatol. 2008;37(5):395–397.
111. Cunnington J, Marshall N, Hide G, et al. A randomized, double-blind, controlled study of ultrasound-guided corticosteroid injection into the joint of patients with inflammatory arthritis. Arthritis Rheum. 2010;62(7):1862–1869.
112. Raynauld JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2003;48(2):370–377.
113. Suntiparpluacha M, Tammachote N, Tammachote R. Triamcinolone acetonide reduces viability, induces oxidative stress, and alters gene expressions of human chondrocytes. Eur Rev Med Pharmacol Sci. 2016;20(23):4985–4992.
114. Buyuk AF, Kilinc E, Camurcu IY, Camur S, Ucpunar H, Kara A. Compared efficacy of intra-articular injection of methylprednisolone and triamcinolone. Acta Ortop Bras. 2017;25(5):206–208.
115. Henrotin Y, Raman R, Richette P, et al. Consensus statement on viscosupplementation with hyaluronic acid for the management of osteoarthritis. Semin Arthritis Rheum. 2015;45(2):140–149.

116. Wehling P, Evans C, Wehling J, Maixner W. Effectiveness of intraarticular therapies in osteoarthritis: a literature review. Ther Adv Musculoskelet Dis. 2017;9(8):183–196.

117. Shahid M, Kundra R. Platelet-rich plasma (PRP) for knee disorders. EFORT Open Rev. 2017;2(1):28–34.

118. Sugahara K, Schwartz NB, Dorfman A. Biosynthesis of hyaluronic acid by Streptococcus. J Biol Chem. (1979) 254:6252–61.

119. Yu HM, Stephanopoulos G. Metabolic engineering of Escherichia coli for biosynthesis of hyaluronic acid. Metab Eng. (2008) 10:24–32.

120. Liu L, Liu Y, Li J, Du G, Chen J. Microbial production of hyaluronic acid: current state, challenges and perspectives. Microb Cell Fact. (2011) 10:99.

121. Chen WY, Marcellin E, Hung J, Nielsen LK. Hyaluronan molecular weight is controlled by UDP-N-acetylglucosamine concentration in Streptococcus zooepidemicus. J Biol Chem. (2009) 284:18007–14.

122. Maclennan AP. The production of capsules, hyaluronic acid and hyaluronidase to 25 strains of Group C Streptococci. J Gen Microbiol. (1956) 15:485–91.

123. Balasz EA, Laurent TC. New applications for hyaluronan. In: Laurent TC, editor. The Chemistry, Biology, and Medical Applications of Hyaluronan and its Derivatives. London: Portland Press (1998) p. 325–36.

124. Ghosh P. The role of hyaluronic acid. (hyaluronan) in health and disease: Interactions with cells, cartilage and components of synovial fluid. Clin Exp Rheumatol. (1994) 12:75–82.

125. Hashizume M, Koike N, Yoshida H, Suzuki M, Mihara M. High molecular weight hyaluronic acid relieved joint pain and prevented the progression of cartilage degeneration in a rabbit osteoarthritis model after onset of arthritis. Mol Rheumatol. (2010) 20:432–8.
126. Necas J, Bartosicova L, Brauner P, Kolar J. Hyaluronic acid. (hyaluronan): a review. Vet Med. (2008) 8:397–411.
127. Prehm P. Release of hyaluronate from eukaryotic cells. Biochem J. (1990) 267:185–9.
128. Laurent TC, Laurent UBG, Fraser JRE. The structure and function of hyaluronan: an overview. Immun Cell Biol. (1996) 74:A1–7.
129. Fallacara A, Baldini E,Manfredini S, Vertuani S. Hyaluronic acid in the Third Millennium. Polymers. (2018) 10:701.
130. Lee JY, Spicer AP. Hyaluronan: a multifunctional, mega-Dalton, stealth molecule. Curr Opin Cell Biol. (2000) 12:581–6.
131. Liang J, Jiang D, Noble PW. Hyaluronan as a therapeutic target in human diseases. Adv Drug Deliv Rev. (2016) 97:186–203.
132. Holmes MWA, Bayliss MT, Muir H. Hyaluronic acid in human articular cartilage. Age-related changes in content and size. BiochemJ. (1988) 250:435–41.
133. Gupta RC, Doss RB, Lall R, Srivastava A, Sinha A. Nutraceuticals in arthritis. In: Gupta RC, Srivastava A, Lall R, editors. Nutraceuticals in Veterinary Medicine. Cham: Springer Nature (2019), p. 365–85.
134. Horton WEJr, Bennion P, Yang L. Cellular, molecular, and matrix changes in cartilage during aging and osteoarthritis. J Musculoskelet Interact. (2006) 6:379–81.

135. Blanco JF, Ochs RL, Schwarz H, Lotz M. Chondrocyte apoptosis induced by nitric oxide. Am J Pathol. (1995) 146:75–85.
136. Charlier E, Relic B, Deroyer C, Malaise O, Neuville S, Collee J, et al. Insights on molecular mechanisms of chondrocytes death in osteoarthritis. Int J Mol Sci. 2016; 17:2146.
137. Conrozier T, Chevalier X. Long-term experience with hylan GF-20 in the treatment of knee osteoarthritis. Expert Opin Pharmacother. (2008) 9:1797–804.
138. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. J Rheumatol. (1993) 39:3–9.
139. McIlwraith CW. Use of sodium hyaluronate. (Hyaluronan) in equine joint disease. Equine Vet Educ. (1997) 9:296–304.
140. Migliore A, Giovannangeli F, Granata M, Laganá B. Hylan g-f 20:review of its safety and efficacy in the management of joint pain in osteoarthritis. Clin Med Insights Arthr Musculoskelet Disord. (2010) 20:55–68.
141. Takahashi K, Hashimoto S, Kubo T, Hirasawa Y, Lotz M, Amiel D. Hyaluronan suppressed nitric oxide production in the meniscus and synovium of rabbit osteoarthritis model. J Orthop Res. (2001) 19:500–3.
142. Studer R, Jaffurs D, Stefanovic-Racic M, Robbins PD, Evans CH. Nitric oxide in osteoarthritis. Osteoarthr Cartil. (1999) 7:377–9.
143. Punji I, Schiavon F, Cavasin F, Ramonda R, Gambari PF, Todesco S. The influence of intra-articular hyaluronic acid on PGE2 and cAMP of synovial fluid. Clin Exp Rheumatol. (1989) 7:247–50.

144. Wang C-T, Lin Y-T, Chiang B-L, Lin Y-H, Hou S-M. High molecular weight hyaluronic acid down-regulates the gene expression of osteoarthritis associated cytokines and enzymes in fibroblast-like synoviocytes from patients with early osteoarthritis. Osteoarthr Cartil. (2006) 14:1237–47.
145. Maneiro E, de Andres MC, Ferández-Sueiro JL, Galdo F, Blanco FJ. The biological action of hyaluronan on human osteoarthritic articular chondrocytes: the importance of molecular weight. Clin Exp Rheumatol. (2004) 22:307–12.
146. Ghosh P, Guidolin D. Potential mechanism of action of intraarticular hyaluronan therapy in osteoarthritis; are the effects molecular weight dependent? Sem Arthr Rheum. (2002) 32:10–37.
147. Aihara S, Murakami N, Ishii R, Kariya K, Azuma Y, Hamada K, et al. Effects of sodium hyaluronate on the nociceptive response of rats with experimentally induced arthritis. Nippon Yakurigaku Zasshi. (1992) 100:359–65.
148. Nelson FR, Zvirbulis RA, Zonca B, Li KW, Turner SM, Pasierb M, et al. The effects of an oral preparation containing hyaluronic acid. (OralviscR) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analysis. Rheumatol Int.(2015) 35:43–52.
149. Gotoh S, Onaya JI, Abe M, Miyazaki K, Hamai A, Horie K, et all Effects of molecular weight of hyaluronic acid and its action mechanisms on experimental joint pain in rats. Ann Rheum Dis. (1993) 52:817–22.

150. Smith MM, Russell AK, Schiavinato A, Little CV. A hexadecylamide derivative of hyaluronan. (HYMOVISR). has superior beneficial effects on human osteoarthritic chondrocytes and synoviocytes than unmodified hyaluronan. J Inflamm. (2013) 10:26.

151. Julovi SM, Ito H, Nishitani K, Jackson CJ, Nakamura T. Hyaluronan inhibits matrix metalloproteinase-13 in human arthritic chondrocytes via CD44 and p38. J Orthop Res. (2011) 29:258–64.

152. Takahashi K, Goomer RS,Harwood F, Kubo T, Hirasawa Y, and Amiel D. The effect of hyaluronan on matrix metalloproteinase-3. (MMP-3), interleukin-1beta. (IL-1beta), and tissue inhibitor of metalloproteinase-1. (TIMP-1). Gene expression during the development of osteoarthritis. Osteoarthr Cartil. (1999) 7:182–90.

153. Siczkowski M, Andrew T, Amos S, Gordon MY. Hyaluronic acid regulates the function and distribution of sulfated glycosaminoglycans in bone marrow stromal cultures. Exp Hematol. (1993) 21:126–30.

154. Borzachhiello A,Mayol L, Ambrosio I,Nicolais L, Schiavinato A. “Evaluation of a novel hyaluronic acid derivative on synovial fluid viscoelastic properties,” in Biomaterials: European Conference on 2002:19.

155. Brun P, Zavan B, Vindigni V, Schiavinato A, Pozzuoli A, Iacobellis C, et al. In vitro response of osteoarthritic chondrocytes and fibroblast-like synoviocytes to a 500-730 kDa hyaluronan amide derivative. J Biomed Mater Res B Appl Biomater. (2012) 100:2073–81.

156. Cake MA, Read R, Edwards S, Smith MM, Burkhardt D, Little C, et al. Changes in gait after bilateral meniscectomy in sheep: Effect of two hyaluronan preparations. J Orthop Sci. (2008) 13:514–23.

157. Smith MM, Cake MA, Ghosh P, Schiavinato A, Read RA, Little CB. Significant synovial pathology in a meniscectomy model of osteoarthritis: Modification by intra-articular hyaluronan therapy. Rheumatology. (2008)47:1172–8.

158. Bagga H, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol. (2006) 33:946–50.

159. Balogh L, Polyak A, Mathe D, Kiraly R, Thuroczy J, Terez M, et al. Absorption, uptake and tissue affinity of high-molecular-weight hyaluronan after oral administration in rats and dogs. J Agr Food Chem. (2008) 56:10582–93.

160. Liu N. Trafficking of hyaluronan in the interstitium and its possible implications. Lymphology. (2004) 37:6–14.

161. Listrat V, Ayral X, Patarnello F, Bonvarlet J-P, Simonnet J, Armor B, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan. (Hyaglan) in osteoarthritis of the knee. Osteoarthr Cartil. (1997) 5:153–60. doi: 10.1016/S1063-4584(97)80010-6

162. Jubb RW, Piva S, Beinat L, Dacre J, Gishen PA. A one-year, randomized placebo. (Saline). Controlled clinical trial of 500-730 kDa sodium hyaluronate. (Hyalgan). On the radiological change in osteoarthritis of the knee. Int J Clin Pract. (2003) 57:467–74.

163. AbateM, Salini V. Hyaluronic acid in the treatment of osteoarthritis: what is new? In: Chen Q, editor. Osteoarthritis-Diagnosis, Treatment and Surgery. Pescara: InTech (2012). p. 101–22.

164. Lussier A, Cividino AA, McFarlane CA, Olszynski WP, Potashner WJ, Medicis RD, et al. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. J Rheumatol. (1996) 23:1579–85

165. Albert C, Brocq O, Gerard D, and Roux C, Euller-Ziegler L. Septic knee arthritis after intra-articular hyaluronate injection: Two case reports. Joint Bone Spine. (2006) 73:205-7

166. Hunter DJ. Viscosupplementation for osteoarthritis of the knee. New Engl J Med. (2015) 372:1040–7.

167. R. W. Chang, J. Falconer, S. D. Stulberg, W. J. Arnold, L. M. Manheim, and A. R. Dyer, "A randomized, controlled trial of arthroscopic surgery versus closed- needle joint lavage for patients with osteoarthritis of the knee," Arthritis and Rheumatism, vol. 36, no. 3, pp. 289–296, 1993.

168. D. J. Ogilvie-Harris and D. P. Fitsialos, "Arthroscopic management of the degenerative knee," Arthroscopy, vol. 7, no. 2, pp. 151–157, 1991.

169. P. Siparsky, M. Ryzewicz, B. Peterson, and R. Bartz, "Arthroscopic treatment of osteoarthritis of the knee: are there any evidence-based indications?" Clinical Orthopaedics and Related Research, vol. 455, pp. 107–112, 2007

170. R. W. Jackson and D. W. Rouse, “The results of partial arthroscopic meniscectomy in patients over 40 years of age,” Journal of Bone and Joint Surgery B, vol. 64, no. 4, pp. 481– 485, 1982.

171. W. Widuchowski, P. Lukasik, G. Kwiatkowski et al., “Isolated full thickness chondral injuries. Prevalance and outcome of treatment. A retrospective study of 5233 knee arthroscopies,” Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca, vol. 75, no. 5, pp. 382–386, 2008.

172. K. H. Pridie, “A method of resurfacing osteoarthritic knee joints,” Journal of Bone and Joint Surgery, vol. 41, pp. 618– 619, 1959.

173. K. Mithoefer, T. Mcadams, R. J. Williams, P. C. Kreuz, and B. R. Mandelbaum, “Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis,” American Journal of Sports Medicine, vol. 37, no. 10, pp. 2053–2063, 2009

174. L. Hangody, P. Feczko, L. Bartha, G. Bod ´ o, and G. Kish, ´ “Mosaicplasty for the treatment of articular defects of the knee and ankle,” Clinical Orthopaedics and Related Research, supplement 391, pp. S328–S336, 2001s

175. R. P. Jakob, P. Mainil-Varlet, and E. Gautier, “Isolated articular cartilage lesion: repair or regeneration,” Osteoarthritis and Cartilage, vol. 9, supplement A, pp. S3–S5, 2001.

176. M. Brittberg, A. Lindahl, A. Nilsson, C. Ohlsson, O. Isaksson, and L. Peterson, “Treatment of deep cartilage defects in the knee with

autologous chondrocyte transplantation," The New England Journal of Medicine, vol. 331, no. 14, pp. 889– 895, 1994.

177. D. B. F. Saris, J. Vanlauwe, J. Victor et al., "Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture," American Journal of Sports Medicine, vol. 36, no. 2, pp. 235–246, 2008.

178. P. G. Maquet, Biomechanics of the Knee: With Applications of the Pathogenesis and the Surgical Treatment of Osteoarthritis, Springer, New York, NY, USA, 2nd edition, 1984.

179. M. B. Coventry, "Osteotomy of the upper portion of the tibia for degenerative arthritis of the knee. A preliminary report," The Journal of Bone and Joint Surgery, vol. 47, pp. 984–990, 1965.

180. Y. Fujisawa, K. Masuhara, and S. Shiomi, "The effect of high tibial osteotomy on osteoarthritis of the knee. An arthroscopic study of 54 knee joints," Orthopedic Clinics of North America, vol. 10, no. 3, pp. 585–608, 1979.

181. D. W. Murray, "Unicompartmental knee replacement: now or never?" Orthopedics, vol. 23, no. 9, pp. 979–980, 2000.

182. J. T. Moller, R. E. Weeth, J. O. Keller, and S. Nielsen, "Unicompartmental arthroplasty of the knee. Cadaver study of the importance of the anterior cruciate ligament," Acta Orthopaedica Scandinavica, vol. 56, no. 2, pp. 120–123, 1985.

183. J. H. Lonner and P. A. Lotke, “Aseptic complications after total knee arthroplasty,” The Journal of the American Academy of Orthopaedic Surgeons, vol. 7, no. 5, pp. 311–324, 1999.

184. F. Walter, M. B. Haynes, and D. C. Markel, “A randomized prospective study evaluating the effect of patellar eversion on the early functional outcomes in primary total knee arthroplasty,” Journal of Arthroplasty, vol. 22, no. 4, pp. 509– 514, 2007.

185. Leardini G, Mattara L, Franceschini M, Perbellini A. Intra-articular treatment of knee OA. A comparative study between hyaluronic acid and 6-methyl prednisolone acetate. Clin Exp Rheumatol. 1991; 9(4):375–381.

186. Adams ME. An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. J Rheumatol (suppl). 1993; 39:16–8.

187. Puhl W, Bernau A, Greiling H, Kopcke W, Pfor-ringer W, Steck KJ, et al. Intraarticular sodium hyaluronate in osteoarthritis of the knee: a multi-centre double-blind study. Osteoarthritis Cart. 1993; 1:233–41.

188. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-

year double-blind, placebocontrolled study. Arthritis Rheum. 1994; 37:521–8.

189. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lackof efficacy. Ann Rheum Dis 1994; 53: 529–534.

190. Adams ME, Atkinson MH, Lussier AJ, Schulz JI, Siminovitch KA, Wade JP, et al.The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicentre trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage 1995; 3(4):213-25.

191. Jones AC, Pattrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. Osteoarthritis Cartilage 1995; 3: 269–273.

192. Lohmander LS, Dalén N, Englund G et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind,Placebo controlled multicentre trial. Ann Rheum Dis 1996; 55: 424–431.

193. Wu JJ, Shih LY, Hsu HC, Chen TH. The double-blind test of sodium hyaluronate (ARTZ) on osteoarthritis knee. Zhonghua Yi Xue Za Zhi 1997; 59: 99–106

194. Wobig M, Dickhut A, Maier R, and Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther 1998; 20: 410–423.

195. Frizziero L, Govoni E, Bacchini P. Intra-articular hyaluronic acid in the treatment of osteoarthritis of the knee: clinical and morphological study. Clin Exp Rheumatol 1998; 16(4):441-9.

196. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol 1998; 25(11):2203-12.

197. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. Rheumatology 1999; 38: 602–607.

198. Kotz R, Kolarz G. Intra-articular hyaluronic acid: duration of effect and results of repeated treatment cycles. Am J Orthop 1999;28(11 Suppl):5-7.

199. Goorman SD, Watanabe TK, Miller EH, Perry C. Functional outcome in knee osteoarthritis after treatment with hylan G-F 20: a prospective study. Arch Phys Med Rehabil 2000; 81(4):479-83.

200. Payne MW, Petrella RJ. Viscosupplementation effect on proprioception in the osteoarthritic knee. Arch Phys Med Rehabil 2000; 81(5):598-603.

201. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT. Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthopaed Related Res 2001; 385:130-43.

202. Tamir E, Robinson D, Koren R, Agar G, Halperin N. Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: a randomized, double blind, placebo controlled study. Clin Exp Rheumatol 2001; 19(3):265-70.

203. Bunyaratavej N, Chan KM, Subramanian N. Treatment of painful osteoarthritis of the knee with hyaluronic acid: results of a multicenter Asian study. J Med Assoc Thai 2001; 84(Suppl 2):576-81.

204. Evanich JD, Evanich CJ, Wright MB, Rydlewicz JA. Efficacy of intraarticular hyaluronic acid injections in knee osteoarthritis. Clin Orthopaed Related Res 2001; 390:173-81.

205. Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med 2002; 162(3):292-8.

206. Miltner O, Schneider U, Siebert CH, Niedhart C, Niethard FU. Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis—a prospective clinical trial. Osteoarthritis Cartilage 2002; 10(9):680-86.

207. Raynauld JP, Torrance GW, Band PA, Goldsmith CH, Tugwell P,Walker V, et al. A prospective, randomized, pragmatic, healthoutcomes trial evaluating the incorporation of hylan G-F 20into the treatment paradigm for patients with kneeosteoarthritis (part 1 of 2): clinical results. Osteoarthritis Cartilage. 2002;10(7):506–17.20

208. Espallargues M, Pons JM. Efficacy and safety ofviscosupplementation with Hylan G-F 20 for the treatment ofknee osteoarthritis: a systematic review. Int J Technol AssessHealth Care. 2003; 19(1):41–56.

209. Leopold SS, Redd BB, Warme WJ et al. Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee. A prospective, randomized trial. J Bone Joint Surg Am 2003; 85: 1,197–1,203.

210. Altman RD, Akermark C, Beaulieu AD, Schnitzer T. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2004; 12:642–649.

211. Day R, Brooks P, Conaghan PG, Petersen M. A double blind, randomized, multicenter, parallel group study of the effectiveness and tolerance of intraarticular hyaluronan in osteoarthritis of the knee. J Rheumatol 2004; 31: 775–782.

212. Aggarwal A, Sempowski IP. Hyaluronic acid injections forknee osteoarthritis. Systematic review of the literature. CanFam Physician. 2004; 50:249–56.

213. Modawal A, Ferrer M, Choi HK, Castle JA. Hyaluronic acidinjections relieve knee pain. J Fam Pract. 2005; 54(9):758–67.

214. Neustadt D, Caldwell J, Bell M et al. Clinical effects of intraarticular injection of high molecular weight hyaluronan (Orthovisc) in osteoarthritis of the knee: a randomized, controlled, multicenter trial. J Rheumatol 2005; 32:1,928–1,936.

215. Petrella RJ, Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular

hyaluronic acid for osteoarthritis of the knee. J Rheumatol 2006; 33: 951–956.

216. Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, JordiB, et al. Viscosupplementation Trial Group. Efficacy and safetyof intraarticular hylan or hyaluronic acids for osteoarthritis ofthe knee: a randomized controlled trial. Arthritis Rheum.2007; 56(11):3610–9.

217. Heyworth BE, Lee JH, Kim PD, Lipton CB, Strauch RJ, Rosenwasser MP. Hylan versus corticosteroid versus placebo for treatment of basal joint arthritis: a prospective, randomized, double-blinded clinical trial. J Hand Surg Am. 2008; 33(1):40–48.

218. Raman R, Dutta A, Day N, Sharma HK, Shaw CJ, Johnson GV.Efficacy of hylan G-F 20 and sodium hyaluronate in thetreatment of osteoarthritis of the knee – a prospectiverandomized clinical trial. Knee. 2008; 15(4):318–24.21.

219. Diracoglu D, Vural M, Baskent A et al. The effect of viscosupplementation on neuromuscular control of the knee in patients with osteoarthritis. J Back Musculoskelet Rehabil 2009; 22: 1–9.

220. Chevalier X, Jerosch J, Goupille P et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis 2010; 69: 113–119.

221. Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, De laSerna AR, Naranjo A, et al. A 40-month multicentre,randomised placebo-controlled study to assess the efficacyand carry-over effect of repeated intra-

articular injections ofhyaluronic acid in knee osteoarthritis: the Amelia project.Ann Rheum Dis. 2011;70(11):1957–62.18.

222. Merolla G, Sperling JW, Paladini P, Porcellini G. Efficacy of Hylan G-F 20 versus 6- methylprednisolone acetate in painful shoulder OA: a retrospective controlled trial. Musculoskelet Surg. 2011;95(3):215–224

223. Rutjes AW, Jüni P, Da Costa BR, Trelle S, Nüesch E,Reichenbach S. Viscosupplementation for osteoarthritis ofthe knee: a systematic review and meta-analysis. Adv InternMed. 2012; 157(3):180–91.29.

224. Zavan B, Ferroni L, Giorgi C, et al. HA induces activation of the k-opioid receptor. PLOS ONE. 2013; 8:e55510.

225. Treatment of osteoarthritis of the knee – evidence-basedguideline. 2nd ed. Rosemont: American Academy of Orthopaedic Surgeons; 2013.

226. Miller LE, Block JE. US-approved intra-articular hyaluronicacid injections are safe and effective in patients with kneeosteoarthritis: systematic review and meta-analysis ofrandomized, saline-controlled trials. Clin Med InsightsArthritis Musculoskelet Disord. 2013; 6:57–63.

227. Campbell KA, Erickson BJ, Saltzman BM, et al. Is local viscosupplementation injection clinically superior to other therapies in the treatment of OA of the knee:

Systematic review of overlapping meta-analyses. Arthroscopy. 2015; 31(10).2036–45.e14.

228. Askari A, Gholami T, NaghiZadeh MM, Farjam M, Kouhpayeh SA, Shahabfard Z. Hyaluronic acid compared with corticosteroid injections

for the treatment of osteoarthritis of the knee: a randomized control trail. Springerplus. 2016; 5:442.

229. Vaishya R, Pandit R, Agarwal AK, Vijay V. Intra-articular hyaluronic acid is superior to steroids in knee osteoarthritis: A comparative, randomized study. Journal of Clinical Orthopaedics and Trauma. 2017; 8:85–88.

230. Hermans, J., Bierma-Zeinstra, S.M.A., Bos, P.K. et al. The effectiveness of high molecular weight hyaluronic acid for knee osteoarthritis in patients in the working age: a randomised controlled trial. BMC Musculoskelet Disord .2019;20: 196

231. Vincent P. Intra-Articular Hyaluronic Acid in the Symptomatic Treatment of Knee Osteoarthritis: A Meta-Analysis of Single-Injection Products. Curr Ther Res Clin Exp. 2019; 90:39–51.

232. Sudheer U, Jayaprakash C. Clinical outcome of intra-articular hyaluronic acid injection for knee joint osteoarthritis: a prospective interventional study from a tertiary care hospital. Int J Res Orthop. 2017;3:595-601

233. Jesalpura B, Gajjar S. Intra articular hyaluronic acid injection, is it a wastage of money or justified? International Journal of Research in Orthopaedics. 2017; 3:795.

234. Bowman E, Hallock J, Throckmorton T, Azar F. Hyaluronic acid injections for osteoarthritis of the knee: predictors of successful treatment. International Orthopaedics. 2018; 42:733-740.

235. Das D, Narendran D, Saurabh D, Singh D. How efficacious are intra-articular viscosupplements in the management of early osteoarthritis

knee?- A detailed comparative study with various outcome measures. International Journal of Orthopaedics Sciences. 2017; 3:426-430.

236. Sancheti P, Shetty V, Dhillon M, Sprague S, Bhandari M. India-Based Knee Osteoarthritis Evaluation (iKare): A Multi-Centre Cross-Sectional Study on the Management of Knee Pain and Early Osteoarthritis in India. Clinics in Orthopedic Surgery. 2017; 9:286.

237. Pal S, Thuppal S, Reddy K, Avasthi S, Aggarwal A, Bansal H et al. Long-Term (1-Year) Safety and Efficacy of a Single 6-mL Injection of Hylan G-F 20 in Indian Patients with Symptomatic Knee Osteoarthritis. The Open Rheumatology Journal. 2014; 8:54-68.

238. Pal CP, Sadana A, Goyal A, Mehrotra R, Kumar P. Therapeutic Efficacy of Intra-Articular Hyaluronic Acid in Osteoarthritis Knee. Journal of Bone and Joint Diseases Jan – June 2017; 32:44-49 .

239. Shishir R, Sharma VK , Rajesh C, Sivaraman ST , open label multi central trial on safety and efficacy of intra articular hyaluronic acid in the treatment of osteoarthritis of the knee, Journal indian academy of clinical medicine. 2005;6:232-5

PATIENT INFORMATION SHEET

Study title: A prospective study on effectiveness of visco supplementation in osteoarthritis knee

Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details-

Patients aged between 40 and 80 years diagnosed having osteoarthritis knee came to opd basis to the department of orthopaedics to R.L.Jalappa Hospital will be included in this study.

Patients in this study will have to undergo routine investigations and x ray of both knee in standing position for AP view and lateral view of affected knee .

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the secretary of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

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ರೋಗಿಯ ಮಾಹಿತಿ ಪತ್ರ

ಅಧ್ಯಯನ ಶೀರ್ಷಿಕೆ : ಮೊಣಕಾಲಿನ ಸಂದೀವಾತಕ್ಕೆ ವಿಸ್ಕೋ ಪೊರೈಕೆಯಿಂದಾಗ ಬಹುದಾದಪರಿಣಾಮ ಕಾರಿತ್ವದ ಬಗ್ಗೆ ಒಂದು ಮುಂದವರೆದ ಅಧ್ಯಾಯನ.

ಅಧ್ಯಾಯನದ ಸ್ಥಳ : ಆರ್.ಎಲ್.ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ಶ್ರೀ ದೇವರಾಜ ಅರಸ್ ವೈದ್ಯಕೀಯ ವಿದ್ಯಾಲಯದಡಿಯಲ್ಲಿ ಟಮಕ, ಕೋಲಾರ

ವಿವರಗಳು :

40 ಮತ್ತು 80 ವರ್ಷಗಳಾಗಿ ಮೊಣಕಾಲಿನ ಸಂದೀವಾತದಿಂದನರಳುತ್ತಿರುವುದಾಗಿ ನಿರ್ಣಯಿಸಿರುವ ರೋಗಿಯು ಆರ್.ಎಲ್.ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆಯ ಮೂಳೆ ಚಿಕಿತ್ಸಾ ವಿಭಾಗಕ್ಕೆ ಹೊರ ರೋಗಿಯಾಗಿ ಬರುವ ರೋಗಿಗಳನ್ನು ಈ ಅಧ್ಯಯನಕ್ಕೆ ಒಳಪಡಿಸಲಾಗುವುದು. ಅಂತಹ ರೋಗಿಗಳನ್ನು ಹಲವು ಪರೀಕ್ಷೆಗಳಿಗೆ ಮತ್ತು ಸಂಧಿವಾತದ ಎರಡು ಮೊಣಕಾಲುಗಳ ನಿಂತಸ್ಥಿತಿಯಲ್ಲಿ ಎರಡೂ ಕಡೆಯ (ಎಪಿ) ಮತ್ತು ಪಾರ್ಶ್ವ (ಲ್ಯಾಟರಲ್) ನೋಟದ ಕ್ಷಕಿರಣಕ್ಕೆ ಒಳಪಡಿಸಬೇಕಾಗುವುದು.

ದಯವಿಟ್ಟು ಈ ಕೆಳಕಂಡ ಮಾಹಿತಿಯನ್ನು ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ. ಈ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಪಟ್ಟ ಹಾಗೆ ಯಾವುದೇ ರೀತಿಯ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಬಹುದು. ನೀವು ಒಂದು ವೇಳೆ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪಿದ್ದಲ್ಲಿ ನಿಮ್ಮಿಂದ ಅಥವಾ ನಿಮ್ಮ ಜವಾಬ್ದಾರಿ ಹೊತ್ತಿರುವವರ ಅಥವಾ ನಿಮ್ಮಿಬ್ಬರಿಂದ ಹಲವು ಮಾಹಿತಿಗಳನ್ನು ನಾವು ಸಂಗ್ರಹಿಸುತ್ತೇವೆ.

(ನಮ್ಮ ಪ್ರೋಫಾರ್ಮ ನೀಡಿರುವ ರೀತಿಯಲ್ಲಿ) ಅವಶ್ಯಕ ಮಾಹಿತಿಗಳನ್ನು ಸಂಗ್ರಹಿಸುವುದು, ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಲಾದ ಈ ಮಾಹಿತಿಯನ್ನು ಕೇವಲ ಪ್ರೌಡ ಪ್ರಬಂಧಕ್ಕೆ (ಡಿಸ್ಟ್ರೇಷನ್) ಮತ್ತು ಪ್ರಕಠಣೆಗಳಗಷ್ಟೆ ಬಳಸಲಾಗುವುದು.

ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿರುವ ಮಾಹಿತಿಗಳೆಲ್ಲವನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು ಮತ್ತು ಇವುಗಳನ್ನು ಬೇರೆಯಾರಿಗೂ ಬಹಿರಂಗ ಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತನ್ನು ಬಹಿರಂಗ ಪಡಿಸುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನವು ನಮ್ಮ ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿ ವತಿಯಿಂದ ವಿಮರ್ಶಿಸಲಾಗಿರುತ್ತದೆ. ಮತ್ತು ನೀವು ಈ ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯ ಕಾರ್ಯದರ್ಶಿಯನ್ನು ಸಂಪರ್ಕಿಸಬಹುದಾಗಿರುತ್ತೆ, ಅಧ್ಯಾಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಿಮ್ಮ ಮೇಲೆ ಯಾವುದೇ ರೀತಿಯ ಒತ್ತಡ ಇರುವುದಿಲ್ಲ. ಒಂದುವೇಳೆ ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಿರಾಕರಿಸಿದರೆ, ನಿಮಗೆ ಸಿಗಬಹುದಾದ ಚಿಕಿತ್ಸಾ ಸೇವೆಯಲ್ಲಿ ಯಾವುದೇ ರೀತಿಯ ಬದಲಾವಣೆಗಳನ್ನು ಮಾಡಲಾಗುವುದಿಲ್ಲ.

ನೀವು ಸ್ವಯೇಚ್ಚೆಯಿಂದ ಈ ಅಧ್ಯಾಯನದಲಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪಿದಾಗ ಮಾತ್ರ ನೀವು ಈ ಪತ್ರದಲ್ಲಿ ನಿಮ್ಮ ಸಹಿ ಮತ್ತು ಹೆಬ್ಬಟ್ಟಿನ ಗುರ್ತು ನೀಡಬೇಕಾಗುವುದು.

ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ ಸಂಪರ್ಕಿಸಿ.
ಡಾ॥ ಶಕ್ತಿಕೇಸವನ (ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ)
ಮೂಳೆ ಚಿಕಿತ್ಸಾ ವಿಭಾಗ :
ಶ್ರೀ ದೇವರಾಜ ಅರಸ್ ವೈದ್ಯಕೀಯ ಮಹಾವಿದ್ಯಾಲಯ, ಟಮಕ, ಕೋಲಾರ
ಸಂಪರ್ಕಿಸುವ ದೂರವಾಣಿ ಸಂಖ್ಯೆ: 9443092010

INFORMED CONSENT FORM

I/we the patient attenders have been explained about outpatients condition i.e., osteoarthritis knee and the need for the procedure i.e., intra articular hyaluronic acid injection in the treatment of osteoarthritis knee.

The procedure and complications associated with this procedure i.e., intra articular hyaluronic acid injection have been explained to me in my own understandable language. I am willing to pay for the procedure and the treatment.

I have been explained regarding the study design and I am participating in the study with my wilful consent. I have been also explained by the investigator that I am free to participate in the study, I can withdraw from the study at any point of time and I would continue to receive the standard care and treatment in this hospital as long as I wish to receive the treatment.

I/we the patient and the patient attenders hold the full responsibility for the procedure and the further consequences. I don't hold any treating doctor, nursing staff and hospital management for any untoward consequences.

I hereby give my consent for the same.

SIGNATURE OF THE PATIENT: SIGNTURE OF DOCTOR:

WITTNESS:

1.

2.

DATE :

ಅನುಮತಿ ಪತ್ರ

ನಾನು/ನಾವು ಹೊರ ರೋಗಿಯಾಗಿ ನನ್ನ ಮೊಣಕಾಲಿನ ಸಂಧಿವಾತದ ಪರಿಸ್ಥಿತಿಯ ಬಗ್ಗೆ ಮತ್ತು ಅದಕ್ಕೆ ನೀಡಬೇಕಾದ ಚಿಕಿತ್ಸೆ (ಇಂಟ್ರಾ ಆರ್ಟಿಕ್ಯುಲಾರ್ ಇಂಜಕ್ಷನ್ ಹ್ಯಾಲುರೋನಿಕ್ ಆಸಿಡ್ ಚಿಕಿತ್ಸೆ) ಬಗ್ಗೆ ನನಗೆ / ನಮಗೆ ಸಂಪೂರ್ಣವಾಗಿ ತಿಳಿಯಪಡಿಸಿರುತ್ತಾರೆ.

ಇದರ ಚಿಕಿತ್ಸಾ ವಿಧಾನ ಮತ್ತು ಇದರಿಂದ ಉಂಟಾಗಬಹುದಾದ ತೊಡಕುಗಳ ಬಗ್ಗೆ ನನಗೆ ಅರ್ಥವಾಗುವ ಸರಳ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಿರುತ್ತಾರೆ. ನಾನು ಈ ಚಿಕಿತ್ಸಾ ವಿಧಾನಕ್ಕೆ ಮತ್ತು ಚಿಕಿತ್ಸೆಗೆ ಹಣ ಪಾವತಿಸಲು ಒಪ್ಪಿರುತ್ತೇನೆ.

ನನಗೆ ಈ ಅಧ್ಯಯನದ ವಿನ್ಯಾಸದ ಬಗ್ಗೆ ವಿವರಿಸಿರುತ್ತಾರೆ. ಮತ್ತು ನಾನು ನನ್ನ ಸ್ವಂತ ಇಚ್ಛೆಯಿಂದ ಇದಕ್ಕೆ ಒಪ್ಪಿರುತ್ತೇನೆ. ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಸ್ವತಂತ್ರವಾಗಿ ಪಾಲ್ಗೊಳ್ಳಲಬಹುದೆಂಬುದರ ಬಗ್ಗೆ ಸಂಶೋಧಕರು ಸಹಾ ತಿಳಿಯ ಪಡಿಸಿರುತ್ತಾರೆ. ನಾನು ಈ ಅಧ್ಯಯ ನಡೆಸುವ ಯಾವುದೇ ಸಂರ್ಧಬದಲ್ಲಾದರೂ ಹೊರಬರಲು ಸ್ವತಂತ್ರನಗಿರುತ್ತೇನೆ ಮತ್ತು ಈ ಆಸ್ಪತ್ರೆಯ ವತಿಯಿಂದ ನಾನು ಬಯಸಿದಷ್ಟು ಸಮಯದವರೆವಿಗೂ ಉತ್ತಮ ನೆರವು ಮತ್ತು ಚಿಕಿತ್ಸೆ ಪಡೆಯಬಹುದಾಗಿರುವುದೆಂದು ನಾನು ಅರಿತಿದ್ದೇನೆ.

ನಾನು/ನಾವು ಹೊರ ರೋಗಿಯಾಗಿ ಮತ್ತು ರೋಗಿಯ ಸಂಬಂಧಿಗಳಾಗಿ ನಾವು ಈ ಚಿಕಿತ್ಸಾ ವಿಧಾನ ಮತ್ತು ಅದರಿಂದ ಮುಂದೆ ಉಂಟಾಗಬಹುದಾದ ಯಾವುದೇ ರೀತಿಯ ಪರಿಣಾಮಗಳಿಗೆ ನಾವೇ ಜವಾಬ್ದಾರರಾಗಿರುತ್ತೇವೆ. ಯಾವುದೇ ಸಂದರ್ಭದಲ್ಲಿ ನಾನು ನನಗೆ ಚಿಕಿತ್ಸೆ ನೀಡಿದ ವೈದ್ಯರನ್ನಾಗಲೀ, ದಾದಿಯರನ್ನಾಗಲಿ ಮತ್ತು ಈ ಚಿಕಿತ್ಸೆಯಿಂದಾಗಿ ಉಂಟಾಗಬಹುದಾದ ದುಷ್ಪರಿಣಾಮಗಳಿಗೆ ಆಸ್ಪತ್ರೆಯ ವ್ಯವಸ್ಥಾಪಕರನ್ನು ಜವಾಬ್ದಾರರೆಂದು ದೋಷಿಸುವುದಿಲ್ಲ.

ಮೇಲ್ಕಂಡ ವಿವರಗಳನ್ನೊಪ್ಪಿ ನನ್ನ ಒಪ್ಪಿಗೆ ನೀಡುತ್ತಿದ್ದೇನೆ.

ರೋಗಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ **ವೈದ್ಯರ ಹೆಸರು ಮತ್ತು ಸಹಿ**

ಸಾಕ್ಷಿಗಳು ಹೆಸರು ಮತ್ತು ಸಹಿ :

1)

2)

ದಿನಾಂಕ :

ಸ್ಥಳ :

The Western Ontario and McMaster Universities Osteo arthritis Index(WOMAC)

Name:_____Date:_____

Instructions:

Please rate the activities in each category according to the following scale of difficulty:

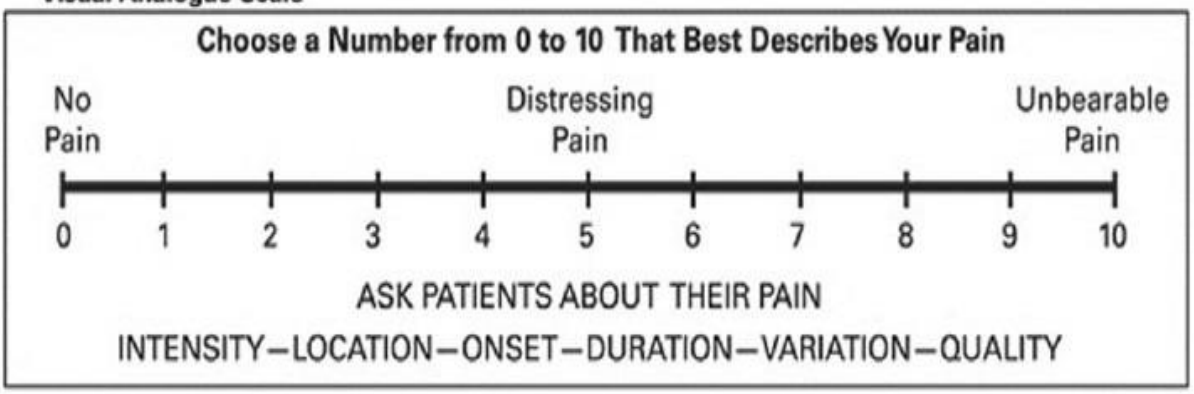
0=None,1=Slight,2 =Moderate,3=Very,4=Extremely

Circle one number for each activity Pain

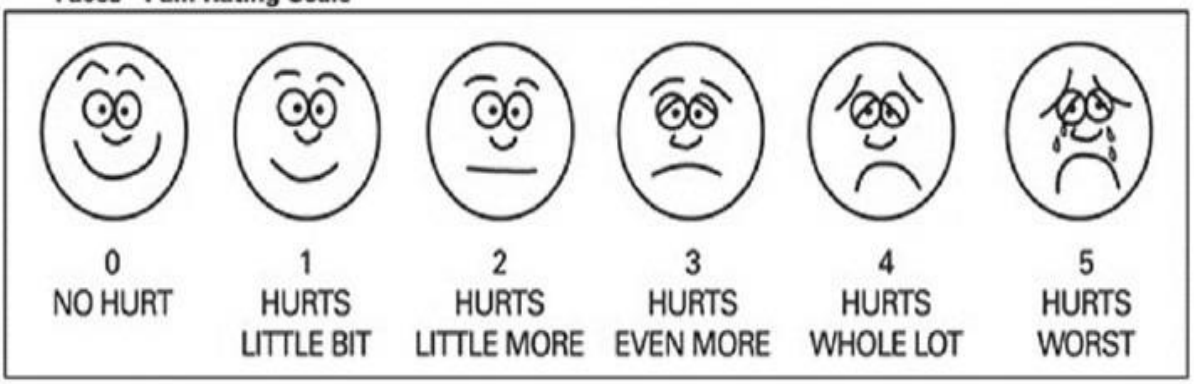
PAIN						
1.	Walking	0	1	2	3	4
2.	Stair Climbing	0	1	2	3	4
3.	Nocturnal	0	1	2	3	4
4.	Rest	0	1	2	3	4
5.	Weight Bearing	0	1	2	3	4
STIFFNESS						
1.	Morning stiffness	0	1	2	3	4
2.	Stiffness later in the day	0	1	2	3	4
PHYSICAL FUNCTION						
1.	Descending stairs	0	1	2	3	4
2.	Ascending stairs	0	1	2	3	4
3.	Rising from sitting	0	1	2	3	4
4.	Standing	0	1	2	3	4
5.	Bending to floor	0	1	2	3	4
6.	Walking on a flat surface	0	1	2	3	4
7.	Getting in /out of car	0	1	2	3	4
8.	Going Shopping	0	1	2	3	4
9.	Putting on socks	0	1	2	3	4
10.	Lying in bed	0	1	2	3	4
11.	Taking off socks	0	1	2	3	4
12.	Rising from bed	0	1	2	3	4
13.	Getting in / out of bath	0	1	2	3	4
14.	Sitting	0	1	2	3	4
15.	Getting on / off toilet	0	1	2	3	4
16.	Heavy domestic duties	0	1	2	3	4
17.	Light domestic duties	0	1	2	3	4

Figures: Tools Commonly Used to Rate Pain

Visual Analogue Scale



"Faces" Pain Rating Scale



PROFORMA

Name : Case no :

Age : Ip/op no :

Sex : DOB :

Address : Date :

Phone no:

Chief complaints :

History of presenting illness :

Past history :

Family history :

Personal history :

General physical examination

BP -

RR -

PR -

Temp-

Systemic examination

1. CVS
2. RS
3. PA
4. CNS

LOCAL EXAMINATION:

Inspection:-

Palpation :-

Movements:-

Measurements:-

X ray of knee (right / left /both) :-

Kellergen and Lawrence grading :-
Diagnosis :

WOMAC scoring during follow ups:-

DATE	WOMAC SCORE	VAS SCORE

ASSESSMENT OF RESULT:

Signature of candidate: Signature of Guide:

KEY WORD TO MASTER CHART

WOMAC 0	WOMAC score at pre injection
WOMAC 1	WOMAC score at one month post injection
WOMAC 3	WOMAC score at 3rd months post injection
WOMAC 6	WOMAC score 6 months post injection
VAS 0	VAS score at pre injection
VAS 1	VAS score at one month post injection
VAS 3	VAS score at 3 months post injection
VAS 6	VAS score at 6 months post injection
P	Pain score
S	Stiffness score
PF	Physical function
PH	Post hysterectomy status
DM	Diabetes mellitus
HTN	Hypertension
BA	Bronchial asthma

MASTER CHART

S.No.	Name	Age	Sex	Side	GRADE	IP No:	DOI	WOMAC (0) P	WOMAC (0) S	WOMAC (0)PF	WOMAC (0) T	WOMAC (1) P	WOMAC (1) S	WOMAC (1)PF	WOMAC (1)T	WOMAC (3) P	WOMAC (3) S	WOMAC (3) PF	WOMAC (3) T	WOMAC (6)P	WOMAC (6) S	WOMAC 6() PF	WOMAC (6)T	VAS (0)	VAS (1)	VAS (3)	VAS (6)	BMI	ASSOCIATED CO MORBIDITIES
1	LALITHAMMA	65	F	RIGHT	II	540155	01.02.2018	18	5	59	82	14	4	45	63	11	4	37	52	9	3	28	40	10	8	8	6	30.6	DM
2	NARAYANAMMA	45	F	LEFT	II	540147	01.02.2018	19	7	63	89	16	6	52	74	11	5	44	60	6	2	27	35	10	8	6	4	27.8	HTN
3	THOLASAMMA	80	F	LEFT	II	508653	01.03.2018	19	7	62	88	15	6	51	72	12	5	39	56	8	3	29	40	10	8	6	6	28.1	DM
4	NARAYANAMMA	56	F	LEFT	II	554411	08.03.2018	16	5	48	69	13	5	45	63	10	4	29	43	9	4	35	48	10	8	6	6	18.8	PH
5	SHAMANTHAMMA	52	F	RIGHT	II	500029	04.04.2018	20	4	60	84	17	4	51	72	14	4	38	56	11	3	28	42	8	6	6	6	26.7	
6	KHAMRUNNISHAA	70	F	RIGHT	II	569636	16.04.2018	16	6	63	85	13	5	51	69	11	4	42	57	9	3	34	46	10	8	6	6	38.2	DM
7	SRINIVASAPPA	65	M	LEFT	II	419689	16.04.2018	18	6	64	88	15	6	49	70	11	5	39	55	7	4	29	40	10	8	6	6	35.1	DM
8	VENKATALAKSHMA MMA L	50	F	LEFT	II	604267	18.07.2018	18	5	61	84	15	5	48	68	15	5	48	68	11	4	39	54	10	8	8	6	20.8	PH
9	VENKATARAVANAM MA	45	F	LEFT	II	554788	21.08.2018	17	7	56	80	12	5	44	61	9	5	37	51	7	3	25	35	10	8	6	4	25.7	
10	KEMPAMMA	60	F	LEFT	II	613194	24.08.2018	18	5	55	78	15	4	48	67	12	3	31	46	10	3	30	43	8	6	6	4	24.9	HTN
11	VENKATALAKSHMA MMA R	50	F	RIGHT	II	604267	28.08.2018	18	5	61	84	15	5	52	72	13	5	43	61	10	4	33	47	10	10	8	4	20.8	
12	YELLAPPA	46	M	LEFT	I	621967	31.08.2018	11	4	45	60	10	5	42	57	8	5	31	44	7	3	27	37	8	8	6	4	26.6	
13	RAMAKKA	65	F	LEFT	II	669501	03.01.2019	17	8	58	83	16	7	56	79	14	6	48	68	13	6	42	61	10	7	3	1	31.3	DM
14	NEELAMMA	56	F	RIGHT	I	679947	01.02.2019	19	6	61	86	17	6	64	77	14	5	43	62	10	3	31	44	10	8	5	3	38.1	HTN
15	VANITHA	45	F	LEFT	II	652687	05.02.2019	18	6	55	79	14	5	43	62	11	4	34	49	8	3	26	37	8	6	4	1	33.8	
16	MAHALAKSHMI	43	F	RIGHT	I	692804	20.02.2019	15	5	52	72	15	4	45	62	13	4	42	51	10	3	36	49	8	7	5	4	24.9	PH
17	CHANDRAMMA	65	F	RIGHT	II	666916	31.12.2018	19	6	62	87	16	6	47	69	13	4	36	53	9	3	24	36	9	7	5	1	35.2	DM
18	SANTHOSINI	53	F	RIGHT	I	692803	20.02.2019	18	6	50	74	15	6	42	63	12	4	34	50	7	2	25	34	8	5	4	1	23.1	
19	VANITHA	42	F	RIGHT	II	652687	06.03.2019	17	7	62	86	16	6	57	79	14	5	47	66	12	4	41	57	9	7	4	2	33.8	BA
20	RANGA RAO	50	M	RIGHT	I	692880	06.03.2019	18	7	54	89	15	5	43	63	12	4	35	51	6	1	21	27	8	6	3	1	31	
21	VENKATESH	50	M	LEFT	II	589055	27.03.2019	17	7	53	77	11	5	37	53	7	3	23	33	3	1	13	17	8	5	3	1	25.8	BA
22	SRINIVAS K G	58	M	RIGHT	II	701683	29.03.2019	18	5	52	75	14	4	36	54	8	2	22	32	3	1	9	13	8	6	3	1	26.5	
23	VENKATALAKSHMA MMA	65	F	LEFT	II	604267	29.03.2019	18	7	55	80	13	5	39	57	9	3	27	39	4	2	11	17	10	3	1	0	24.2	DM
24	KRISHNAMURTHY	65	M	RIGHT	II	568892	27.03.2019	18	6	58	82	15	5	45	65	11	3	32	46	7	1	14	22	8	6	3	1	28.3	HTN
25	RAVI	48	M	RIGHT	I	611127	05.04.2019	18	7	54	89	14	5	39	59	9	2	22	33	3	1	12	16	10	7	4	0	27.7	
26	SHANTHAMMA	55	F	RIGHT	I	706065	09.04.2019	17	6	56	79	11	4	34	49	6	3	23	32	9	4	28	41	9	6	4	2	23.9	
27	MUNIVENKATAMMA	60	F	RIGHT	II		11.04.2019	18	7	54	89	14	5	46	65	9	3	31	43	5	1	14	20	10	7	4	1	25.5	DM
28	MUNIRATHNAMMA	42	F	LEFT	I	707252	12.04.2019	17	6	56	79	15	5	42	62	14	5	42	61	11	3	32	46	8	5	3	1	32.8	
29	SHARADHAMMA	42	F	LEFT	I	717857	10.05.2019	17	6	56	79	13	5	46	64	10	4	37	51	7	2	24	33	8	6	4	1	23.9	PH
30	VENKATESHAMMA	42	F	RIGHT	I	720444	17.05.2019	18	7	54	89	16	4	40	60	11	2	28	41	6	1	19	26	8	6	3	1	26.7	PH
31	KALAMMA	50	F	RIGHT	I	721836	21.05.2019	17	7	58	82	15	6	47	68	12	5	39	56	8	3	27	38	9	6	3	2	30.2	DM
32	JAGADAMBAL	44	F	RIGHT	I	622344	24.05.2019	16	6	52	74	13	4	37	54	9	2	27	38	4	1	15	20	9	5	3	0	24.9	
33	PRAMILAMMA	45	F	LEFT	II	637990	27.05.2019	8	7	54	79	16	4	45	65	12	3	33	48	6	2	21	29	10	6	2	0	27.3	
34	NARAYANASWAMY	46	M	RIGHT	II	534708	31.05.2019	18	7	61	86	16	6	49	71	11	5	33	49	4	3	12	19	10	7	4	1	26.1	
35	SUNANDHAMMA	55	F	LEFT	I	733245	31.05.2019	17	7	54	78	19	5	41	65	10	3	24	37	4	1	11	16	8	7	4	1	23.9	DM
36	RATHNAMMA	50	F	RIGHT	I	733313	31.05.2019	17	7	53	77	13	6	53	72	13	6	51	69	11	5	48	64	8	8	6	5	29.4	PH