OBESITY ASSOCIATED OSTEOARTHRITIS OVERVIEW OF CURRENT PERSPECTIVES ON PREVENTION AND TREATMENT

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Abstract

Obesity associated osteoarthritis represents a significant risk factor of worldwide. While overload on the weight-bearing joints has long been considered the explanation for the connection between obesity and OA, epidemiological surveys have established a definite relationship between the severities of knee or hip OA and a heightened body mass index as well as some relief from pain and disability after weight loss. Inflammation has been obtained a significant correlation with obesity. Adipose tissues are significant in that context as they are the main sources of cytokines, chemokines, and metabolically active mediators called adipokines. Osteoarthritis has yet, no therapies approved by regulatory authorities. While weight loss produces dramatic improvements in the symptoms of mechanical function and metabolic health in obesity-related osteoarthritis, cartilage and anti-fibrotic approaches are becoming increasingly likely. Future therapeutic options are expected to include personalized treatment strategies accounting for the potential introduction of pharmaceutical adaption targeting specific molecules involved in the pathogenesis of obesity-related osteoarthritis.

Keyword: Adipokines, Body mass index, Cartilage, Chemokines, Cytokines, Inflammation, Osteoarthritis.

1. Introduction

Obesity is a rising global health Problem. The World Health Organization reported that prevalence has almost tripled since 1975, and it was predict to affect more than 650 million people worldwide[1, 2]. Obesity is one of the leading risk factors for osteoarthritis (OA). For many years, the connection between obesity and Osteoarthritis was believed to be simply due to overload on weight-bearing joints. However, population-based studies have shown a consistent association between increasing severity of Osteoarthritis and an increasing body mass index [3]. Obesity is recognized as the most significant risk factor for the development and progression of osteoarthritis (OA) in both weight-bearing joints and non-weight-bearing joints. A common trait among patients with OA and obesity is chronic low-grade inflammation, (also referred to as meta-inflammation)[4]. Studies have suggested that obesity-related Osteoarthritis represents a distinct Osteoarthritis phenotype that has obesity-related features. Some of the features are increased macrophage infiltration in adipose tissue and abnormal production of inflammatory cytokines throughout the body, which are consistent with low-grade chronic inflammation or metabolic induced inflammation mediated by the innate immune system [5].

The first signs of osteoarthritis (OA) may be abnormal metabolism, followed by anatomical and physiological abnormalities like osteophyte formation, cartilage degradation, bone restructuring, joint inflammation, and loss of joint function. OARSI defines OA as a joint disorder caused by cell stress and extracellular matrix (ECM) degradation, triggered by micro- and macro-injury, which sets off maladaptive repair responses within the pro-inflammatory pathways of innate immunity. In obese Osteoarthritis patients, systemic alterations may be reflected in the local inflammatory processes within the joint. The existence of macrophage-associated synovitis, a new actor in the pathophysiology of Osteoarthritis, is responsible for the clinical manifestations of swelling, pain, and stiffness. In addition to chronic inflammation, obesity-induced Osteoarthritis is caused by aberrant mechanical strain on weight-bearing joints, which results from an increase in body weight[6].
In this review, discussion over how obesity-induced Osteoarthritis involves both localized and systemic inflammation, as well as how changed mechanical loading affects pathological alterations in the synovial joint. Additionally, we discuss the main obstacles of cell-based treatments for Osteoarthritis and look at the current approaches in cartilage tissue engineering. We also offer illustrations of creative approaches and viable plans to address the difficulties in treating Osteoarthritis brought on by obesity.

2. Epidemiology

The World Health Organization (WHO) has established a number of weight classifications based on Body Mass Index (BMI), such as obese(BMI > 30 kg/m2) and overweight (BMI > 25 kg/m2)[7].

Table 1: Represented as body mass index (BMI) in different classes which include as class I to class III.

Class I	Obesity (BMI 30-34.99 kg/m^2)
Class II	Obesity(BMI 35-39.99kg/m^2)
Class III	Morbidly obese (Defined as ≥40 kg/m^2)

According to the prediction, 36% of women and 47% of men in the UK between the ages of 21 and 60 would be obese by 2025. Predictions worsen by 2050, when 25% of youngsters under sixteen and 60% of adult men and women are expected to be obese. Obesity is linked to higher healthcare costs in addition to the additional health risks to the individual, such as chronic conditions like diabetes, heart disease, high blood pressure, osteoarthritis, rheumatoid arthritis and elevated cholesterol. It is estimated that obese patients have 27% higher outpatient and 46% higher inpatient costs [8, 9].

A progressive, complex condition, knee OA is linked to increased patient morbidity, decreased mobility, and persistent pain. Knee OA is responsible for about four out of five cases of OA worldwide, and its prevalence rises with age and obesity. Due to the influence of geographic location, income, development, and other socioeconomic factors, incidence and prevalence differ significantly between nations; in 2020, they were expected to be approximately 86.7 million and 654.1 million worldwide, respectively[10].

3. Pathphysiology

Obesity-related Osteoarthritis is probably multi-factorial in its Pathophysiology. It is believed that structural joint deterioration is caused by both mechanical reasons, involving decreased muscular strength, higher stresses around the joint, and changed biomechanics during daily tasks as well as metabolic variables. Because obesity raises the incidence of osteoarthritis in non-weight-bearing joints like the hands and leg [11].

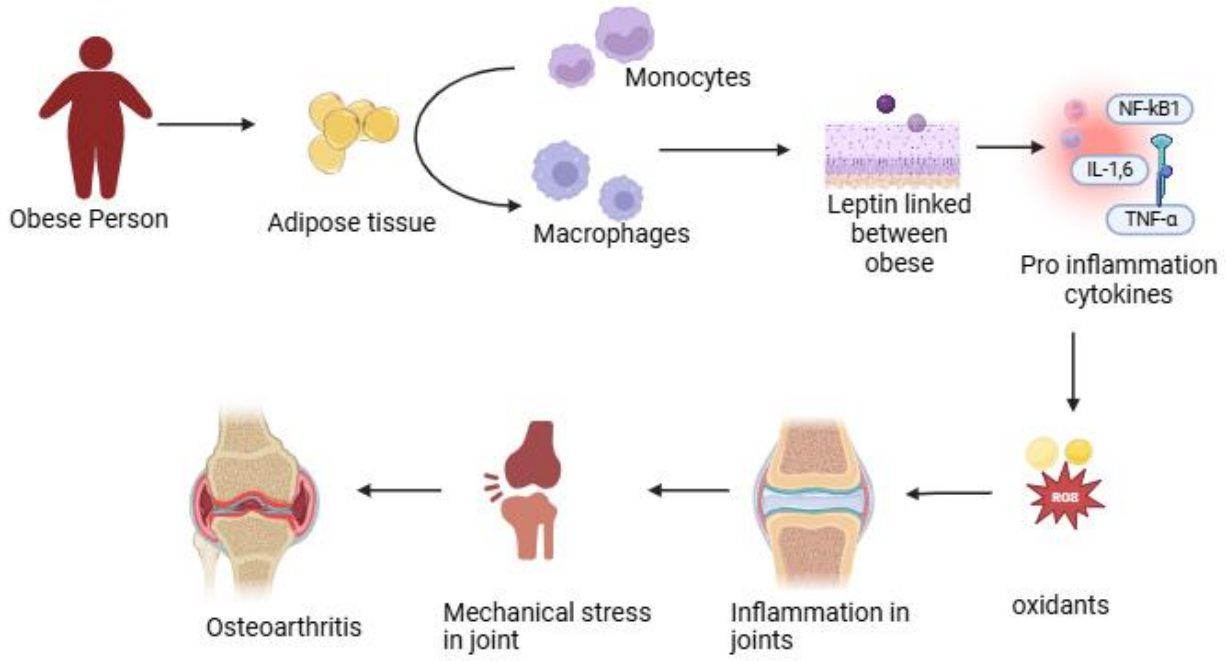

Fig 1: Pathphysiology of obesity associated osteoarthritis: Interlink between obesity and the development of osteoarthritis. Excess adipose tissue in obese individuals recruits monocytes, activating macrophages and increasing leptin production. Leptin triggers pro-inflammatory cytokines (IL-1, TNF-α, NF-kB) and oxidants, leading to joint inflammation. Inflammation combined with mechanical stress on joints results in cartilage damage and osteoarthritis.

Obesity is a low-grade inflammatory condition that impacts various organ systems, including joints. Abnormal adipokine expression, particularly leptin and adiponectin, is believed to cause joint tissue destruction and remodeling. Obese individuals may have higher levels of leptin and adiponectin, which may contribute to osteoarthritis. The pathophysiology of primary osteoarthritis in obese individuals may start with adipose tissue expansion, leading to increased synthesis of endocrine factors like leptin. Obese individuals may also have altered cartilage characteristics due to the systemic inflammatory effect of excess adipose tissue [12, 13]

The two adipokines that are most often generated are leptin and adiponectin, and chondrocytes express their receptors subchrondral osteoblasts and synoviocytes [14]. Monocytes are circulating into macrophages, particularly inflammation. It has been discovered that leptin increases the synthesis of pro-inflammatory cytokines and degradative enzymes such nitric oxide and matrix metalloproteinases (MMPs). Because obesity may create a biochemical environment that makes it difficult for chondrocytes to adapt to such challenges, levels of adipokines in obese individuals may be especially significant [15,16].
Adiponectin's significance in joint illness is less well understood, despite its pro- and anti-inflammatory properties. Qualities were reported, in contrast to its anti-inflammatory actions on the system. In a recent study, obese individuals with Osteoarthritis who experienced

significant weight loss showed elevated levels of adiponectin and lower levels of leptin in their blood [17].

The pathophysiology of primary Osteoarthritis in obese individuals may start with adipose tissue expansion, which may result in increased synthesis of endocrine factors like leptin that act on other tissues, and the growth and changes in these tissues will give rise to the alterations seen in Osteoarthritis. Obese individuals may also have altered cartilage characteristics due to the systemic inflammatory effect of the excess adipose tissue[18].

4. Risk factor include obesity associated osteoarthritis

Elderly persons who find themselves obese in middle age are in much higher danger of having, later in life, osteoarthritis forming in the knee. Does a higher weight at a younger age predispose to a higher chance of the knee having such problems[19, 20].The relationship of body weight to later hip osteoarthritis has not been investigated when specifically focusing on predictable studies. Indeed, if indeed development of osteoarthritis in a weight-bearing joint is linked to cumulative stress upon it, one might speculate that heavy weight acquired at young ages might be considered more dangerous than weight gained later in life. Obesity has been found to carry an increased risk specifically in relation to incident tibiofemoral knee OA. There is some conflicting evidence regarding the association between body mass index and the progression of osteoarthritis associated with knee symptoms[21]. Although this relationship is not corroborated by other studies, high levels of BMI are related to an enhanced risk for the progression of osteoarthritis in the knee. The association, however, is such that in most cases it will be intermediate between BMI and the risk for progressive osteoarthritis, as opposed to the risk for incident disease.

Metabolic syndrome is generally considered a combination of being overweight and having hypertension, dyslipidemia and impaired glucose tolerance. Knee osteoarthritis and multiple sclerosis share some common risk factors such as age and obesity[22]. Numerous investigators have associated osteoarthritis with various metabolic syndrome components. Lawrence was the first to report diastolic blood pressure as associated with osteoarthritis[23]. A higher body mass index across a Throughout the entire range of values posed an increased risk for incident knee osteoarthritis, and this was the case; Various findings supported the interpretations of raised blood pressure, wherein exposure to high-body mass index poses explanation-oriented risk, which raises knee osteoarthritis risk even below the conventional. From this, it can be inferred that odds of being afflicted with knee osteoarthritis increase progressively with degrees of excess weight, with no observed threshold effect upto any convoy standards of BMI. In multivariate analysis, adjusting for birth year, baseline physical activity, and subsequent lower-extremity injuries, body mass index became a risk factor for knee osteoarthritis in young adults[24, 25].

Generally, risk factors for the development of OA can be divided into person-level factors and joint-level factors [Table 2].

Table2: Some major risk factors for the development of obesity cause osteoarthritis.

PERSONL LEVEL RISK FACTORS	JOINT LEVEL RISK FACTORS
Age	Knee injury
Genetic	Abnormal Mechanical loading
Obesity	Repetitive joint
Gender	Bone deformity
Socioeconomic factors	Muscle weakness
Dietary habits	Joint laxity

4.1 Systemic inflammation of osteoarthritis

According to osteoarthritis, systemic inflammation plays a significant role in obesity-related osteoarthritis. Studies show that weight loss, in particular with gastric bypass surgery, significantly increases physical function, reduces pain, and systemic inflammation positively impacting the cartilage health. The major contributor to this obesity-induced inflammation is the polarization of macrophages to the pro-inflammatory (M1) phenotype, which leads to the production of cytokines including TNF-a, IL-1B, and IL-6. These cytokines induce insulin resistance, lipolysis, and chronic inflammation. The presence of obesity reduces the number of anti-inflammatory (M2) macrophages which possess the ability to participate in tissue repair and resolution of inflammation thus hastening the course of OA. Macrophage recruitment and activation are mediated in obese adipose tissues and synovial joints by chemokines such as CCL2/CCR2 that correlate to the symptoms of osteoarthritis. Furthermore, macrophage-associated proteins (S100A8/S100A9) stimulate the formation of osteophytes, cartilage deterioration, and inflammation. Adipokines such as leptin and adiponectin, which are secreted by adipose tissue, influence the pathophysiology of Osteoarthritis [26].

From among adipokines, leptin is one of the key pro-inflammatory agents heightening osteoarthritis; it also creates inflammation and subsequent breakdown of cartilage. High levels have been associated with increased BMI, osteoarthritis biomarkers, and synovial inflammation. In obese-osteoarthritis models, this leptin played crucial roles, reduced macrophage infiltration and inflammation[27]. On the other hand, adiponectin is an anti-inflammatory adipokine that plays a very versatile role in osteoarthritis. Adiponectin may, through questionable signaling pathways, reduce inflammation as well as prevent the calcification of cartilage; although many studies show their association to pro-inflammatory activities and cartilage degeneration. Because of the interaction between inflammatory agents, cytokines, and adipokines, further investigations are propelled to gain a holistic insight into the dysfunction brought by obesity-induced osteoarthritis[28].

4.2 Inflammation on osteoarthritis

Localized inflammation of the synovial membrane, once thought of as a consequence of cartilage deterioration, recently has been recognized as an important mechanism contributing to the development and progression of Osteoarthritis, more so in obesity-induced Osteoarthritis. Synovitis at baseline is a predictor of the advancement of cartilage in overweight persons while weight gain further worsens Bone marrow lesions, cartilage abnormalities, and synovial inflammation[29]. All these mechanisms are tethered with macrophage activation and during obesity, the synovial macrophages polarize into the M1 phenotype, increasing osteophytes formation, synovitis, and cartilage destruction. Such a relationship between diets containing high amounts of pro-inflammatory fatty acids and the obesity-induced OA would create alterations in bone structure, cartilage destruction, and synovial inflammation. Their depletion establishes the participation of these cells within OA pathology, thus attenuating these other pathological changes. Interaction with M1chondrocytes invokes inflammatory cytokines and cartilage destruction while M2 chondrocytes favor tissue repair. Well-controlled M2 polarization reduces the degree of cartilage injury and synovial thickening suggesting a therapeutic opportunity. Interaction between M1chondrocytes incites inflammation and cartilage destruction[30].

4.3 Excessive and altered mechanical loading

A correlation between obesity and the risk of knee Osteoarthritis was demonstrated by some authors shows the risk of knee Osteoarthritis increased by 35% for every unit increase in body mass index (BMI). Additionally a cohort study revealed that individuals with grade II obesity (BMI > 35 kg/m2) had a 4.7-fold increased risk of developing knee Osteoarthritis in comparison to those of normal weight.[31, 32].

Certain inflammatory pathways, including interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), and nuclear factor-kappa B (NF-κB), may be triggered by joint stress, resulting in irreversible matrix deterioration and apoptosis. By triggering anabolic elements, physiological mechanical stress is essential for healthy cartilage [33],[34].

Adipose tissues are a major source of cytokines, chemokines, and metabolically-active mediators known as "adipokines." Some of these mediators are responsible for systemic low-grade inflammation associated with obesity, which creates an environment that promotes catabolic factors that degrade the joint, while others have been reported to preserve the cartilage integrity and minimize the development of osteophytes[35]. It is surprising to learn that obesity has also been found to be strongly associated with hand and wrist OA, despite the fact that these joints are not weight-bearing, which is why the mechanical loading hypothesis is unable to explain the relationship between obesity and OA in these non weight-bearing joints[36].

5. Mechanism of action

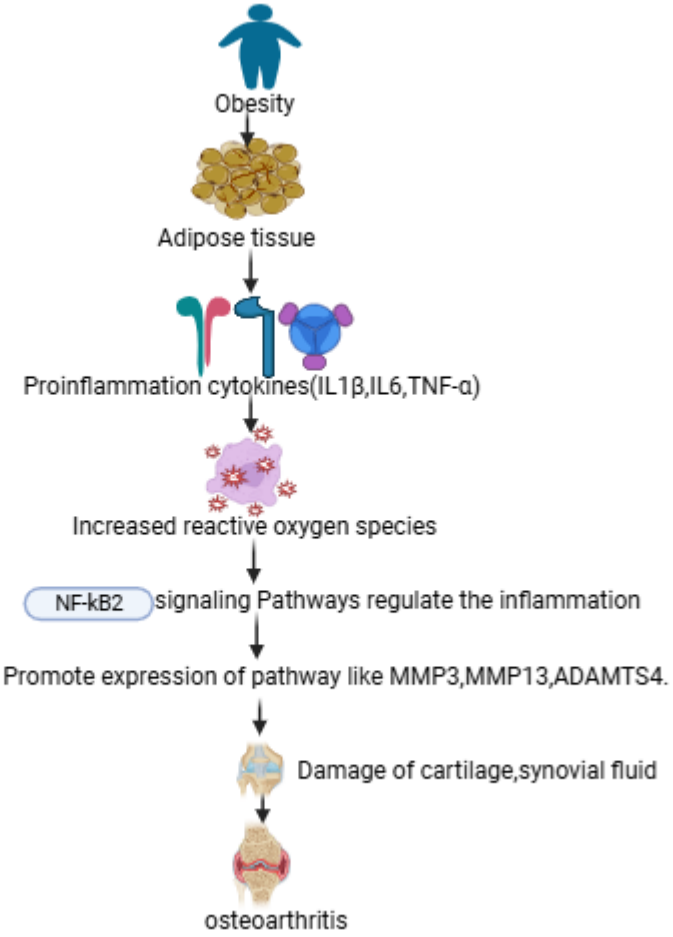

Figure 1: Mechanism of action for obesity associated osteoarthritis: The mechanism linking between obesity to osteoarthritis. In obesity, excess adipose tissue releases pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α which elevate reactive oxygen species levels.ROS and cytokines activate NF-κB2 signaling pathways, regulating inflammation and promoting the expression of cartilage-degrading enzymes like MMP3, MMP13, and ADAMTS4.Finally the progressive damage of cartilage and synovial fluid within the joints, leading to the osteoarthritis.

Low-grade inflammation in adipocytes is caused by the proinflammatory cytokine TNF-α, found in adipose tissues of obese people. Immune cells like macrophages also contribute to low-grade inflammation and oxidative damage. NLRP3, a polyprotein complex, releases proinflammatory cytokines in macrophages. Mature NLRP3 promotes low-grade inflammation in organs, including joints, and the release of cytokines. Knee malalignment, a factor affecting stress distribution at the knee, may contribute to obesity-associated knee OA. Varus malalignment may mediate the relationship between obesity and knee OA by mediating body weight forces. The association between body mass and knee OA severity has not been explored [37-39] .

6. Therapeutic approaches

The safety and efficacy profiles of current Osteoarthritis therapies in clinical development are insufficient for regulatory approval, and total knee arthroplasty is the last resort, exposing a gap in joint-preserving treatments[40].

Cartilage tissue engineering shows promise in treating Osteoarthritis, but obesity-induced Osteoarthritis poses particular difficulties because of coexisting conditions like diabetes and cardiovascular diseases, low-grade inflammation, impaired wound healing, altered joint stability, and even accelerated wear and tear of the prosthetic components, which increases the risk of intra-operative and postoperative hazards.

The obesity-related fibrosis in osteoarthritis leads to worsened outcomes in patients. Repurposing anti-fibrotic drugs or devising new interventions targeting the PI3/AKT/mTOR pathway, TGF-β signaling and pro-inflammatory cytokines may slow the progression of the disease and enhance the quality of life of patients. Emerging therapies directed toward epigenetic modifications or genetic mutations provide opportunities for intervention.

Patients with knee OA are strongly advised to adhere to dietary weight management and this is especially true for cases of obesity-related osteoarthritis. Moreover, symptom and functional improvement improves with the amount of weight loss. Compared to less weight loss, clinical symptoms and mechanical properties were significantly impacted by long-term weight loss of 10–19.9% of baseline body weight. Actually, better clinical and mechanical results are linked to weight loss of at least 5%. Additionally, patients with obesity-related Osteoarthritis who lose weight had improved metabolic abnormalities and traditional cardiovascular risk markers. Weight loss measures are also of special importance in cases of established Osteoarthritis, in order to slow down disease progression.

7. Prevention and treatment

Hypothesize that regular physical activity and weight management may be crucial in preventing early onset of OA or increased risk of the disease. Some advocates suggest a screening process that begins in adolescence, in which family history is reviewed. The lack of effective treatments to prevent OA in younger obese populations is partly due to the difficulties of long-term prospective research and the lack of control in documenting processes that may influence the onset of OA.

There are a number of ways to lose weight, such as bariatric surgery, exercise, nutrition, and medication. A patient who is obese should have their treatment plan customized to suit their circumstances. To reduce discomfort and kinesophobia, innovative staging of therapies for progressive weight loss in OA may be used, depending on the degree of obesity and OA.
In order to cause weight loss, medications can be used either alone or in combination with other drugs like orlistat as treatments for obesity. A gastric and pancreatic lipase inhibitor,

orlistat reduces intestinal fat absorption by about 30% and also 33% of patients who take 120 mg of orlistat three times a day see weight loss of 5% or more, according to a meta-analysis. Sibutramine's effectiveness when used for 6–24 months has been endorsed by writers in a number of studies[41].

Losing weight can reduce the risk of OA. According to estimates, the chance of developing knee OA would drop by more than 50% if a person could reduce their body mass index by 2 units, or roughly 5 kg of weight loss. Furthermore, according to a meta-analysis of observational studies assessing the risk of OA, 30% of symptomatic knee OA and 40% of joint replacements owing to knee OA may be avoided in Scandinavian nations if obesity (defined as a BMI > 30 kg/m2) could be completely prevented[42]. It was found that a significant decrease in systemic low-grade inflammation in obese patients with knee OA after bariatric surgery was clearly associated with a reduction in CRP and IL-6. This, in turn, linked it with pain relief, improved functioning, and decreased cartilage degeneration as suggested by reduced COMP levels. Notably, in contrast with a weight control program, the fat mass reduction and enhanced physical activity seem to associate with relief of symptoms of knee OA.

Obesity remains a growing issue, and osteoarthritis (OA) urgently lacks disease-modifying drugs. Leptin, a cartilage-degrading factor, is a promising target for OA treatment, especially in obese patients. Strategies include leptin inhibition, intra-articular leptin antagonist therapy, and enhancing SOCS-3 expression to mitigate OA progression.

In the treatment of knee OA, aerobic activity and muscle strengthening are commonly advised therapies. These consist of stationary bicycle riding and walking on a treadmill or supervised indoor fitness walking. While dynamic exercise, which combines isokinetic and isotonic training, is based on resistance training targeted at muscle strengthening, isometric exercise entails exercising at specific joint angles[43].

While some oral NSAIDs and intra-articular corticosteroids are well established and commonly prescribed for treating OA of the knee in general, care should be taken to avoid recommending these agents for obesity-associated OA because of the risk of cardiovascular comorbidities. Glucosamine and chondroitin are slow-acting symptomatic medications that may help patients with this disease; certain antioxidants such as ginger extracts and curcumin may also provide some benefits. Given that the topical formulations of NSAIDs have a similar effect on knee pain and are associated with a lower risk of side effects due to their slow absorption into the general circulation, use of these formulations is favored rather than the oral forms.

Injecting CSs and hyaluronic acid intraarticularly is usually thought to be advantageous and to have few negative effects. Intraarticular CS injections of duloxetine may offer temporary pain relief; however, hyaluronic acid administration may have a greater impact on pain reduction over a longer period of time (12 weeks and beyond) and a more favorable safety profile than repeated CS injections.

Finally, in patients with knee OA, which has a significant influence on ambulation, joint stability, and discomfort, devices such tibiofemoral or patellofemoral bracing and gait aids are helpful. It has been demonstrated that foot orthotic devices reduce the need for analgesic drugs while also improving knee pain and stiffness.

These findings results are unless a low-calorie diet and physical exercise targeted at weight loss and reduced adipose tissue deposits remain the cornerstones of therapeutic therapy, any pharmacological interventions in obesity-related knee OA would have a lower success rate [94]. Lastly, anti-obesity medications may help patients with comorbidities and a BMI above 30, but their effectiveness in treating individuals with concurrent OA has not been thoroughly studied, and it is uncertain if adding them would be helpful[44].

7.1 Exercise and Diet: RCTs (randomized control trails) of exercise therapies in the elderly population. RCTs that have been published have looked at weight reduction and functional outcomes following programs of resistance and aerobic exercise, multimodal training with or without calorie restriction, and multimodal exercise programs. Resistance training was incorporated in a number of RCTs. Bodyweight strengthening exercises, resistance training machines, and at-home strengthening exercises are all offered by Resistance exercise. Aerobic exercise usually entails prolonged major muscle action, including walking, stair climbing, stationary cycling, or aerobic swimming.

The benefit of exercise for OA in obese patients is that it can be used to treat the disease and help prevent or delay its onset. Ideally, a well-rounded program to treat OA symptoms would include AX to increase caloric expenditure and RX to strengthen the muscles supporting the joints. Exercise can be used at any stage of the disease to help relieve pain, strengthen the muscles surrounding the arthritis. The benefits of Exercise are useful for OA in obese patients because it can help prevent or delay the onset of the disease and treat it. Ideally, a well-rounded program to treat OA symptoms would include AX to increase caloric expenditure and RX to strengthen the muscles supporting the joints. Exercise can be used at any stage of the disease to help reduce pain, strengthen the muscles surrounding the arthritic joint, and help control or reduce body weight, which is the main modifiable factor underlying OA.

7.2 Bariatric Surgery: Because lifestyle modifications are unpleasant and long-term adherence is usually low, meaningful weight loss is challenging for obese people. If the postoperative guidelines are followed, bariatric surgery can result in significant weight loss.

In morbidly obese individuals, joint pain in the hip, knee, ankle, spine, neck, shoulder, elbow, wrist, and hand, as well as in the knee, ankle, and foot, can be reduced or eliminated. The most frequent postoperative time point was roughly two years, despite methodological discrepancies in the measurement follow-up durations for joint pain within and within studies.

Reductions in BMI values ranged from 6.2-14.7 kg/m2, which meant that, depending on the joint and the research, knee and back pain resolved in 5%–100% of patients while pain

severity decreased in 31%–94% of patients[45]. All latest treatment guidelines now recommend exercise, weight loss, and education.

8. CONCLUSION

Global problems include the rising prevalence of obesity and the advancement of Osteoarthritis. Which are exacerbated by an aging and obese population. Obesity contributes significantly to the onset of osteoarthritis by means of systemic inflammation and mechanical strain. Increased body weight aggravates bone remodeling and cartilage deterioration by causing recurrent stress, aberrant mechanical loading, and joint malalignment. Some the Research has indicated that there is a considerable increase in the likelihood of developing knee OA for every unit increase in body mass index. Adipose tissue is viewed as an active endocrine organ that releases adipokines like leptin and adiponectin as well as pro-inflammatory cytokines. These agents are involved in meta-inflammation, a low-grade chronic inflammation that affects both weight-bearing and non-weight-bearing joints, such as the hands. Joint pain, stiffness, and loss of function are the results of this systemic inflammatory response, which also speeds up cartilage degradation, encourages the growth of osteophytes, and exacerbates synovial inflammation.

Improving patient outcomes requires effective management techniques, such as pharmaceutical therapies, lifestyle changes, and weight loss. To improve therapeutic success, future studies should concentrate on tailored medicines that target inflammatory and metabolic processes. There is promise for better patient outcomes by focusing on exercise and Diet which may help to reduce symptoms and alter the course of the illness.

Author contributions

All authors have contributed equally and substantially.

Funding

No funding.

Acknowledgement

The authors would like to express their sincere gratitude to all the researchers and scholars whose work has contributed to the development of this review. We are particularly thankful to swamy Vivekanandha college of Pharmacy, Head of the department of Pharmacology for their support and guidance throughout the preparation of this manuscript. We also appreciate the constructive feedback from the reviewers, which helped enhance the clarity and quality of this article.

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