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A Current Therapeutic Perspectives for Osteoarthritis.

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ABSTRACT
The information on Osteoarthritis (OA) includes, that is the most common form of arthritis in the world. It is a chronic, degenerative disorder of unknown cause characterized by gradual loss of articular cartilage. It is the most prevalent disease in our society, with a worldwide distribution. Its prevalence after the age of 65 years is about 60% in men and 70% in women. Its diagnosis can be done through the system of pain, functional disability is another key element in osteoarthritis. Osteoarthritis causes changes in mobility and function; Patients frequently experience physical limitations, difficulties with personal care, work ability and even problems with maintaining their household. A number of environmental risk factors, such as obesity, occupation, and trauma is a reason for OA. Non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, corticosteroid injections and tramadol are prescribed to many patients with OA for symptom which is used as a treatment of, but now a days there is availability of novel treatment. The novel drugs include collagen type II, nutraceuticals (such as glucosamine and chondroitin) are commonly used for relieving pain and discomfort. Many studies have shown that UC-II improves joint mobility, flexibility, and comfort by preventing the immune system from attacking and damaging the articular cartilage. On the severe stage OA has to be treated through surgeries.
Keywords – Osteoarthritis, Risk factors, Treatment strategies, Conventional

I. INTRODUCTION

Osteoarthritis (OA), the most common form of arthritis in the world, is thought to afflict 10% of men and 18% of women over the age of 60. In 2017, 303 million people worldwide were affected by the relatively widespread rheumatic musculoskeletal disorder osteoarthritis (OA).It falls under the categories of primary osteoarthritis and secondary osteoarthritis. However, the illness is clinically quite varied and can show as just an asymptomatic accidental finding to a devastating and permanently crippling disorder. OA typically manifests with joint discomfort and loss of function [1, 2].

Clinical symptoms of the illness include joint pain, discomfort, crepitus, stiffness, and movement restriction, along with sporadic effusion and varying degrees of local inflammation. The main risk factor for OA is getting older. There are a number of biological processes that have been postulated to explain how ageing affects the course of OA joint degradation[3].

Any joint can be affected, although the knee, hands, hip, and spine are most frequently affected. OA has a significant effect on both society and the patient, causing pain and disability. Additionally, OA has a significant financial impact on patients as well as society. There are two categories of osteoarthritis. Both localised and generalised primary osteoarthritis are possible; the latter is more frequently seen in postmenopausal women and is accompanied by the formation of Heber den's nodes. Trauma, obesity, Paget's disease, or inflammatory arthritis are some of the underlying causes of secondary osteoarthritis [4, 5].

II. PATHOPHYSIOLOGY

Osteoarthritis is a chronic condition that impairs joint function and causes discomfort. Articular cartilage loss and subchondral bone sclerosis are the disease's major symptoms. Principal matrix degrading enzymes, such as those in the "a disinterring and metalloproteinase with thrombosponding motif" (ADAMTS) family and the MMPs, which break down aggrecan (ADAMTS) and collagen (MMPs), respectively, are responsible for the breakdown of articular cartilage. Higher quantities of cytokines including Tumour Necrosis Factor-alpha (TNF) and IL-1, which can induce and activate these catabolic enzymes, are secreted by OA chondrocytes [6].

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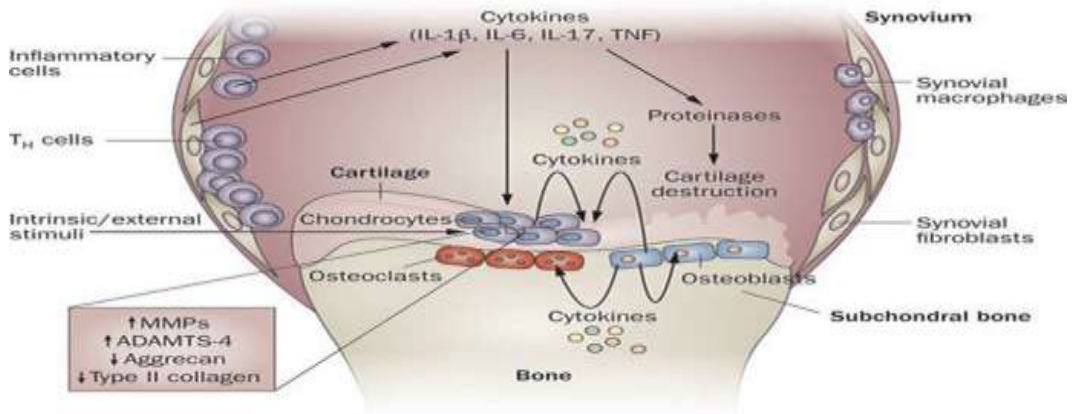

Fig.2.1: Pathophysiological mechanisms underlying OA. The cellular and molecular mechanisms undying OA are complex and involve multiple components. In general, cells in OA joints release increased concentrations of pro inflammatory cytokines resulting in the secretion of proteases from chondrocytes which degrade cartilage.

Uncertainty exists on the importance of joint inflammation in causing tissue breakdown. Human OA is characterised by the infiltration of mononuclear cells into the synovial membrane, and there is strong evidence that disease-related innate immune system activation occurs. When inflammation is present, tissue breakdown will be accelerated and painful disease episodes will result [7].

OA-related pathophysiological processes. The cellular and molecular systems that prevent OA from dying are intricate and comprise numerous parts. In general, cells in OA joints emit higher levels of pro-inflammatory cytokines, which trigger chondrocytes to secrete proteases that break down cartilage [8].

When the joint's natural physiological defences fall short, it becomes unstable. The articular cartilage is destroyed, which makes it less able to transmit heavy loads, more prone to stress, And less able to lessen friction in the joint area. These permanent modifications reduce the joint gap, enabling direct contact between the bone and the opposing bone surface. When articular cartilage wears away, the body develops osteophytes, which are new outgrowths of Bone, and chronic inflammation that causes the release of cytokines and metalloproteinase into the joint [9].

OA is thought to be a metabolically active, dynamic process that involves both the breakdown and restoration of cartilage. There are a variety of biochemical and mechanical disturbances that can start these processes. Loss of proteoglycans and collagen reduces the stiffness of cartilage [10].

The first signs of OA in articular cartilage include a decline in the amount of superficial proteoglycans, deterioration of the collagen fibrils, and an increase in the water content. These changes occur because chondrocytes' capacity for repair is impaired, which also causes a decrease in the concentration of proteoglycans and a decline in collagen fibrillation. This procedure causes cartilage splits that extend all the way to the bone. Because the collagen network in the degraded cartilage cannot regrow, the OA tissue is pushed past the point of no return. Although it has long been believed that the pathophysiology of osteoarthritis is cartilage-driven, recent research indicates that bone and synovial tissue also play a significant part in the disease, and patchy chronic synovitis is a symptom of the condition. Even with mild damage, cartilage heals very slowly, if at all, despite the extended half-life of its collagen [11, 12].

III. DIAGNOSIS

Osteoarthritis can only be clinically diagnosed when the patient displays symptoms, and any intervention seeks to decrease or prevent these symptoms. In reality, many seek care outside of screening or research programmes because of their symptoms [13].

Ethics-acceptable interventions must have a minimal risk profile and demonstrated efficacy when patients have little or no symptoms. Due to the poor correlation between symptoms and structure, treating structural osteoarthritis will not always result in a positive clinical outcome. Therefore, research attempting to improve structural disease in order to treat the initial stages of osteoarthritis must also consider symptoms [14].

Patients with OA typically experience pain as their primary symptom. Daily activities start to be impacted as time goes on as pain and other joint

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problems become less predictable and more constant. In more advanced phases, unpredictable, intense, and severe pain are present together with ongoing dull, aching pain, which makes it difficult to engage in some activities [15].

Osteoarthritis alters mobility and function; patients commonly struggle with physical limits, challenges with personal care, employment capacity, and even difficulty with household maintenance.

Osteoarthritis is typically diagnosed in a clinical context utilising accepted techniques such as Radiographic changes and clinical recommendations, which are used as a "diagnostic reference" [16].

3.1 EXAMINATION FINDINGS

The knee, hip, distal and proximal interphalangeal joints, first trapezia metacarpal (carpometacarpal) joints, first metatarsophalangeal joint, and facet joints of the spine are typical joints affected by OA. Less frequently used joints are the elbow, wrist, shoulder, and ankle.

3.2 Radiography

The knee joint is typically evaluated using the extended-knee radiograph, which is a bilateral antero posterior image acquired while the patient is weight-bearing, with both knees in fullextension [17].

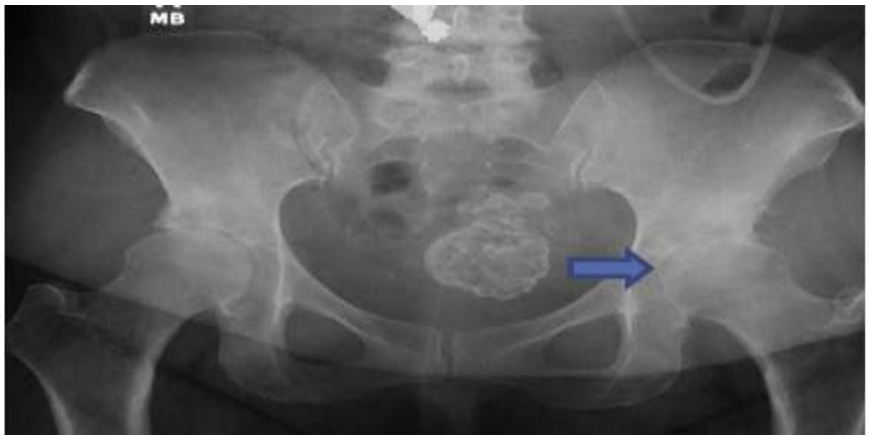

Fig 3.1: Severe left narrowing of the hip joint space (arrow).

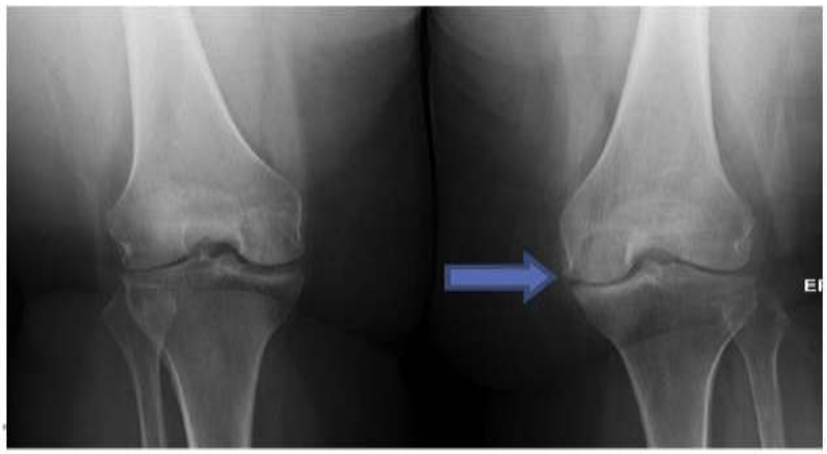

Fig 3.2: Severe narrowing of the medial compartment (arrow).

3.3 MRI

In an MRI, picture contrast is altered to emphasise various tissue types. Proton density (PD), T2-weighted imaging, and 2D or multi-slice T1-weighted imaging are common contrast Techniques. Focused cartilage abnormalities can be assessed using the imaging Techniques spin echo (SE) and fast-spin echo (FSE).

The morphology (volume, area, and thickness) and integrity (quality) of articular cartilage can be objectively and quantitatively assessed using MRI [18, 19].

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3.4 Optical Coherence Tomography (OCT)

By taking cross-sectional Echo graphs of infrared light, OCT captures images of articular cartilage in almost real time. The endoscope must be placed directly on the cartilage for this procedure to be used, hence an arthroscopy is required. OCT has been shown to be sensitive to changes in collagen structural changes caused by acute stress and degeneration as well as changes in cartilage fibres connected to OA [20, 21].

TABLE.3.1 – Diagnostic criteria for Osteoarthritis

Hand (clinical)

Osteoarthritis if 1, 2, 3, 4 or 1, 2, 3, 5 are present:

1 Hand pain, aching, or stiffness for most days of previous month

2 Hard tissue enlargement of two or more of ten selected joints

3 Swelling in two or more metacarpophalangeal joints

4 Hard tissue enlargement of two or more distal interphalangeal joints

5 Deformity of two or more of ten selected hand joints

Hip (clinical and radiographic)

Osteoarthritis if 1, 2, 3 or 1, 2, 4 or 1, 3, 4 are present:

1 Hip pain for most days of previous month

2 Erythrocyte sedimentation rate of less than 20 mm in the first hour

3 Femoral or acetabular osteophytes on radiographs

4 Hip joint space narrowing on radiographs

Knee (clinical)

Osteoarthritis if 1, 2, 3, 4 or 1, 2, 5 or 1, 4, 5 are present:

1 Knee pain for most days of previous month

2 Crepitus on active joint motion

3 Morning stiffness lasting 30 min or less

4 Age 38 years or older 5 Bony enlargement of the knee on examination

Knee (clinical and radiographic)

Osteoarthritis if 1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6 are present:

1 Knee pain for most days of previous month

2 Osteophytes at joint margins on radiographs

3 Synovial fluid typical of osteoarthritis (laboratory)

4 Age 40 years or older

5 Crepitus on active joint motion

6 Morning stiffness lasting 30 min or less

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EPIDEMOLOGY OF OA

Females have a higher frequency and severity of OA than men, and they are more likely to have hand, foot, and knee OA.

One of the most powerful indicators of OA is age. However, the precise mechanism behind the increasing frequency and incidence of OA with age is unknown.

Obesity has become a global issue, resulting in increased morbidity and death. Obesity is one of the most major risk factors for OA in peripheral joints such as the knee and hip, according to a large body of research. Because obesity is becoming more common and is also a risk factor for OA development, it is expected that more people may be impacted by knee OA in the future [22].

The mechanism through which smoking is connected to a decreased risk of OA is unknown, however it may be mediated in part by smokers having a lower BMI than non-smokers.

The osteoarthritis index (WOMAC) scores at Western Ontario and McMaster Universities differed considerably by age, gender, and BMI in an unselected general population sample. When compared to general population norms, these data can be used to measure the pain, stiffness, and function of OA patients before and after therapy [23].

It is possible to predict which OA patients will be more negatively affected by the disease in the future using disease burden predictors to some extent. Age, BMI, the degree of baseline knee discomfort, joint flexibility, and proprioceptive inaccuracy have all been associated with decreased physical function in knee OA after three years, according to The Western Ontario and McMaster Universities Arthritis Index [24].

TREATMENT OF OSTEOARTHRITIS

Self-care and therapy are used in treatment. Medication, physiotherapy, and, in certain cases, surgery can help relieve discomfort and keep joints moving.

A. Conventional treatments for OA

1. Drug therapy

1.1Anti-inflammatory agents with analgesic properties

Many patients with OA are prescribed paracetamol, NSAIDs, corticosteroid injections, and tramadol for symptom relief in clinical practise, which is supported by guidelines.

Acetaminophen is the first-line oral medication in OA, chosen for its efficacy against mild to moderate pain and minimal side effect profile. Cyclooxygenase-2 selective inhibitors have the same effectiveness as nonselective NSAIDS and may have better gastrointestinal side effect profiles, but they may have a higher risk of cardiac consequences like ischemia and myocardial infarction than nonselective NSAIDS [25]. Opiate analgesics are often utilised for analgesia when pain becomes moderate to severe and unresponsive to other medications.According to the literature, topical NSAIDS are more effective than topical capsaicin, salicylates, and analgesics such as menthol, as well as local anaesthetics, despite the fact that all of these agents have been utilised successfully [26].

Acetaminophen (paracetamol) is the first-line therapy for osteoarthritis, whereas non-steroidal anti-inflammatory medications (NSAIDs) such as ibuprofen are used to treat inflammatory arthritis. Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) may be less well tolerated.Topical NSAIDs, on the other hand, may have superior safety profiles than oral NSAIDs. Intra-articular corticosteroid injections may be explored for more severeinstances of osteoarthritis. Oral NSAIDs are recommended for managing pain associated with OA when the response to acetaminophen is insufficient [27, 28].

To limit the risk of related complications such as renal, GI, cardiovascular, or hepatic disorders, the lowest effective dose should be administered for the shortest length of time, and the benefits must exceed the risks. Caution should be used in older persons, people with major comorbidities, and people who are taking other drugs that cause GI difficulties. NSAIDs should be avoided throughout the first and third trimesters of pregnancy. NSAID usage during the first trimester has been linked to an increased chance of miscarriage, but NSAID use during the third trimester has been linked to pre-mature closure of the ductusarteriosus, foetal renal impairment, suppression of platelet aggregation, and delayed labour and delivery. If the potential advantages outweigh the hazards, highly protein bound formulations such as Ibuprofen or naproxen are favoured if administered during breastfeeding[29].

Selective COX-2 inhibitors such as celecoxib (Celebrex) and meloxicam (Mobic) have been shown to reduce pain in patients. Celecoxib and meloxicam, like other NSAIDs, Have box warnings for significant cardiovascular and gastrointestinal consequences [30].

Hyaluronic acid, a key component of joint fluid, is a substrate of glucosamine sulphate (an

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Amino-monosaccharide), glycosaminoglycans, and pro-teoglycans. The most extensive research has been done on glucosamine, chondroitin, and the two in combination. Modest trials have shown some improvement in pain and functional indicators, as well as a decrease in joint-space width loss.Although data remains equivocal, S-Adenosylmethionine (SAMe) has been discovered to have the ability to alleviate pain and increase functioning [31,32].

Doxycycline is also being studied for its potential disease-modifying capabilities as well as its ability to decrease cartilage deterioration. When used for intra-articular injections to treat knee osteoarthritis, hyaluronic acid has varied efficacy [33].

1.2. Opioids

Codeine and oxycodone (Oxecta, Oxycontin, and Roxicodone) are used to treat acute exacerbations of pain and/or moderate to moderately severe pain for brief periods of time. Because of an increased risk of potentially catastrophic or even fatal cardiac rhythm abnormalities, the opioid propoxyphene (Darvon), which was formerly used to treat moderate to moderately severe OA pain, is no longer accessible in the United States [34].

1.3. Naturopathy

Acupuncture is a therapy that is frequently included in the preceding category. Acupuncture has been used in the nonpharmacological treatment of OA in many traditional and modernized forms. Randomized controlled trials comparing acupuncture, sham acupuncture, and regular therapy in patients with OA found a modest pain-relieving impact, but it faded with time and lasted no more than 6 months [35, 36].

1.4. Alternative medicine

More study is needed to evaluate whether transcutaneous electrical nerve stimulation (TENS) for knee osteoarthritis is useful in pain reduction. Although there is preliminary Evidence that pulsed electromagnetic field treatment (PEMFT) improves functionality, there is no proof that it improves pain in osteoarthritis. PEMFT has not been authorized by the FDA for the treatment of arthritis. PEMF devices are officially licensed by Health Canada in Canada to treat pain related with arthritic diseases. Low-level laser treatment may be investigated for the reduction of arthritis-related pain and stiffness [37, 38].

2. Surgical Treatments

Traditional surgical techniques for treating OA include arthroscopic treatments, decompressive procedures, arthrodesis (surgical fusion, as in the case of the carpal bones), osteotomies, and partial or whole joint replacements.

2.1.Arthroscopic Procedures – In arthroscopic operations, joints are irrigated or lavened using regularsalineArthroscopy's effectiveness is still debatable. Debridement is a further aspect of arthroscopic operations that is known to be advantageous when OA is connected to a radiographic finding of an intra-articular loose body. There is limited information on another arthroscopic operation called arthroscopic abrasion of sclerotic bones [39].

2.2.Decompressive Procedures – Pain, paresthesias, and probable sensory and/or motor impairment can result from the impingement of nerves in the spinal canal caused by degeneration and subsequent overgrowth of bone (usually creating spinal stenosis or foraminal stenosis). Interventional pain management treatments or decompressive surgical operations can be utilised to relieve nerve impingement or provide room in the spinal canal in an effort to reduce pain brought on by spinal stenosis [40, 41].

2.3.Arthrodesis- Since contemporary arthroplasty methods have a greater success rate, arthrodesis has largely lost favour for major joints due to its resulting restriction in range of motion, such as in the hips or knees. The treatment of OA in smaller joints, such as those in the hands, foot, and ankles, still involves fusion. Instability caused by multilevel decompressive spine surgery may be corrected by spinal fusion surgery [42].

2.4. Osteotomy-Unicompartmental OA of the medial knee has been successfully treated with osteotomy in younger (about 60 years old) active individuals using the high tibial osteotomy approach. In this treatment, a wedge is removed from the tibia to reduce uneven weight bearing over arthritic joint surfaces in patients with varus deformity of the knees. Osteotomy, nevertheless, could only have transient effects [43].

B. Novel treatment for OA

Recent advances in knowledge of the disease's aetiology have resulted in innovative therapies. By modulating the activities of osteoprotegerin, RANK ligand, and matrix metalloproteinases generated by osteoblasts, strontium ranelate reduces subchondral bone resorption. The fact that strontium boosts proteoglycan production, which stimulates cartilage

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matrix development in vitro, suggests that it may have a direct influence on cartilage [44].

Tanezumab is an immunoglobulin G2 osteoarthritis 13 antibody that is highly selective against NGF. Several trials have indicated that tanezumab improves knee pain, stiffness, and function in people with moderate to severe knee OA when compared to placebo. However, the FDA has placed the medicine on hold due to adverse effects such as osteonecrosis [45].

COLLAGEN TYPE II- A NOVAL DRUG USED IN OA

OA therapy has traditionally comprised on pain relief with joint replacement for end-stage illness [46].

This technique is restricted by poor timing in the early stages of the illness and the load imposed by arthroplastyprocedures. Nutraceuticals (such glucosamine and chondroitin) are frequently used to alleviate pain and discomfort [47].According to current clinical studies and meta-analyses, they have generated only minor-to-moderate symptomatic effectiveness in adults with OA [48].

Type-II collagen is a vital connective tissue in the body, giving flexibility and support to joints [49].

Undenatured type II collagen (UC II) is extracted from the sternum of chickens and has been shown to alleviate pain while also improving joint mobility and flexibility [50, 51].

Tong et al. revealed that UC II might potentially slow the progression of arthritis by significantly decrease inflammatory cytokines [52].

UC-II and its Action Mechanism

Collagens are extracellular matrix molecules that cells utilise for structural integrity as well as a variety of other activities [53].

Several ideas have been proposed to elucidate the specific methods by which collagen products improve articular cartilage health [54].

According to pre-clinical study, UC-II appears to promote joint health through oral tolerance. Oral tolerance is a defence mechanism used by the body to discriminate between harmless molecules (e.g., food proteins, gut microbes) and potentially dangerous external invaders. It occurs in the gut-associated lymphoid tissue (GALT). The GALT is mostly composed of mesenteric lymph nodes and patches of lymphoid tissue (Peyer's patches) next to the small intestine [55].

It converts naive T-cells into Treg cells that preferentially target type II collagen. Treg cells then circulate throughout the body. Treg cells release anti-inflammatory mediators (cytokines) when they detect type II collagen in joint cartilage, such as transforming growth factor-beta (TGF-beta), interleukin 4 (IL-4) and interleukin 10 (IL-10) (IL-10) [56].

This activity aids in the reduction of joint inflammation and the healing of cartilage. Active epitopes in undenatured type II collagen can interact with Peyer's patches and produce oral tolerance. Collagen and proteoglycans are the primary structural components of cartilage tissue in animals (aggrecan) [57].

The fundamental natural ingredients of cartilage and synovial fluid are glucosamine, hyaluronic acid, and chondroitin sulphate. Denatured type II collagen, on the other hand, lacks these critical structural components. Preclinical research supports oral tolerance as the method of action of UC-II® Undenatured type II collagen and confirms that the undenatured form of type II collagen is essential for joint health: Only undenatured type II collagen protected against joint injury in a RA animal model (mouse), an activity linked to oral tolerance. Undenatured type II collagen relieved RA symptoms in a rat model, which was described to oral tolerance and regulating inflammatory pathways.

Treg cells specific for type II collagen released anti-inflammatory cytokines in a cell research, which play a key role in the cells' capacity to establish oral tolerance.

UC-II has been demonstrated in several trials to increase joint mobility, flexibility, and comfort by preventing immune system from attacking and destroying the articular cartilage. [58, 59]

UC-II, Safety, Efficacy, and Adverse Effects

Collagen fibrils, which are predominantly made up of type II collagen, serve as the structural foundation of the cartilage matrix [60].

Although regulatory bodies have typically acknowledged collagen hydro lysate as a harmless food component, it is determined by the enzymatic hydrolysis of collagenous tissues such as bone and cartilage, as well as from animals such as chicken and fish [61].

The important aspect of UC-II is its amino acid profile, which contains high quantities of glycine and proline two critical amino acids for cartilage tissue stability and regeneration.

The tertiary and quaternary glycoprotein integrity of UC-II has been found to be intact, allowing epitope recognition and hypo-responsive immune activation, whereas denatured type II

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collagen has no tertiary or quaternary glycoprotein integrity [62, 63].

A combination of radiography and histology methods revealed that therapy with UC-II reduces the size of the osteophytes and may improve joint mobility and functioning [64].

A transmission electron microscope was used to examine the structural integrity of undenatured type II collagen as an active UC-II sample, while an ELISA was used to measure the quantity of Undenatured type II [65].

IV. CONCLUSION

We have summarised current knowledge about the pathophysiology, diagnosis epidemiology, treatment and management of osteoarthritis.

OA therapy has traditionally comprised on pain relief with joint replacement for end stages replacement. The novel drug like undenatured collagen type II has been found effective in the treatment of osteoarthritis.OA was found to be, that involved both the breakdown and restoration of cartilage. Moreover, along with surgical treatments novel treatment has also found to be more effective.

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