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# Effect Of Pharmacological Therapy and Physiotherapy on The Serum Levels of Proinflammatory Cytokines (IL 6 And TNFα) And Vitamin D In Osteoarthritis Patients

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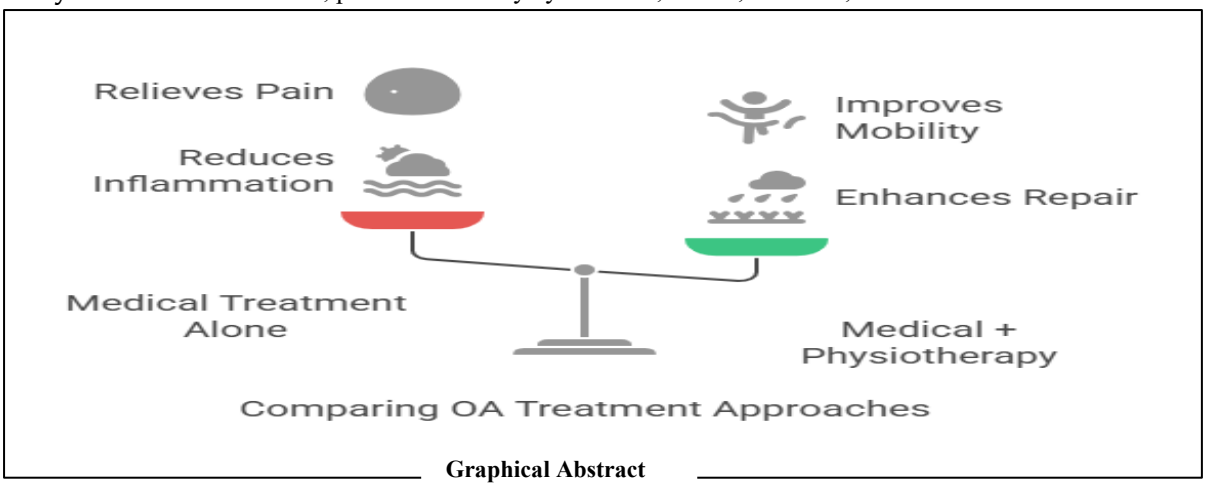
**Abstract:** One of the gradual joint degenerative diseases is osteoarthritis (OA). Pro-inflammatory cytokines play a critical role in the development and progression of OA. Our study aimed to compare the effect of medical treatment alone and medical treatment with physiotherapy on the levels of pro-inflammatory cytokines and serum vitamin D. This study was conducted on 200 OA patients divided into 2 groups. The result showed there was a significant difference between the two groups regarding the serum level of vitamin D and proinflammatory cytokines IL6 and TNF-α. We concluded that while medical treatment alone can reduce inflammation and pain, combining it with physiotherapy leads to a more balanced cytokine profile, promoting joint repair and better functional outcomes.

**Keywords:** Osteoarthritis 1, pro-inflammatory cytokines 2, IL-6 3, TNF-α 4, Vit D 5.




**Graphical Abstract**



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# 1. INTRODUCTION

Two hundred and fifty million people around the world suffer from osteoarthritis (OA), one of the most prevalent degenerative orthopedic conditions [1] . Pain, stiffness, swelling, and restrictions in joint function are among the clinical signs of this disease, which involves several anatomical and physiological changes of joint tissues, such as osteophyte production, bone remodeling, and cartilage deterioration [2]. OA is a complex illness with an unclear cause. It is regarded as a discontinuous phasic disease that gradually changes every tissue in the afflicted joint. With a frequency of between 30% and 40% in the elderly population, the most common site of OA is the knee joint, subsequent to the hand and the hip [3].

By controlling the MAPK signaling pathways and NF-κB (nuclear factor-kB), proinflammatory cytokines produce inflammatory mediators during the pathophysiology of OA, causing articular cartilage to degenerate, degrade, and destruct [4]

From endogenous polypeptides, proinflammatory cytokines are mostly produced by immune system cells and have a large scale of potent biological effects. They can also mediate different immune responses. Presently, IL-1β, TNF-α, IL-6, IL-15, IL-17, and IL-18 are the primary proinflammatory cytokines implicated with OA [5].

IL-6 and TNF- α are markers of interest in our study. Considered to be the primary cytokine responsible for the alterations in the subchondral bone layer, IL-6 causes inflammation in synovial tissue, increases cartilage permeability, speeds up the formation of osteoclasts, and causes the absorption, deterioration, and destruction of cartilage, all of which contribute to increased FLS proliferation. Additionally, research has shown that IL-6 works in concert with TNF-α and IL-1β [5].

TNF-α is both a cartilage catabolic agent and a proinflammatory cytokine. TNF-α causes cartilage to break down by encouraging synovial fibroblasts to secrete matrix metalloproteinases. By suppressing SOX9 synthesis, it also prevents chondrogenesis via the NF-kB pathway [6].

People with OA are particularly concerned about chronic pain, which can impair their physical function, mental health, and quality of life. Although there are currently no authorized disease-modifying treatments, the field of pain management for OA patients is developing [7].

Non-steroidal anti-inflammatory medicines (NSAIDs) are the most frequently used drugs in the treatment of OA in order to relieve pain, although their usage is frequently limited due to their negative effects. Traditionally, the care of OA has been limited to symptom relief [8].

Known as disease modifying OA medicines (DMOADs), chondroprotective medications like glucosamine and chondroitin sulphate have mainly targeted structural alterations of disease by attempting to either inhibit chondro-degrading factors or boost cartilage synthesis [9].

However, new therapies that target inflammation, chondro-metabolism, and subchondral remodeling of bones, such as TNF α inhibitors and IL1 inhibitors, may slow the disease's structural progression and cause remission. These medicines hold promise for improving the management of OA in the future [8].

Additionally, it has been established that vitamin D affects bone and cartilage biologically. It is known to prevent bone loss or to improve bone mass. Vitamin D insufficiency has been linked in studies to an increased the opportunities of the advancement of OA. Numerous studies have demonstrated that vitamin D supplements can help OA patients with improvement of their knee pain and function [10].

According to national and international OA guidelines, patients with hip and knee OA should receive conservative non-pharmacological care as their first line of treatment, which includes physical therapy, patient education, and weight loss [11].

So, our study aimed to compare between the effect of medical treatment alone and medical treatment with physiotherapy on the serum levels of pro-inflammatory cytokines and vitamin D, which can help to improve symptoms and functions of the joints in osteoarthritis patients.

# 2. METHODS

### 2.1. Subject:

This study was done on 200 patients attending the outpatient clinic of Rheumatology and Rehabilitation departments, El Sahel teaching Hospital. Our patients were diagnosed with

osteoarthritis based on history, clinical examination and investigations. The patients who have advanced osteoarthritis were excluded from the study based on x-ray findings. The nature of our study was explained to all participants. All patients gave their informed consent prior to their inclusion in the study.

**2.2. Methods**:

Full history-taking and clinical examination, and radiographic imaging for the knee joints (the most commonly involved joints in osteoarthritis) was performed for all the patients.

Laboratory investigations were carried out for all our patients, including complete blood count (CBC), lipid profile, in addition to assessment of the serum levels of pro-inflammatory cytokines (IL6 and TNF-α) and vitamin D.

All laboratory investigations were done by withdrawing 10 cm of patient's venous blood before and after treatment.

Our patients were divided into two groups, **group 1** includes 100 patients who received medical treatment only, **group 2** includes 100 patients who received medical treatment and physiotherapy, and we compared the levels of pro-inflammatory cytokines in the two groups at the beginning of the study and then after two months of treatment.

Our patients received medical treatment in the form of analgesics, NSAIDs, chondroprotective drugs ± steroid injection as follow:
1) Chondroprotectives: Glucosamine sulfate 1500 mg/ day + Chondroitin sulfate 1200mg/ day
2) Acetaminophen 500 mg: two tabs twice daily on need (PRN)
3) NSAID: Etoricoxib 90 mg / day on need (PRN)
4) topical NSAID 3 times daily
5) intra articular steroid injection if needed using 1 amp of depomedrol or betamethadone

Physiotherapy program which was performed to (group 2) patients in physiotherapy department in El Sahel teaching hospital (three sessions per week) included the following:
1] Management of pain by specific techniques and treatments such as:
a) Heat and Ice packs or cryotherapy device to relax tense and tired muscles
b) TENS (transcutaneous electrical nerve stimulation)
c) Electrotherapy techniques such as: ultrasound waves and low-level laser
d) Manipulation to decrease pain and stiffness, ease muscular tension, and increase a joint's range of motion.
e) ± Splints to support swollen or painful joints
2] A program of specific graded exercises including: (Strengthening, Stretching, general fitness and Proprioceptive) to increase mobility, strength, flexibility, and fitness that can be maintained at home.

**2.3. Data Analysis:**

The findings were gathered, tallied, and subjected to statistical analysis. Version 15 of the Statistical Package for Social Science (SPSS) software was utilized to analyze the data. For quantitative variables, the mean ± standard deviation (mean± SD) was used to describe the data; for categorical variables, the numbers and percentages were used. The difference between the two groups is compared using the student's-t test. When comparing quantitative data, the chi-square test is employed. The associations between the parameters under study are examined using Pearson's correlation. It is deemed statistically significant when the P-value is less than 0.05.

Materials and Methods should be described with sufficient details to allow others to replicate and build on published results. Please note that publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

## 3. RESULTS

3.1. **Demographic and clinical data of studied population:**

As shown in table 1 there was no significant difference between the studied groups regarding **demographic, clinical and laboratory data at the beginning of the study. While** as shown **in table 2** there was a significant difference between the studied groups regarding BMI, Systolic and Diastolic BP, hemoglobin concentration, WBCs, cholesterol and TG levels after treatment.

**Table 1.** Baseline characteristics of studied population before treatment

| | **Osteoarthritis with medical treatment group** | **Osteoarthritis with medical and physical therapy group** | ***P value*** |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | |
| **Age (Years)** | 56.27 ± 5.67 | 55.49 ± 6.64 | 0.36 |
| **Sex N (%)** | | | |
| **Male** | 37(44.6) | 46(55.4) | 0.38 |
| **Female** | 63(50.8) | 61(49.2) | |
| | 32.81 ±5.76 | 31.70 ±6.42 | |
| **Systolic BP (mm Hg)** | 120.7 ± 12.11 | 117.33 ± 10.22 | 0.34 |
| **Diastolic BP (mm Hg)** | 74.55 ± 11.22 | 73.44 ± 10.21 | 0.67 |
| **Hb (g/dL)** | 11.45 ± 1.55 | 11.22 ± 1.77 | 0.43 |
| **WBC/ µL** | 11005 ± 33.89 | 444.22 ± 114500.55 | 0.56 |
| **Cholesterol (mg/ dL)** | 200.43 ± 39.61 | 202.33 ± 35.77 | 0.75 |
| **TG (mg/ dL)** | 196.34 ± 27.55 | 200.47 ± 25.52 | 0.39 |

**Table 2.** Characteristics of studied population after treatment

| | **Osteoarthritis with medical treatment** | **Osteoarthritis with medical and physical therapy** | ***P value*** |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | |
| **BMI (Kg/ m$^2$)** | 32.3 ± 3 | 30.59 ± 2.99 | 0.0001** |
| **Systolic BP (mm Hg)** | 122.2 ± 14.64 | 114.56 ± 9.75 | 0.0001** |
| **Diastolic BP (mm Hg)** | 73.74 ± 10.72 | 70.86 ± 9.29 | 0.04* |
| **Hb (g/dL)** | 11.49 ± 1.25 | 10.9 ± 1.24 | 0.0001** |
| **WBC/ µL** | 10008 ± 3215.89 (4500- 17000) | 732.67 ± 4405.55 (700 - 29000) | 0.0001** |
| **Cholesterol (mg/ dL)** | 172.78 ± 41.01 (87- 280) | 148.12 ± 18.31 (115 - 203) | 0.0001** |
| **TG (mg/ dL)** | 189.77 ± 24.76 (120- 270) | 147.77 ± 23.33 (121 - 220) | 0.0001** |

** Highly significant done by student t test, chi square and exact fisher test

### 3.2. Baseline serum level of inflammatory markers and vitamin D:

As shown in (table 3) there was no significant difference in the serum levels of vit D, IL6 and TNF-α between two groups at the beginning of the study.

**Table 3.** Baseline serum level of inflammatory markers and vitamin D in the studied groups

| | **Osteoarthritis with medical treatment group** | **Osteoarthritis with medical and physical therapy group** | **P value** |
|---|---|---|---|
| | **Mean ± SD** | **Mean ± SD** | |
| **Vit D** | 30.21±8.7 | 30.65±10.4 | 0.746 |
| **IL 6** | 29.5 ±8.5 | 28.45±9.83 | 0.420 |
| **TNF alpha** | 32.1±11.3 | 31.49±12.35 | 0.717 |

** Highly significant done by paired t test

### 3.3. Effect of medical treatment on serum level of inflammatory markers and vitamin D:

As shown in (table 4) there was a significant increase in the serum level of vit D (*P value* = 0.0001), and a significant decrease in the serum levels of both IL6 and TNF-α (*P value* = 0.0001) in Osteoarthritis patients before and after receiving medical treatment alone (Group 1).

**Table 4.** Changes in serum level of inflammatory markers and vitamin D before and after medical treatment only

| | Osteoarthritis with medical treatment only | | P value |
|---|---|---|---|
| | Mean ± SD before treatment | Mean ± SD after treatment | |
| **Vit D** | 30.21±8.7 | 37±9.1 | 0.0001** |
| **IL 6** | 29.5 ±8.5 | 25.2±7.8 | 0.0001** |
| **TNF alpha** | 32.1±11.3 | 28.1±10.2 | 0.0001** |

** Highly significant done by paired t test

### 3.4. Effect of combined medical treatment and physiotherapy on serum level of inflammatory markers and vitamin D:

As shown in (table 5) there was a significant increase in the serum level of vit D (*P value* = 0.0001), and a significant decrease in the serum levels of both IL6 and TNF-α (*P value* = 0.0001) in Osteoarthritis patients before and after receiving medical treatment combined with physiotherapy (Group 2).

**Table 5.** Changes in serum levels of inflammatory markers and vitamin D before and after medical treatment and physiotherapy

| | Osteoarthritis with medical treatment and physiotherapy | | P value |
|---|---|---|---|
| | Mean ± SD before treatment | Mean ± SD after treatment | |
| **Vit D** | 30.65±10.4 | 42.57±10.49 | 0.0001** |
| **IL 6** | 28.45±9.83 | 20.31 ±8.27 | 0.0001** |
| **TNF alpha** | 31.49±12.35 | 22.36 ±9.92 | 0.0001** |

** Highly significant done by paired t test

### 3.5. Comparison between serum levels of inflammatory markers and vitamin D in the studied group after treatment:

Interestingly, there was a significant difference between the two groups regarding the serum level of vitamin D and proinflammatory cytokines IL6 and TNF-α (*P value* = 0.0001) after treatment as shown in (table 6).

**Table 6**. Comparison between serum levels of inflammatory markers and vitamin D in the studied group after treatment:

| | Osteoarthritis with medical treatment group | Osteoarthritis with medical and physical therapy group | P value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| **Vit D** | 37±9.1 | 42.57±10.49 | 0.0001** |
| **IL 6** | 25.2±7.8 | 20.31 ±8.27 | 0.0001** |
| **TNF alpha** | 28.1±10.2 | 22.36 ±9.92 | 0.0001** |

## 4- DISCUSSION:

Osteoarthritis (OA) is recognized as a progressive condition that causes the breakdown of cartilage in synovial joints, often accompanied by some level of inflammation. Since no treatments exist to modify the course of the disease, current guidelines prioritize managing symptoms to enhance patient's quality of life [12].

Obesity is associated with the incidence and progression of OA. Weight loss in OA can impart clinically significant improvements in pain and delay progression of joint structural damage [13]. It exerts its effects both directly and indirectly through various modifiable risk factors associated with OA-related pain. Adipose tissue dysfunction is highly involved in OA-related pain through local and systemic inflammation, immune dysfunction, and the production of pro-inflammatory cytokines and adipokines. Adipose tissue dysfunction is intricately connected with metabolic syndrome, which independently exerts specific effects on OA-related pain, distinct from its association with BMI [14]

Rheumatoid arthritis (RA) is associated with an abnormal lipoprotein pattern. Most treatments for RA tend to improve the atherogenic index (total/HDL cholesterol ratio). The improvement in

the lipoprotein profile in RA appears to be associated with suppression of inflammation[15].

Cholesterol accumulates in chondrocytes during OA progression, and accumulated cholesterol leads to deterioration of mitochondrial activity or transformation into oxysterols that activate nuclear receptor Rora. Activated Rora induces cartilage-degrading enzymes, in turn promoting OA development. Accordingly, novel therapeutic strategies involving modulation of serum cholesterol or intracellular cholesterol levels in chondrocytes may have potential clinical efficacy against OA [16].

One important aspect affecting the progression and severity of OA symptoms is inflammation [17]. Various inflammatory molecules, such as pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6, play a central role in the disease's pathophysiology. Among these, TNF-α and IL-1β are key contributors to the degradation of cartilage macromolecules [18].

Pro-inflammatory cytokines drive condro-degradation and intensify pain, whereas anti-inflammatory cytokines like IL-10 and TGF-β play a vital role in repairing tissue and alleviating inflammation [17.]

In the deeper layers of cartilage, where nutrients have restricted access, chondrocytes can shift to a secretory phenotype, leading to the release of reactive oxygen species (ROS) and inflammatory cytokines like TNF-α, IL-6, and IL-1. These substances serve as crucial to the cartilage matrix's breakdown [19].

Existing treatment methods, including the use of medications such as analgesics, NSAIDs, corticosteroids, and opioids, primarily focus on alleviating symptoms. However, they provide minimal options for preventing the advancement of the disease [20].

Comparing medical treatment alone with a combination of medical treatment and physiotherapy can offer valuable perspectives on the optimal strategies for improving OA symptoms and enhancing joint functionality.

Pain is a prominent symptom of OA, and a common misunderstanding among individuals with OA is the belief that engaging in exercise might worsen pain or cause additional harm to their joints [21]. A single exercise session, regardless of its kind or intensity, does not, however, exacerbate pain in people with OA, according to [22].

Modern sedentary lifestyles, especially those linked to inadequate nutrient supply in thicker cartilage areas like the knee and hip joints, can have significant implications [19]

Our findings demonstrated that combining medical treatment with physiotherapy successfully regulated the inflammatory mechanisms in OA, leading to a reduction in critical inflammatory markers. Additionally, this approach may have helped in decelerating disease progression, as pro-inflammatory cytokines are central to this process.

According to *Sun et. al.* [18], NSAIDs like ibuprofen and corticosteroids like prednisone and betamethasone reduced the expression of IL-6 and IL-8 and prevented the STAT3 and NF-κB signaling pathways from being activated.

In addition, TNF-α can stimulate the release of IL-6, IL-8, and IL-10. Moreover, IL-6 has the ability to trigger the synthesis of tissue inhibitors of metalloproteinases [18].

Products of matrix degradation, such as cartilage oligomeric matrix protein (COMP) and fibronectin proteolytic fragments (FN-fs), can trigger feedback loops to cause mild inflammation. This highlights the potential role of chondroprotective agents in breaking this cycle. Glucosamine, in particular, has been extensively researched for its ability to reduce catabolic activity and promote anabolic processes [23].

By reducing the expression of matrix metalloproteinases and pro-inflammatory cytokines, it has been shown to increase the synthesis of proteoglycans, including hyaluronic acid and sulfated glycosaminoglycans, while halting their enzymatic degradation [20], It showed that in cultured chondrocytes, glucosamine sulfate efficiently inhibits IL-1β-induced gene expression and reduces the generation of pro-inflammatory cytokines [24].

NSAIDs have an impact on articular cartilage degradation. Although the median meniscus was destabilized to cause OA, clinical trials have shown limited long-term joint protection, particularly across a range of patient populations [25].

Aerobic/endurance and strength/resistance training are two exercise categories that are generally beneficial despite the diverse diseases. They may enhance muscle strength and functional results as well as secondary complaints like tiredness and discomfort that arise from muscle loss. The majority of exercise therapy are well tolerated and safe. For patients with myopathy, regular neuromuscular treatment should include exercise prescriptions [26].

Physical activity and circadian rhythms are essential for controlling cartilage metabolism and joint health, which lays the groundwork for creative methods of maximizing chondroprotective treatments [27].

Anabolic and catabolic activity in cartilage fluctuates rhythmically, regulated by external factors such as physical stress as well as endogenous biological clocks [27]. These cycles create important windows for intervention in therapy during which results can be greatly improved by coordinating the time of medication administration and focused exercise regimens with the cartilage's basic rhythms [28] .

Additionally, new data suggests that diffusion barriers including synovial fluid and the extracellular matrix may restrict the bioavailability of popular chondroprotective drugs in cartilage tissue [27].

Exercise causes a brief increase in inflammatory cytokines, which may be accompanied with pain in the muscles after the workout. After stopping activity, inflammatory cytokine levels usually drop within a few hours, and muscular discomfort usually goes away 24 to 72 hours later [22] Where IL-6, which is well-known for its pro-inflammatory properties, is a key player in the pathophysiology of OA [29].

Additionally, it is believed that exercise-induced elevations in circulating IL-6 contribute significantly to energy production by promoting lipolysis and glucose absorption [30]. Consequently, increased IL-6 after exercise in RA patients may not be regarded as an adverse inflammatory reaction [31].

The benefits of coordinated treatments are further supported by joint mobility, which encourages the synthesis of synovial fluid elements like hyaluronic acid and makes it easier for nutrients and medications to reach the cartilage [28] .

Frequent exercise has been shown to enhance joint wellness by maximizing the circadian rhythm-regulated homeostatic processes in cartilage tissue. Regular exercise like this promotes metabolic synchronization, enhances mitochondrial performance, lowers oxidative stress, and ultimately maintains cartilage integrity and delays deterioration [32]. During cycling activity, mechanical joint movement guarantees constant synovial fluid agitation, creating a well-agitated environment that facilitates drug absorption across cartilage in articular joints and lessens coatings of static fluid [33].

Arino et al., shown the transcriptome alterations that take place in the cartilage and synovium after both one-time and recurrent mechanical stress, including downregulation of chondrogenic genes in the cartilage and persistent inflammation in both tissues [33] .

Long-term immobilization due to disease, trauma, resting in bed or being in microgravity can cause alterations in tissue biology and structure in the synovial joints' articular cartilage, which can result in cartilage atrophy. Mechanical load is necessary for the health of cartilage [34]. Poor physical performance in the elderly has been linked to vitamin D insufficiency, and 63% of patients with primary knee OA had low vitamin D status. Lower 25-hydroxyvitamin D levels were thereby linked to worse quadriceps function, higher radiographic OA development, and increased knee discomfort [35]. Regular exercise changed the gene expression of vitamin D's receptor and activating enzyme in muscle tissue, as well as serum vitamin D levels. These alterations were connected to muscular lipid metabolism, physical health, and signs of disease [36]. When middle-aged women with vitamin D deficiency engage in resistance training, their insulin resistance and vitamin D levels significantly improve [37]. Serum levels of TNF-α and IL-6 are elevated, hip and knee osteoarthritis is more severe, and there is more pain and functional impairment when vitamin D levels are lower [38].

## 5. CONCLUSIONS

Medical therapy by itself can lessen pain and inflammation, but when combined with physical therapy, the cytokine profile becomes more balanced, encouraging joint repair and improved functional results. In terms of symptom relief, preserving joint function, and possibly delaying the progression of OA, this combination works better. Furthermore, we came to the conclusion that OA's underlying inflammatory process could be better modulated by physical activity with medical therapy (Figure 1).

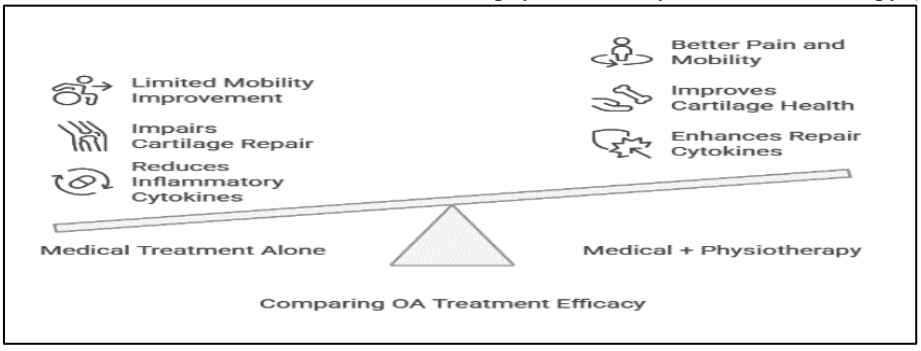


**Figure 1.** Comparing OA Treatment efficacy.

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**Conflicts of Interest:** The authors declare no conflict of interest.

**Ethical Statement:** The study obtained an approval from ethical committee of organization of teaching hospitals and institutes (No. HS000128, Date: 01-05-2024), and a written informed consent from each patient participating in the research. Any medical problems will be referred to the consultant accordingly

**Author Contribution: Ghada M. Gouda:** Diagnosis of cases, follow-up treatment and physical therapy**. Heba A. Abdelmonem:** Statical analysis of the result. **Amal A. Mohamed:** Conceptualization, Supervision of experimental design and reviewing the manuscript. **Sara M. Sayed & Abrar G. Hassan:** carried out the practical work & wrote the manuscript**. Nesreen H. Mahmoud**: sample collection & sharing in practical work. **Mona A. Abdulmohsen:** follow-up treatment and physical therapy. All authors provided critical feedback and helped shape the research, analysis and manuscript.

**List of abbreviation:** OA: osteoarthritis; NF-κB: nuclear factor-kB; IL: Interleukin; NSAIDs: Non-steroidal anti-inflammatory medicines; DMOADs: Disease modifying OA medicines; TENS: Transcutaneous electrical nerve stimulation; RA: Rheumatoid arthritis; ROS: reactive oxygen species; COMP: cartilage oligomeric matrix protein; FN-fs: fibronectin proteolytic fragments.

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