

Osteoarthritis: From complications to cure

Background: Osteoarthritis (OA) is a degenerative disorder that affects the cartilage of bones and characterized by severe pain in joint, joint lock and instability. Factors associated with its risks are obesity, past trauma, advancing age, female sex and genetics. Women and older people are more susceptible to the risk of OA. There are different types of OA on basis of joint affects as hip, knee, hand etc. Innate immunity plays an important role in pathogenesis of OA. Activation of innate immunity as a result of small fragments e.g., of protein results in secretion of cytokines (IL-1 β and TNF- α , IL-8, IL-17 etc.) and enzymes (MMP and ADAMTS) which cause degradation of bone and imparts inflammatory effect. Aging also plays an important role in OA as chondrocytes show reduced autophagy with aging, so risks of OA increases. Different drugs have been in use for the treatment of OA which provide anti-inflammatory, analgesic effects and help in improving bone integrity. Acetaminophen is usually prescribed as first line drug. Oral NSAIDs and opioids provide an alternative when it does not prove effective. But these are associated with the high risks of gastrointestinal (GI) tract, cardiovascular (CV) and renal system, and liver toxicity. Topical NSAIDs can also be used as alternative to oral NSAIDs for their safety. Another option is topical capsaicin which can be used as an adjunctive treatment with only local adverse effects such burning, itching etc. Intra-articular injections of hyaluronic acid and corticosteroids are also used. Both are considered almost safe with local adverse effects. Non-pharmacological treatments for OA includes education, exercise, therapies, surgery and regenerative therapies. In this study, we have briefly enlightened the pathogenesis of osteoarthritis. Moreover, pharmacological as well as non-pharmacological treatment for OA is also explained.

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Introduction

Osteoarthritis is a degenerative disorder that affects the cartilage of bones and other surrounding tissues [1,2]. It is characterized by severe pain in joint that increases by movement [1]. The development of this disease is slow but with the passage of time, it may leads to joint failure [2]. Obesity, past trauma, advancing age, female sex and genetics are the risk factor for this disorder. Joint pain is the most common symptom of osteoarthritis that may leads to joint locking or instability. Joints that are commonly affected by this disorder are spine, knee, hand and hip [1].

Occurrence range of radiographic hand OA has been reported from 27% to over 80%. Knee osteoarthritis occurs less than hand osteoarthritis, and more common in female gender with female to male ratio 1.5:1 and 4:1. Hip osteoarthritis

is less common as compare to hand and knee arthritis. The occurrence of hip osteoarthritis in Asia is 1.4% [2]. The incidence of osteoarthritis among People with 60 years of age or more is almost 10% in men and 13% in women [3]. The data from population based survey indicated the prevalence of hand osteoarthritis to be 29.5% in people with age 25 years or more. Another survey indicates the occurrence of knee osteoarthritis in Chinese population with age \geq 60 years to be 22% in men and 43% in women, and this prevalence of osteoarthritis was 45% greater as compare to US white population. According to a survey, 30% women and 11% men of Japanese population were affected by knee osteoarthritis. A study conducted in a Japanese village indicated the prevalence of radiographic spine osteoarthritis to be 42% of men and 36% of women [4]. A survey conducted in Karachi, at Liaquat National Hospital, from 2007-2008

showed that females with age more than 55 often visit tertiary health care centers because of knee osteoarthritis [5]. According to another study, the prevalence of knee osteoarthritis in north Pakistan was 3.6% in rural and 3.1-4.6% in urban region [6].

Osteoarthritis is a disorder of whole joint so combination of different techniques is used to diagnose synovial tissue, menisci, cartilage, bones and ligaments effectively. To examine bony structure, radiography is used. Optical coherence tomography (OCT) is used to check the condition of articular cartilage. Visualization of all intra-articular structures is done by magnetic resonance imaging (MRI) and ultrasound (US) permits the examination of ligaments and the synovium [7]. Early diagnosis of osteoarthritis can be done by using near-infrared (NIR) fluorescent probes that are sensitive to cathepsin B. When this method is used to diagnose osteoarthritis in mice in which arthritis is introduced by mean of collagenase injection in left knee joint, the results showed 3-folds contrast in signal intensity between affected and normal joints after 24 hours [8].

Osteoarthritis can be treated by different means: chondroitin sulphate is useful for the treatment of arthritis [9]. The most common dietary supplements for the treatment of osteoarthritis are glucosamine and chondroitin sulfate. In 2004, the estimated sale of these supplements is almost \$730 million [10]. Viscosupplementation are Intra-articular hyaluronic acid injections [1]. Viscosupplementary devices are implanted in the compartment of which the treatment is required. These devices retain in the compartment for various period of time and help to restore the healthy condition of that area [11].

Mesenchymal stem cells (MSCs) have ability to regenerate articular cartilage and have potential to improve joint function without any adverse side effect [12]. Duloxetine (analgesic) is a drug that effectively reduces the pain and improves function of effected joint [13]. Mild osteoarthritis can be treated with acetaminophen (analgesic). When acetaminophen fails to treat the symptoms, the patient is transfer to nonsteroidal anti-inflammatory drugs (NSAIDs). It includes ibuprofen, naproxen, diclofenac and inhibitors of Cyclooxygenase-2 such as celecoxib (Celebrex). Opioids are another class of drugs that is used to treat pain. It is prescribed at low dosage because of its abusive potential and also causes constipation. Another option for treatment is

injections of corticosteroids they give relief from pain for four to eight weeks. For immediate pain relief lidocaine is a good option [1].

Non-pharmacological treatment of osteoarthritis involves proper exercise, irrespective of pain and age, and weight. These strategies are core treatment in non-pharmacological treatments. Surgical treatment of osteoarthritis is recommended only when the disease become too severe to bear the pain [14-18]. In this article, the main focus is to discuss the pathogenesis and treatment of OA which would help in understanding the basics of OA.

Pathogenesis of osteoarthritis

Role of innate immunity in osteoarthritis pathogenesis

One of the central feature of osteoarthritis is the activation of innate immunity. Innate immunity refers to specific host immune responses through identifying specific patterns molecules produced by invading pathogens, bacteria, fungi and viruses through specific pattern recognition receptors (PRRs). One of the common studied class of PRR is Toll-like receptors (TLR). Histological studies show increase expression of two toll like receptors in case of OA patients which includes TLR2 and TLR4 [19].

There is another class of receptors termed as damage associated molecular patters (DAMPs). Both these receptors signal to immune system a stage of stress or injury to initiate repair process or encounter infection [20]. DAMPs may include hyaluronan, high mobility, heat-shock proteins group box (HMGB)-1, members of the S100/calgranulin [21] and fragments generated from proteins, proteoglycans or residue of cellular breakdown such as uric acid. DAMP produces an inflammatory response through interaction with pattern recognition receptors (PRRs) such as Toll-like receptors on immune cell surfaces or with PRR in cell cytoplasm such as NOD-like receptors (NLR). Under normal conditions, the activation of DAMP trigger innate immunity for wound healing but in this case, it leads to further tissue damage ultimately leading to joint swelling causing osteoarthritis [22].

The activation of NLR (NOD-like receptors) leads to inflamosome assembly that further leads to activation of inflamosome mediated inflammation pathways. In addition to inflammatory response of cytokines, chondrocytes also have ability to activate complement system. Also, activation of mechanoreceptors in cartilage cause upregulation

of various inflammatory mediators [23]. The inflammatory response is further amplified by synovial T-cells, B cells and infiltrating macrophages [24].

As inflammatory response is generated, it causes upregulation of various catabolic factors such as proinflammatory cytokines (IL1- β and TNF- α), chemokines, proteolytic enzymes and down regulation of anabolic factors such as growth factors and anti-inflammatory cytokines. The major inflammatory cytokines and chemokines linked to OA includes IL-8, IL-17, IL-18, IL-21 and leukemia inhibitor factor. Both IL1- β and TNF- α diffuse into synovial fluid and act on chondrocytes and suppress matrix synthesis [25].

The major enzymes that causes catalytic breakdown includes MMP and ADAMTS. Histological studies show that MMP-1, MMP-3 and MMP-13 were isolated were OA patients chondrocytes with MMP-13 being highly expressed [23,26-30]

Various ECM (extracellular cartilage matrix) components produced during an injury that activates immune system includes COMP, NC4 domain of type-4 collagen and fibromodulin. The amount of MAC found in synovial membrane through histological studies directly links it with synovial inflammation. C5a components of complement system were found to be upregulated in OA chondrocytes. Also, CD59 that is a naturally occurring complement inhibitors is found to be upregulated in synovium of OA patients that shows complement system is chronically activated in OA (Table 1) [22].

Innate immunity can be triggered by crystals that includes calcium pyrophosphate dihydrate and basic calcium phosphate crystals that are commonly present in OA joint and tissues. These crystals further interact with NALP-3 inflammasome that activates IL1- β and IL-18 cleaving procaspase-1 to caspase-1 [19].

Role of aging in pathogenesis

Aging is one of the prominent risk factor osteoarthritis development and onset. Chondrocytes exhibits reduced activity in aging collagen as compared to normal chondrocytes

with evidence of senescent secretory phenotype [23]. In aging tissues, advanced glycation end products (AGEs) are produced by a non-enzymatic process that modifies cartilage by weakening its mechanical properties. AGEs trigger chondrocytes activation by binding to RAGE receptors present on chondrocytes. This leads to production of inflammatory mediators such as chemokines and cytokines [19,31,32]. The aging causes loss of autophagy of chondrocytes during stress condition that further increases chances of osteoarthritis (Figure 1) [19].

Pharmacological treatment for osteoarthritis

The pharmacological treatment generally used for the treatment of the osteoarthritis includes non-steroidal inflammatory drugs, opioids, acetaminophen, topicals and intra-articular injections of hyaluronic acid or corticosteroids. Table 2 shows their function and side effects.

Acetaminophen

Acetaminophen also known as paracetamol is approved by WHO (World Health Organization) to lessen different types of pains such as headache and fever [33]. For its low cost, effectiveness and safety [1,33,34], it is recommended by most of the guidelines [33,35] for the treatment of mild-moderate OA pain [33,36,37]. It is regarded as the first line choice because of less toxicity compare to NASIDs (non-steroidal anti-inflammatory drugs). It shows little adverse effects (AE) associated with gastrointestinal (GI) tract, renal function and blood pressure. Moreover, it is not reported to cause increase in myocardial infarction [38]. It performs its mechanism of action by inhibiting cyclo-oxygenase (both COX-1 and COX-2) and stimulating antinociception pathways such as descending serotonergic pathways [39]. But high dose of paracetamol is associated with different risks such as liver failure, gastrointestinal bleeding [33] and risks related to cardiovascular system (CV) [36]. Now, it has gained safety concerns because it causes side-effects such as hypertension and liver toxicity even at low dosage [40]. Because of risks associated with

Table 1. ECM components that regulate innate immunity

Components	Role	Ref.
COMP	Regulates complement	[27]
Collagen IX (NC4 domain)	Direct/indirect inhibition of complement	[28]
Hyaluronan (HA)	Triggers inflammasome>IL-1 β	[29]
Fibromodulin	Upregulates C5b-9 (MAC) from human OA sera	[30]

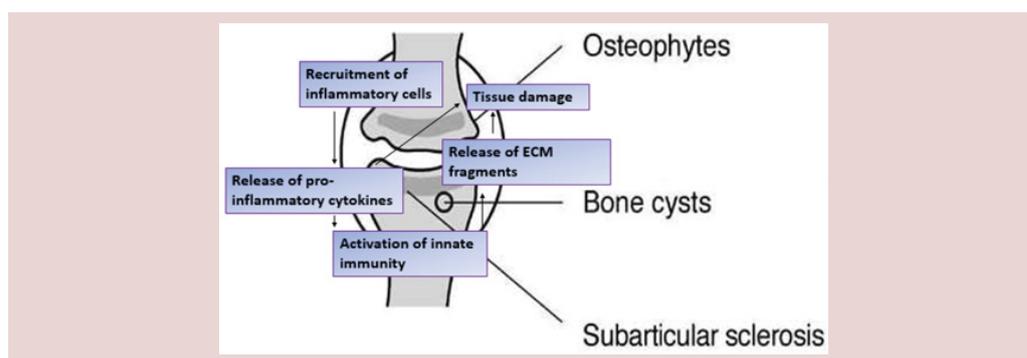


Figure 1. Pathogenesis of osteoarthritis

Table 2. Function and adverse effects of pharmacological treatment			
Drug type	Function	Adverse effects	References
Acetaminophen	Inhibiting cyclo-oxygenase and stimulating antinociception pathways reducing pain	Liver toxicity, CV and GI tract risks, hypertension	[36,39,40]
Oral NASIDs	Inhibit cyclo-oxygenase producing anti-inflammatory, anti-depressant and analgesic effects	Risks of GI tract, CV and renal system.	[38,41,42]
Opioids	Bind MOP receptors in middle brain inhibiting nociceptive neurotransmission release	Risks of GI tract, CV and immune system, addiction, dizziness, nausea.	[33,41,42,44]
Topicals	NASIDs: same as oral NASIDs Capsaicin: Inhibit transient receptor potential vanilloid 1 receptor (TRPV1), thereby inhibiting the release of nociceptive neurotransmitters reducing pain	NASIDs: dermatitis, skin sensitivity. Capsaicin: Damage to nerve end, burning, itching, rashes.	[37,46]
Intra-articular injections	Corticosteroids: binds nuclear steroid receptors and inhibit inflammatory and immune pathway thereby producing anti-inflammatory effect HA: promote HA production and anti-inflammatory effect by nociceptors inhibitions.	Corticosteroids: risks are rare like hypersensitivity. HA: safe, only local side-effects.	[47,48]

acetaminophen, FDA has recommended its quantity to be not exceed from 4325 mg per dosage unit in any prescription [33]. Following FDA, AAOS guidelines also have decreased the recommendation from 4000 to 3000 mg/day. So, acetaminophen must not increase 3 g/per day [40].

Oral NASIDs (Non-steroidal inflammatory drugs)

NASIDs are more effective than acetaminophen in OA treatment [1,33,36] for moderate to severe pain [1,33]. And are suggested to use when acetaminophen or topical NASIDs do not work [40]. The function of NASIDs is to inhibit the function of COX-1 and COX-2 (synthesis of prostaglandin). The NASIDs can be classified into two types; non-selective NASIDs and selective COX inhibitors. This results in antipyretic, analgesic, anti-inflammatory effects [38]. But the use of oral NASIDs is associated with adverse effects related to GI tract, CV and renal system [41,42] which are estimated to be found in ~30% of the people using NASIDs. Per

year 1-2% consumers suffer from GI problems [33] like bleeding which can be minimized using a gastro protective agent [42]. Generally, proton pump inhibitor (PPI) is recommended. These risks are associated to both classes of NASIDs but selective COX-2 inhibitors are considered better [36] due to selectivity [43]. A study showed that they reduce overall risks of GI by 3.7% [36], though they are costly. But it can't be ignored that they are associated with CV risks [1,2] and are nephrotoxic [43]. So, several selective COX-2 inhibitors have gained attention by FDA [33]. For example, cyclocoxib has AE on CV system, risks were found with high doses (200 mg/day) but not at low dose [35]. Other drugs such as rofecoxib due to their side-effects have withdrawn from the market [33]. No clear difference is found between both classes for risks associated with CV system e.g., risks of CV have found to increase using rofecoxib, diclofenac etc. Though, naproxen (conventional NASID) is proved to be the safest for CV system and along with a PPI acts as better option for OA patients susceptible to CV risks [35]. Both types

of NASIDs are equally effective so choice should be made on the basis of side-effects, cost and comorbidity chances in patient [37,40]. OARSI have suggested to use the least effective dose of NASID only for short period [33].

Opioids

Opioids are another option to treat pain moderate to severe [1,33] and used when NASIDs or paracetamol are not proving effective or showing AE [1,33,34]. Greater effectiveness is found in using stronger opioids (oxycodone, oxycodone, oxytrex, fentanyl, morphine sulphate) as compare to weaker such as tramadol [34]. Opioids binds to MOP receptor present in the midbrain which results in the activation of descending inhibitory neurons, finally reducing the transmission of nociceptive from periphery to thalamus [44]. Opioids should be prescribed at low dose in start [1]. Opioids have proven effective for hip and knee OA [36]. The risks associated with opioids use are constipation, vomiting, dizziness, and headache etc. [33]. Oral opioid is problematic because it may interfere with gastrointestinal events when the opioid receptors are activated resulting in constipation. Other AE are on immune system, CV system [41] and problems like fracture [36]. Moreover, the use of opioids is also a controversial issue because of its misuse or addiction. In a research in 2008, 74% of the drug addiction were due to the opioids. Moreover, their long use can develop tolerance and hyperalgesia, decreasing its efficacy. So, their longtime use is limited. Steps have been taken to minimize its misuse e.g., tramadol (weak opioid) offer less misuse and tolerance, and provides a much better option. But other AE are still there which hinders the use of opioids [42].

Topical

Topical NASIDs are reported to be used as an alternative to oral NASID because of its relative safety, though both have comparable effect [34,40]. These are preferred in the patients which have increase chances of adverse effects or not responding to the traditional treatment [36,37,40]. Topical NASIDs available worldwide consists of diclofenac, ibuprofen, naproxen, flurbiprofen and ketoprofen [41]. They are available in different forms such as creams, solutions, bandages, gels, plasters and sprays [41,42]. For the effectiveness, they must be use 3-4 times on daily basis [36]. Topical NASIDs are applied directly to the suffering area. So, absorption of topical NASID is slow

which decreases the chances of adverse effects as related to oral NASIDs [41]. It has seen that only 15% of the patients using topical NASIDs exhibit adverse effects associated with GI [37]. These topical don't cause a high blood pressure as oral NASIDs, which is responsible for diseases of CV system [41]. There are very less systemic effects related to these topical but local effects can be occur in 10-15% patients [35]. These includes sensitivity of skin, contact dermatitis or phyto dermatitis [37] resulting in burning, itching, rashes in the local area [36]. In a study, topical the only adverse effect seen was with diclofenac was drying of skin [45]. Their short time use is safe [35]. These are mostly recommended for knee and hand joints [35,45] but their effectiveness for hip joint is uncertain due the depth of this joint [4,35]. Capsaicin topical is a cream which is derived from the chili peppers [1, 35]. It can be used as adjunctive treatment [1,36,37,42]. It is widely available widely but is costly [1]. It binds to the transient receptor potential vanilloid 1 receptor (TRPV1), thereby inactivating them and inhibiting the release of nociceptive neurotransmitters via cascade pathway [46]. They have found to be effective for pain relief in knee OA [35,36]. Like topical NASIDs, they must be used 3-4 times/day for about 3-4 weeks to get good effective [36,37]. The adjunctive use of this cream may help to decrease systemic adverse effects [41]. But it may result in destruction to sensory nerve endings etc. [46]. Moreover, local adverse effects are itching, burning, rashes [36].

Intra-articular injections

Intra-articular injections of corticosteroids are another option for the treatment of OA [34] and recommended by OARIS for treating moderate-severe pain [33]. Corticosteroids on binding to nuclear steroid receptors interfere with different inflammatory and immune system. Through this, they cause inhibition of inflammatory agents such as prostaglandins, phagocytosis, metalloprotease and its activator [47]. These injections are suitable for only short-term treatment for ~4-8 months [1]. The examples of IA corticosteroids are triamcinolone acetonide and hexacetonide [43]. IA corticosteroids have been recommended by the ACR and AAOS for knee and hip OA treatment [33]. Usually these injections are administrated with a lidocaine (a local anesthetic) to confirm that administration is done in correct area [1]. IA corticostetroids associated AE are rare [47] such as hypersensitivity to corticosteroids, joint fracture, infection etc

[48]. Usual practice is not to use these injections more than 4/year [1]. Hyaluronic acid is basically a glycosaminoglycan and occur naturally in the synovial fluid of healthy as well as diseased person (OA) [35]. It acts as a lubricant for the joint [37] and plays a vital role in the integrity of joint's structure [48]. In OA, depolymerization of this molecule is reported [40]. OARIS has recommended the use of IA HA injections for the treatment of knee and hip OA [33]. IA HA (viscosupplementation) [1,40] maintain bone integrity, stimulates HA production and exhibit anti-inflammatory effects e.g., by inhibition of nociceptors [47]. EULAR have suggested that HA is effective for improving joint function and reducing pain. But repeated injection for about 3-5 weeks must be administrated because of slow onset time of HA, which made its use costly [40]. It is regarded safe for patients with only local side-effects of 2-4% [47].

The comparison of oral NASIDs and IA HA showed no significant difference. ACR and ESCO guidelines have recommended the use of HA for patients in which oral NASIDs did not prove effective [40]. On comparison with corticosteroids, it was seen in a study that both HA and corticosteroids show an equal response for 4-8 weeks but after 8 weeks the effect of corticosteroids decreased suggesting their use only for acute OA pains [20,49]. However, a variation has seen in the effect of HA. While some guidelines recommend its use, others don't [47]. ACR have suggested that the injection must be administrated by experienced person and in sterile conditions to avoid infection [37]. Septic arthritis, though rare, but it is severe problem. In a study in Iceland, 1/2633 corticosteroids injections resulted in infection of joint [43]. Other problems include joint infection, pain, change in skin pigments etc. [48].

Non-pharmacological treatments

Surgical treatment

When the other therapies become failed or OA pain and deformities become so intense than knee and hip replacement therapy is performed. Most common are knee and hip replacements surgeries [49-51].

Regenerative therapies

For the regeneration of cartilage, cell therapy is used involving both mature and immature cells. Chondrocytes have been in use for the cell therapy but it is laborious though it does not have acute side effects. Mesenchymal stem

cells (MSC) therapy, on the other hand, has potential advantage as MSC are easy to obtain, have high rate of proliferation rate as well as immunosuppressive function [33]. Adipose tissue derived Mesenchymal stem cells AD MSCs are to treat knee osteoarthritis. It is administrated via injection and help to reduce pain and improve joint function without any adverse side effect [12]. Likewise, research is also carried on gene therapy to produce gene product at the site of target. But now only one therapy, TGF- β gene therapy is in clinical trials in phase-I and phase-II [33].

Self-assistance and therapists

Patient should protect their joints from damage. They must perform light exercise, light as well as water exercise, on daily basis or they can consult a therapist (physical or occupational) to help them perform joint motions, massages. Moreover, patient can also use assistive devices to help them move such as grab rails, knee braces; appropriate foot ware should be used [50,51]. For obese patients, it is recommended to lose weight as it helps in improving physical performance [40]. Weight is a major factor that linked arthritis with diet and metabolism. Mostly the patients of osteoarthritis are overweight. The weight bearing joints, in obese person, bear an extra burden and contribute to the development of osteoarthritis.

Education

Patient need to be educated about the OA through different sources, for instance, paper/social/online media, pamphlets, seminars. They should be motivated by their relatives and friends as it has shown to help to improve OA pain (Figure 2) [50].

Conclusion

Both pharmacological and non-pharmacological treatments are in use for the treatment of OA with different benefits as well as harms specifically pharmacological treatment. Especially, patients should undergo pharmacological treatment under the guidance of doctor. Research is also carried on new strategies to treat osteoarthritis with minimum side effect. Pro-inflammatory cytokines are one of those factors that disturb the metabolism and also reported to increase the catabolism of joint involved in osteoarthritis. Thus, play important role in pathophysiology of OA. So, the concept to use anti-cytokine drugs for the treatment of OA is promising and it can be expected that an influential treatment of OA will develop that involve the anti-cytokine drugs.

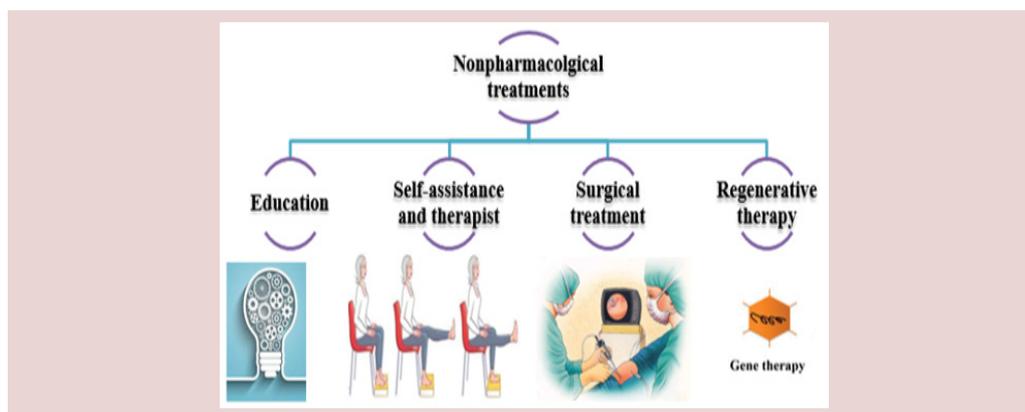


Figure 2. Non-pharmacological treatment of osteoarthritis

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