Osteoarthritis: A multi-disciplinary factual review

By

Nowshin Subah
17126051

Department of Mathematics and Natural Sciences
BRAC University
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Nowshin Subah

Student Full Name

Student ID

17126051

Approval

The thesis/project titled “Osteoarthritis: A multi-disciplinary factual review” submitted by

1. Nowshin Subah (17126051)

of Spring’17 of 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the Bachelor of Science on 9th October 17, 2021.

Examining Committee:

Supervisor: (Member)	Akash Ahmed Lecturer, Mathematics and Natural Sciences Department.
Program Coordinator: (Member)	Mahbubul Hasan Siddique Assistant Professor, Mathematics and Natural Sciences Department.
Departmental Head: (Chair)	A F M Yusuf Haider Professor and Chairperson, Mathematics and Natural Sciences Department.

Ethics Statement

All the information used in this paper are cited properly.

Abstract

Osteoarthritis is a complex multimodal disease. It requires the involvement of different discipline of science to better define and explain the pathobiology and also to design the best treatment method reducing drug toxicity and side effects. The purpose of this review is to discuss facts from past to present and also its possible future direction so that the newcomers i.e., scientists or researchers from any discipline can instantly gain of osteoarthritis.

Dedication

Dedicated to

All the Osteo-arthritic patient out there

Fighting to keep up with their daily life

activities every day!

Acknowledgement

I would like to acknowledge my grand-parents and aunt who had long been suffering from Osteo-arthritis. While doing this review, I was pretty amazed by how precisely they self-disciplined their daily life style and food habit to lower their arthritic pain with other medical conditions. I am extremely thankful to my grandparents whose daily life routine made this review topic more sense to me.

I have this immense gratitude for my supervisor, Akash Ahmed, whose patience, motivation, guidance and support have helped me to initiate, construct and to conclude this comprehensive review. I would like to thank Mahbubul Hasan Siddique Sir, for familiarizing me to the world of research and review. I am also thankful to Mahboob Hossain Sir, and his graspable explanation of immunology and physiology.

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Chapter 1

Introduction and literature review

1.1 Background

Osteoarthritis is the most common joint disorder and the most common form of arthritis affecting the elderly population significantly. It was assessed that 303 million were affected globally in 2017 and estimated to increase over time as there is no satisfactory overarching treatment available yet (Kloppenburg & Berenbaum, 2020). Although there is a strong association of osteoarthritis with people aged 50 and above, there are data that suggests 35% of the incidence initiates earlier than 30 years. This indicates that osteoarthritis is no longer a disease of only the elderly people but also concerns people younger in age. Quality of daily life function of this massive population has declined both personally and professionally. Impaired quality of life and socio-economic loss has drew the attention of researchers and experts to state and resolve this issue clearly and effectively (Pizzorno et al., 2016). To do so, at first it is important to set a proper definition to understand how the disease can be prevented, diagnosed and treated effectively. As for osteoarthritis (OA), it has long been considered simply a wearing and tearing off of bone joints due to mechanical stress. Though osteoarthritis is not only wearing and tearing off of bone joints but more than that. It is a complex and multifactorial disease that is not directly linked with any pathogen or harmful chemicals etc. (Schott et al., 2018) (Musumeci et al., 2015). Gradually, in the late nineteenth century and early twentieth century it was argued that OA was a whole joint disease and inflammation triggered its progression. Then OA was assumed to be linked to neurogenic lesion that extended outside bone joint. Now, OA is identified as multi modal disease with inflammation, immune and CNS dysfunction causing joint damage, pain, injury and disability. The history of OA is imperative to know the underlying complexities and

controversial perspective from past to the present. We are greatly indebted to the past physicians and surgeons who took the challenge to think outside the box to demonstrate OA and its multi-dimensional pathobiology (Dobson et al., 2018).

1.2 OA Pathobiology

OA is a chronic joint degenerative disease characterized by degraded articular cartilage, osteophyte formation and joint space narrowing etc. The most affected sites are hands, knees, hip and spine. The signs and symptoms are often associated with inflammation, stiffness and functional loss as the day advances. From epidemiological and medical point of view, OA is mostly mechanical stress induced by genetical or acquired factors which trigger to its severity. However, it is still indistinct if the bone alteration occurs before or after the symptom reflection because of cartilage degradation. Research findings so far shows the possibility that there is an interplay of cartilage and subchondral bone, between bio-molecules, chondrocytes, osteoblasts, osteoclasts and osteocytes whose signaling pathway activates OA progression (Sharma et al., 2013).

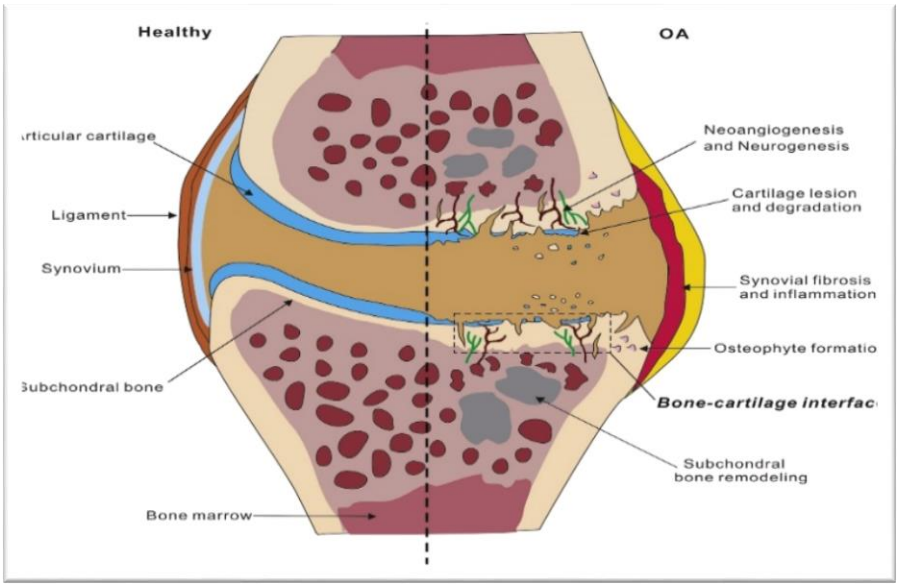


Figure 1: Alteration of healthy to OA bone joint.

Source: (Yuan et al., *2014*)

Cartilage

Articular cartilage is a connective, smooth, lubricative tissue that deals with pressure due to cyclic loading. Chondrocytes, the cells in cartilage synthesize and balance extracellular matrix (ECM) which holds the functional characteristic of cartilage. The ECM of cartilage is basically composed of water, negatively charged proteoglycans and fibrillar to non-fibrillar collagens.

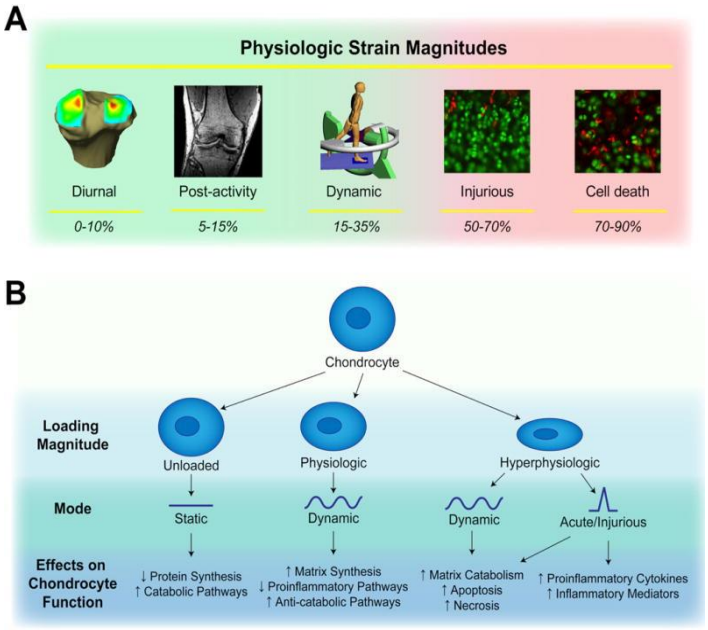


Figure 2: A physiological cyclic load measurement in articular cartilage

This hydrated elastic tissue gets squeezed out each time when cyclically loaded. Due to this visco-elastic property, right after it is loaded, it takes time to return to its initial state. As a result, when cartilage is repetitively loaded without giving it a chance to recover, the cartilage thickness decreases which eventually provokes degradative enzymes and inflammatory mediators (Sanchez-Adams et al., n.d.).

Subchondral bone

Subchondral bone is positioned beneath the calcified cartilage which is highly responsive to cyclic loading stresses and minimizes shear stress from articular cartilage. From subchondral bone, force is then distributed to the trabecular bone and then to the cortical bone. It is the joint shape, ligaments, muscles and tendons that determines force distribution, direction, its responsiveness and balance. The bone joint is adaptable to repetitive loading by bone modeling and bone remodeling. Bone modeling is referred as bone formation and resorption and remodeling is stated as coordination of osteoclast and osteoblast to remove inferior cluster of bone cell with new one. Also to be noted, osteoclast releases proteolytic enzymes which acidifies ECM and osteoblast are responsible for new matrix production (Kwan Tat et al., n.d.). It takes time to replace damaged bone cells, osteoclastic process occurs within weeks on the other hand, osteoblastic process happens within months. This process is termed as osteoporosis, controlled activity is essential to keep this process in order. However, when adaptive capabilities are surpassed along with cartilage degradation; sclerosis, osteoporosis and fibrocartilaginous repair tissues starts to get visible within the osteochondral component. Hence, it reaches the edge to compensate the adaptive process and triggers pathological actions and drives further maladaptation of bone modeling (Trumble et al., 2018).

Interface of cartilage and subchondral bone of OA

The vascular bone to avascular cartilage interface developing microcracks, fissures and alternating signaling pathway is associated with osteophyte formation. This is an important area to understand the pathology of OA. The signaling pathway of cells and molecules are intensely co-related (Fellows et al., 2016). The complex inflammatory diseases like osteo-

arthritis may be resolved with the help of deep phenotyping by molecular, and multi omic techniques including genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics and newly emerging glycomics etc. The morphotypes that are gathered from clinical examinations of patients and their elaborated natural disease history with clinical manifestations are important to classify the condition but not enough to understand the whole pathway. Currently, information reported from OA phenotyping are overlapping with other conditions, it denotes comorbidities that include OA itself with cardiovascular disease, diabetes and other metabolic disorders. This comorbid condition hinders development of druggable pathways of OA by profiling molecules and endotypes. Hence, extracting information from multi cellular and molecular level will help us to understand OA pathophysiology and its relationship with morphotypes (Mobasheri et al., 2021).

Synovium and synovial fluid

The thin layer of synovial cells has the characteristics of macrophages and fibroblasts. As articular cartilage is avascular it has to depend on synovium for nutrients necessary for bone-joint health and removal waste products. Basically, the synovium works as a semipermeable membrane trafficking molecule in from blood plasma also, from cells within the joint tissue and out of the bone joint cavity. The synovium cells have major contribution in the production of synovial fluids components in the joint space i.e., lubricin and hyaluronic acid. These two components reduce frictional shock by lubricating the articular cartilage area. Any changes in synovium cell structure and function hampers the integrity of bone joint releasing variety of inflammatory cells and complement cascade activation which is known as synovitis (Scanzello & Goldring, 2012).

1.3 Classification of Osteo-Arthritis

Historically, OA is divided into two types based on the etiology of the disease.

1. Primary Osteoarthritis: It has no predisposing factor, it means that as people age, bone joint will eventually wear and tear off. For example- Heberden's nodes in postmenopausal women.
2. Secondary Osteoarthritis: It has a predisposing factor which means joint disorder will be triggered by risk factors that promotes cartilage breakdown. For instance: Trauma, obesity, injury etc.

Primary OA and secondary OA concept has been roughly used for basic understanding of OA (Pizzorno et al., 2016). It is quite helpful if OA is classified by genetical and non-genetical factors. However, there have been numerous studies on factors that trigger OA and new insights like genetic alteration, menopause related estrogen deficiency and complex molecular pathophysiology limits the concept of primary OA. This limitation recommends further subset of OA on more detailed etiological, clinical and therapeutical basis (Herrero-Beaumont et al., 2009).

1.4 Risk Factors

According to evolutionary biologists, the term "Mismatch disease" is defined as when genes favored by natural selection and the interacting environment are not well adapted. Inheriting genetic variations with the environmental change is the key to evolution. However, there is a growing mismatch between the evolution of humans and the changing environment causing diseases which did not occur in our ancestors but us, human species. Osteo-Arthritis is a good example of Mismatch disease. The major environmental factors are obesity, metabolic syndrome, dietary changes and physical inactivity (Francis Berenbaum et al.,

2018). However, there have been unending dispute over the difference between *Homo sapiens* and *Homo sapiens neanderthalensis*, but there are studies inclined to the hunchback and bent knees neanderthal for having genes responsible for OA pathology. (Haeusler et al., 2019). Genetics also play crucial role in the pathophysiology of OA. Many genes are thought to be strongly associated with OA pathophysiology (Hafsi et al., 2019).

Aging alters the musco-skeletal, initiates cell senescence triggering OA phenotype and matrix glycation (Shane Anderson & Loeser, 2010). Aging is one strong factor of OA. Telomere length is an age-related biomarker that plays an essential role in regulating genome integrity. Telomeres protect chromosomes from apoptosis, chromosome degradation and end-fusion of chromosomes. As DNA polymerase cannot replicate whole chromosome, thus when cell divides, the telomere shortens by length. The precise function of telomere length and OA is not clear. Although it has been suggested that OA and oxidative stress are closely associated. Again, reactive oxygen species (ROS) have been studied to trigger telomere instability, replicative disorder and malfunction. Many studies reported that short telomeres were identified commonly in participants whose physical activity declined. Especially, blood leukocyte telomere length was significantly associated with physical performance (P et al., 2020). ROS is naturally produced to balance the anabolic and catabolic pathways in cell. However, excess level of ROS leads to oxidative damage and also hampers cell-signaling pathways. It happens due to aging, mitochondria lose its functionality and shows reduced mitochondrial superoxide dismutase (SOD2) and increased ROS in chondrocyte as a result, cartilaginous matrix is degraded. In short, OA factors trigger chondrocyte to produce ROS and then ROS act as the messenger to signal pathways that causes gene to express matrix degrading enzymes (Bolduc et al., 2020). Estrogen deficiency is another trigger for OA. As a result, more women than to men are suffering from OA. Symptoms of OA occurs before the age of 50 in 58% of women than to 20% of men. So, menopausal

women are at great risk of OA (Roman-Blas et al., 2009). Osteoarthritis and metabolic syndrome (MetS) such as dyslipidemia, hypertension and insulin resistance are closely related. About 59% of OA patients is found to have MetS, hence targeting MetS may slow down OA progression (Morales-Ivorra et al., n.d.). Obesity adds excess load on knee, hip and hand. It is one of the great risk factor and many of the population is suffering from being overweight (Reyes et al., 2016). Occupational injury, where one has to lift heavy weight, stand and run for a long time are at great risk to OA (Sulsky et al., 2012). Last but not the least, Bone malignment hampers force distribution throughout the joint which eventually aids OA progression earlier. For example, valgus malalignment increases risk of OA on the lateral knee compartment (Felson et al., 2013).

1.5 OA with comorbid patients

It is vital to understand other medical conditions of OA patients, as presence of other disease can affect patient medication outcome, patient care mode and treatment costs. OA patients with comorbid conditions like diabetes, hypertension and obesity etc. are at elevated risk for OA severity, ineffective medication and therapy which is expected to relieve their arthritic condition.

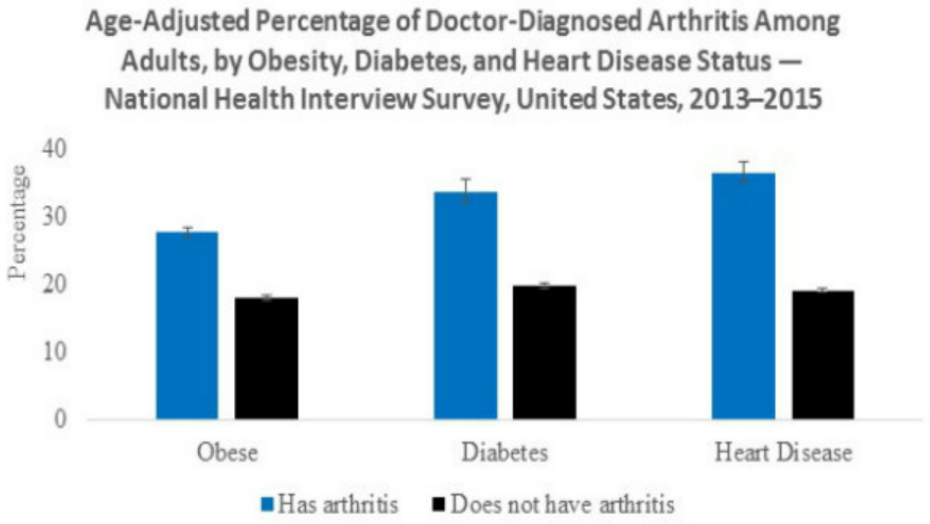


Figure 3: Prevalence of Arthritic patients and non-arthritic patients.

Source:(*Centre for Disease Control and Prevention*, 2013 - 2015.)

Current clinical maintenance of OA patients which concentrates on single or dominant phenotype can be unsatisfactory for large portion of the population who have comorbid conditions (Lentz et al., 2021).

1.6. Pain metric index

Cartilage is aneural and this means it has no pain sensory organ. It is evident from the longitudinal studies that cartilage loss and pain relief is poorly correlated. Data form different studies found that pain has been associated with some factors like bone marrow lesions (BML), synovial thickening/ knee effusion, and periarticular lesions etc. If cartilage is denuded which means subchondral bone is exposed then it is associated with joint pain in patients with OA (O'neill & Felson, 2018). Both peripheral and central processes are associated with OA pain perception which makes druggable pathway more complex. All of the pain sensory type nociceptive, inflammatory and neuropathic pain are reported to a

varying degree in patient in different time. Neovascularization of the articular cartilage and menisci when compressed and hypoxic stimulates formation of new sensory nerves. Sensory and sympathetic nerve may appear in later advance stages of OA. Pain is the primary symptom, neurobiological mechanism of pain is complicated (Fu et al., 2017).

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a patient self-reported outcome measure of knee and hip osteoarthritis pain assessment. It is also used to compare with other outcome measures. The WOMAC is considered as the most efficient measurement criterion and recommended by Food and Drug Administration (FDA), European Medicines Agency guidance and other organizations. In WOMAC metric system, it covers 24 items over 3 subscales i.e., Likert-scale, Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS). Individual patients rate their pain level, stiffness and physical function and then it is sent to process the scores statistically. There is variation in scoring due to the type of subscale used and how item scores are combined. However, there lies a problem in low quality reporting and inconsistency in the measurement of WOMAC. Firstly, the sub scaling range is not clear to fully understand pain level, stiffness and functional disability of the patients. Secondly, there is lack of detailed information of which WOMAC subscale used by the trialist and how the scores were calculated to come into the conclusion. As a result, it hinders comparison of different data set from different trials (Copsey et al., 2019). There is another pain assessment criteria known as Kellgren-Lawrence system. The Kellgren-Lawrence system is also widely used but it is limited by its own cons. Insensitivity to change and disease progression is the most criticized issue of Kellgren Lawrence system (Kohn et al., 2016).

Purpose of review

The purpose of this review is to briefly explore facts of OA gained from past, then to discuss pros and cons of current OA management and finally to conclude with future directions and lifestyle modification.

Chapter 2

Materials and method

Keywords searched with – “Osteoarthritis”, “Cartilage”, “Subchondral bone”, “Chronic pain”, “WOMAC”, “OA guideline”, “Acetaminophens”, “NSAIDs”, “Opioids”, “Corticosteroids”, “OA phenotype”, “Platelet Rich Plasma”, “Monoclonal antibody” and “Personalized medicine”.

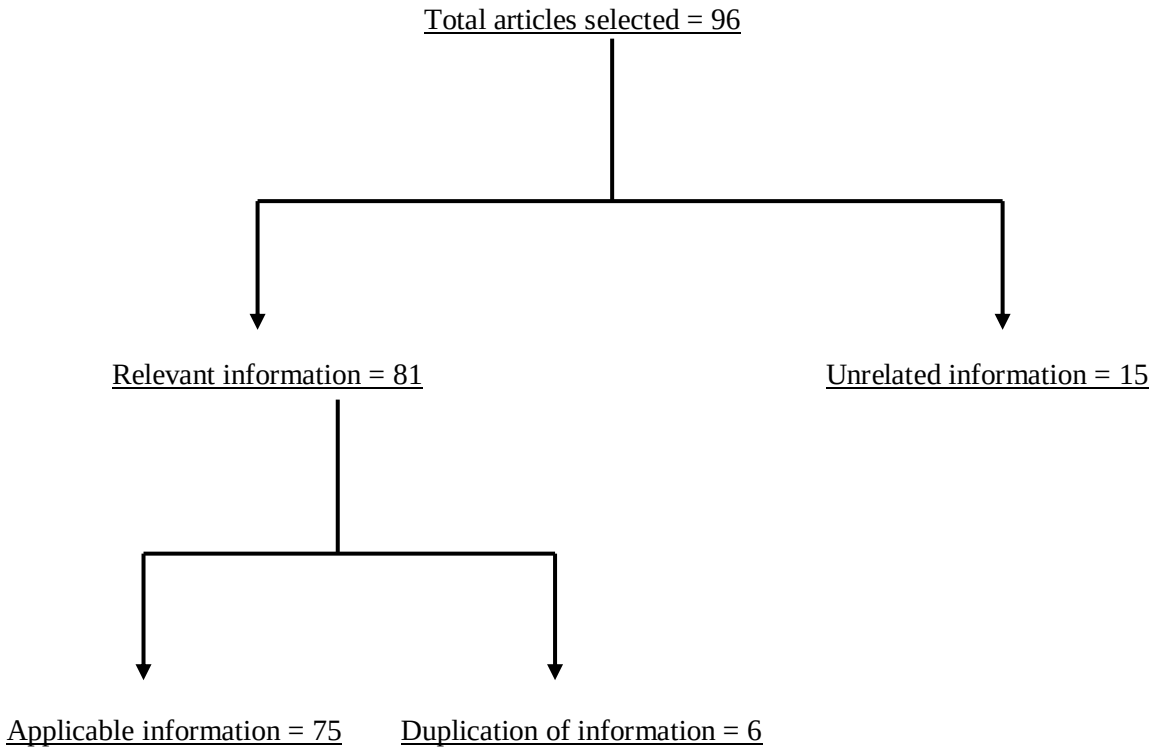
Method of selecting articles – The articles were selected from “Google scholar”, “PubMed”, “ResearchGate” and “Cochrane Library”. While selection, search tool was sorted with free full-text articles but it was not arranged with recent time line. Though when choosing articles update of information was considered manually.

Chapter 3

Methodology

Total of 85 articles were selected among 96 Articles. A flowchart is shown to give ideation about how articles were chosen and why some were rejected for the review.

Flow chart of article selection:



Chapter 4

Discussion

4.1 OA phenotype

OA phenotype is simply defined as the observable characteristic of individual due to their gene expression and environmental factors. Prognostic and Prescriptive phenotyping is necessary to achieve the goal of precise medicine which aims to treat individual patient depending on their genetic and biomarker molecules or psychosocial features. However, one may be at risk of OA early progression to advanced stage due to multiple genetic or environmental factors. Hence, it has become urgent to phenotype OA not only by risk factors but also socio-demographic factors, clinical, imaging, mechanical and bio-molecule marker. Help can be lent from "OMIC" to profile OA in different dimension of biology that will aid in more precise phenotyping as the factors overlap each other multidimensionally (Deveza et al., 2019).

OA phenotype	Agents	OA Pathology	Citation
Molecular	Chemotactic Cytokine Ligand 2 (CCL2)	Facilitates migration and infiltration of monocytes and macrophages promoting neuroflamation.	(Chen et al., 2017)
	Nerve Growth Factor (NGF)	Over expression of NGF causes whole body muscle hyperglasia.	
	A Disintegrin and Metalloprotease with Thrombospondin Motif (ADAMTS)	It aids in cartilage degradation	

	Pathogen associated molecular patterns (PAMPs)	For instance, lipopolysachride (LPS) is generally a structural pattern of microbes and recognized by many innate pathogen recognition receptors (PRR). This activated immune system misplace self-molecules and rage immune system against them.	(Price & Dussor, 2015)
	Damage associated molecular patterns (DAMPs)	For example, presence of calcium pyrophosphate dihydrate (CPPD) crystals mediate innate immune response and chondrocyte production.	(Kato & Svensson, 2015)
Inflammatory	Tumor necrosis factor-a (TNF-a)	Local fatty tissues including infrapatellar fat pad induce TNFa factor and others. COX-2 overexpression is also known to draw this factor.	
	Toll like receptor (TLR) 2 and 4	TLR may fail to recognize natural body components like low molecular weight Hyaluronic Acid, leading to synoviocyte	(F. Berenbaum, 2013)
	Adepokines such as Inter leukin-6 (IL- 6)	Concentration of plasma adepokine is correlated with MetS	
	IL- 1b	Mediates chondrocyte production in Aged people	
Clinical	Medial-to-lateral tibial plateau bone mineral density ratio (M:L BMD ratio)	M:L BMD ratio is influenced by joint loading. Difference between the compartments from standard measure correlates to Joint Space Narrowing, osteophytes and sclerosis.	(LaValley et al., 2017)
	Bone- enlargement	Heberden's node, a bone deformity due outgrowth of bone.	(David Zelman, 2020)

	Subchondral bone Sclerosis	Thickening of subchondral bone causing abnormality in mechanical loading stress absorption	(Donell, 2019)

Table 1: List of some notable OA phenotype

4.2 Disease modifying OA drugs and Symptom modifying OA drugs

For treatment of OA, disease modifying drug had been put forward and it did succeed in pre-clinical and early-clinical trials but failed in phase- 3 trial. It is because OA, a heterogenous disease with different phenotype, potential marker of OA is not clear yet. It will take more time and extensive study for disease modifying OA drug (DMOAD) to takeover current pharmacotherapy effectively (WE et al., 2019).

The symptom modifying drugs on the other hand, will take care of the symptoms. Current m2anagement of OA relies on the symptom modifying drugs to relieve patient from pain and to continue their regular life activity. It has one major drawback that it works for a very short period of time and prolonged use may cause serious adverse effects. Hence, it is leading researchers to search for long lasting treatments and this search led them to few OA modification promising approach. With this approach, OA is basically modified by either balancing cartilage formation, subchondral bone remodeling and/or regulating synovial inflammation. The bone joint health balance and regulation involves growth factors, cytokines, monoclonal antibodies and inhibitors (Mason et al., 2019).

4.3 Current OA management

Biomarker validation and quantification has slowed down the knowledge and therapeutics of OA which ultimately makes OA pathophysiology and rate of OA progression difficult to understand. Developing candidate disease modifying OA drugs with imperfect knowledge of biomarker takes time and laboratory testing is expensive. Current therapeutic of OA relies on biochemical and imaging phenotype to treat symptoms (Hunter et al., 2014). There have been many well recognized guidelines for the symptom treatment of osteoarthritis. However, there is no clear advice about alternative therapy that is classified into medical and surgical approaches. Moreover, about research there are issues relating study design that hinder the assessment of pharmaceutical interventions and thus complicate regulatory approval. Therefore, this huge gap calls for research study properly designed with large participants, enough randomized and blinding is necessary (Fuggle et al., 2020).

Paracetamol

Paracetamol is the most used over the counter (OTC) analgesic and antipyretic prescribed in chronic condition such as Osteoarthritis and other chronic pain. The action mechanism is not clear but this drug is thought to reduce prostaglandins production through cyclo-oxygenase-2 (COX-2) peroxidase function inhibition. The analgesic effect of paracetamol depends on the central neurotransmitter systems such as serotonin, opiate and endogenous cannabinoid systems (Al, 2019) It is estimated that paracetamol does more harm than to its benefit. Although, paracetamol is still recommended in many countries including UK as first choice of treatment and planning to remove paracetamol as an option for treatment guideline but unable because it would leave opioid the next major alternative. Hence, administration

of paracetamol should be prescribed carefully and patients should be monitored for any occurrence of adverse effect (Mccrae et al., 2018).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs mainly target to inhibit COX enzyme that breaks arachidonic acid into prostaglandins that initiates inflammation and pain sensation. There are types of COX enzymes; COX-1 is constitutive in endothelium, stomach and kidney, and the other one is COX-2 which induces inflammatory cytokines. Some NSAIDs were reported to act against both the COX isoforms. There are some other NSAIDs which are more selective to COX-2 for example, celecoxib, etoricoxib, valdecoxib etc. Celecoxib is the only coxib that has the most market share (Al, 2019).

Although celecoxib is one of the most recommended NSAID, however there have been controversy of celecoxib showing adverse effects. A meta-analysis found celecoxib to be associated with gastrointestinal events. Hence NAXOZOl, a compound of naproxen and esomeprazole strontium tetrahydrate is thought to deal with this issue. Naproxen has anti-inflammatory, analgesic and antipyretic property and it is a member of NSAID that aims to inhibit cyclooxygenase-2 (COX-2). Besides, esomeprazole is a proton pump inhibitor which inhibits H+, K+ ATPase in cells. FDA approved the use of esomeprazole due to its better gastrointestinal pH maintenance for longer time. It is not a standardized medication for treating OA patients as participants are insufficient in the clinical study (Park et al., 2020).

Different guidelines such as EULAR, ACR, OARSI, and NICE recommended topical NSAIDs for patients who have mild pain. Topical NSAID such as diclofenac, ibuprofen and piroxicam, etc can be used as solution, gel or patch to reduce pain. A systemic review reported that efficacy and side effects of topical treatment of OA with Eastern Chinese

topical medicine and Western topical medicine were similar, however notably lower than the oral medicines. Another randomized controlled trial pointed out that plaster when combined with exercise therapy can improve pain compared to exercise therapy alone (Z et al., 2020).

Anthraquinone derived rein

Diacerein, an anthraquinone derivative and acts as an Interleukin (IL)-1 beta inhibitor. Number of studies found that cytokines like IL-1 beta and tumor necrosis factor (TNF) signal chondrocytes to release enzymes for cartilage degradation. Other studies focusing on Diacerein administration found to be effective not only on cartilage but also other tissues such as synovial membrane, subchondral bone and chondrocytes. Moreover, diacerein reduces metalloproteinases, nitric oxide and ADAMTS which mediates OA progression (Fidelix et al., 2014).

Opioids

Tramadol is an agreeable choice among the other available opioids due to its dual action and the first action is that having NSAID like property but not gastrointestinal, renal and cardiovascular adverse effects. The other action of tramadol is that it has effect on synaptic transmission of norepinephrine and serotonin and thereby adjusting pain impulse transmissions. However, opioid dependency causes neuronal sensitization and to worsen calling forth physiological adverse effects. In studies, it is found that tramadol like other opioids relieves pain but has low involvement in modifying physical function. These

benefits were so small that it was not clinically significant. In another study, it was found that tramadol when combined with acetaminophen had more benefits than tramadol alone. Although the quality of these trials was low to moderate to contemplate a conclusion due to its lucid risk of bias and weak study designs (MS et al., 2006).

Corticosteroids

Glucocorticosteroids have been practiced in health care for over 50 years, especially in the case of arthritis pain. Dexamethasone a member of glucocorticosteroid has earned the fame of rescuing cartilage matrix from wearing off and longer retention of chondrocyte. It is assumed that it could be used as a disease modifying drug due to its effectiveness in animal models, cartilage explant in injured tissue and post traumatic osteoarthritis patient. However, glucocorticosteroid use is controversial, there have been a study on the effectiveness of dexamethasone that sheds light on drug safety on the basis of dosage, duration and the animal model used for experiment. These studies conclude with the urge for more detailed study to understand the conditions when dexamethasone shows beneficial effects and when harm chondrocytes by triggering apoptosis (R & AJ, 2019).

.Corticosteroids have anti-inflammatory property that suppresses immune system. Inspite of the debate about long term use of intra-articular corticosteroids for the treatment of OA, it is recommended to the patients whose first line of treatment is ineffective. An analytical study of multiple time points stated that the effect of injecting intra articular corticosteroid decreases over time but there is no clear evidence if the effect lasts six months (Martin & Browne, 2019).

Hyaluronic Acid

Hyaluronic acid is a natural and important component of articular cartilage to lubricate the joint and that act as the weight bearing shock absorber. Hyaluronic Acid is injected in a clinical setting when analgesics fail and before going for surgical approach (AG et al., 2015). In trials difference between IA-HA and placebo were not significant. There was not significant reduction in pain and functional outcomes (Khai Tran, 2019). There have been some reports against patient treatment with intra-articular hyaluronic acid which might had been contaminated with pathogenic microbes due to failing to follow aseptic technique (ET et al., 2019)

SNRI

Despaired quality of life leads to anxiety, sleep disturbances and disability. As a result OA patients report depressed mood frequently (S. S et al., 2010). About 75% of the clinical practice guidelines approved antidepressant for lower back pain and recently two osteoarthritis guidelines were published recommending antidepressants. As a result, it is the fourth most prescribed drug, even prescribed more than opioid analgesics. Duloxetine, a Serotonin-noradrenaline reuptake inhibitor (SNRI) is recommended by the American College of Physicians for low back pain. Again, duloxetine or amitriptyline is recommended for neuropathic pain management of Osteoarthritis. Although evidence is not strong enough to guide this drug confidentially, and deeper study design is needed in different time point to gain proper knowledge (Osani & Bannuru, 2019).

Glucosamine and Chondroitin

Glucosamine and chondroitin are naturally found in human body and act as the prime substrate in the production of proteoglycan. Both glucosamine and chondroitin are thought to be partially absorbed and then migrate to the joints, relieving joint pain and protects cartilage from further loss. There have been a lot of study debating on the administration of glucosamine and chondroitin for the treatment of OA. Some studies found them to be significantly effective in the treatment of OA, on the other hand, some studies found it ineffective in pain relief and improving daily life activities; this controversy calls for broad randomized study designs to resolve this issue. Although Osteoarthritis Research Society International (OARSI) guidelines of 2014 do not recommend glucosamine and chondroitin supplementation for the treatment of OA, in some cases it is prescribed to slow down OA progression in combination with other therapies (X et al., 2018).

Capsaicin

Capsaicin is a compound found in chilli peppers that makes it taste 'hot'. It selectively binds to the vanilloid compound receptor (TRPV1) of type C afferent fibre and increases P substance in synaptic cleft contributing to analgesia. When capsaicin is initially applied patients, experience burning sensation for a short period of time. And when it's use is continued, sensory nerve is depleted and selective afferent fibre is destroyed. This neuronal desensitization effect is important in OA to block senses of nociceptive fibre on joint cartilage. For this reason, capsaicin holds a safer profile. However, it is reported that 40% of the patients experienced local skin irritation and burning sensation. Although the trials that reported had major limitations i.e., short duration and difficulty in blinding which hampers to draw clear conclusion and calls for appropriate study designs (V et al., 2018).

Chronic opioid therapy has been recommended for Chronic non cancer pain (CNCP) by American Pain Society (APS) and American Academy of Pain Medicine (AAPM). Long term usage of Opioid analgesics is debated for its inefficacy and adverse effects for instance, opioid induced neurotoxicity, tolerance and dependence. According to the report of CDC, about 130 persons (approx.) die a day from overdoses of opioid and 68% deaths for opioid related medication. These statistics infer major public health issues signifying as Opioid crisis and calls for nationwide recognition. At present, managing pain with original analgesic three step ladder guideline is ill-suited for its limitation and controversies. The American Society of Interventional Pain Physicians (ASIPP) in its 2018 guidelines recommended non-opioid pharmacological, and pharmacological treatments i.e., acetaminophen or other NSAIDS and Minimal invasive techniques. Many studies came up with many concepts for example, four step ladder that includes multi-modal pain management or five step ladders to include anesthetic therapies and opioid switching. Asian countries such as India, China and Thailand compared to USA and Europe have lower opioid associated substance abuse. The low consumption of opioid analgesics in China may have characterized into two factors; first of all, they have easy access to many ancient Chinese medicinal herbs and physical therapies i.e., acupuncture, cupping and Tai chi etc. and the second factor is they have greater control over drug administration. In 2007, The Chinese Health Ministry separated Pain Medicine department from other Medical Subjects to expertise skills in pain management. This approach of China may have significantly lowered drug-dependence, most importantly opioids administration. Also, this clinical approach may help in revising analgesic ladder model for pain management (Z et al., 2020).

Recent COVID-19 pandemic has made us rethink about the chronic use of drugs and its effect, especially the drugs used for the treatment of OA. The researchers found it intriguing

that the activity of anti-inflammatory drugs in reducing inflammatory response to control OA and also in lowering cytokine storm due to disease complexity in Covid-19 patients. Although the line of treatment and dosage is reconsidered for patients with OA because of their susceptibility to COVID-19. In studies, paracetamol was found safer to use as it did not draw pleuropulmonary complications unlike NSAIDs. In a mouse study, paracetamol administration showed lower morbidities due to Influenza A viral infection by reducing inflammatory cell infiltration into the airways. However, frequent paracetamol administrated patients were reported to have liver function abnormality and hepatic complications (E et al., 2020).

Drug name	Mode of application	Direct target of drug	Effect of treatment	Location of drug activity	Amount of intake	Disadvantage of treatment	Citation
Paracetamol	Oral	Inhibition of prostaglandin synthesis	Analgesic and antipyretic	Central Nervous System and Liver (Hypothetical), PNS	Regular and short term	GI bleeding, kidney injury, hypersensitivity reactions, hypertension and anemia etc.	(Przybyła et al., 2021)
					Overdose and long term	Serious liver damage, liver failure, thrombocytopenia, acute kidney damage and skeletal muscle cytolysis	
NSAIDs	Oral	Selective and nonselective inhibition of COX enzyme	Anti-inflammatory, analgesic and antipyretic	Liver, Plasma protein (Albumin)	Regular dose and short term	Renal impairment, electrolyte imbalance and high blood pressure	(Ho et al., 2020)
					Overdose and	Heart failure, water retention, hypertension and	

					long term	acute kidney damage	
	Topical	Inhibition of COX enzymes	Analgesic	Skin, plasma near the skin site of application	Short term and long term	Mild skin reaction with rashes and itching	(S. S et al., 2010)
Anthraquinone	Oral	Inhibition of IL, TNFa, NF-kB signaling pathways and metalloprotease	Anti-inflammatory, Anti-coagulant	Liver, Systemic absorption	Short term and long term	Mild skin reaction, discoloration of urine and diarrhea	(Oliveira et al., 2020)
Opioids	Oral	Activation of m-opioid receptors with the inhibition of noradrenaline and serotonin uptake	Analgesic	Liver, Nervous system	short term and long term	Respiratory depression, constipation, tolerance, dependence	(Bravo et al., 2017)
Cortico-steroids	Oral	Suppression of cytokine by inhibiting Phospholipase-A2 and arachidonic metabolic acid pathway	Anti-inflammatory, analgesic	Albumin	Short term	Cardiac infarction and suppressed immune system	(Knezevic et al., 2018)
	Intra-articular			Injection into epidural space	Long term		
Hyaluronic acid	Intra-articular	Synthesis of proteoglycan and viscoelastic maintenance	Anti-inflammatory, lubricative and chondroprotective	Natural substance found in body; Injection into joint space	Long term	Sepsis if aseptic technique not followed	(Bowman et al., 2018)

Anti-depressant	Oral	a serotonin and noradrenalin reuptake inhibitor	Analgesic	CNS	Short term and long term	Constipation, diarrhea and drowsiness	(Jesus et al., 2016)
Glucosamine and Chondroitin	Oral	Inhibit metalloproteinase, prostaglandin E2 release, nitric oxide production and degradation of glycosaminoglycans	Anti-inflammatory	Natural substance found in bone joints	Short term and long term	Allergic dermatitis, *H. pylori* gastritis,	(Hochberg et al., 2016)
Capsaicin	Topical	Numb peripheral nociceptors	Analgesic	Skin, blood stream under skin	Short term and long term	Burning sensation of skin, tolerance	(Persson et al., 2018)

Table 2: Current OA management and its side effects

4.4 Emerging Treatments

Mesenchymal stem cell

Mesenchymal Stem Cells (MSC) are thought to repair bone cartilage and inhibit the progression of OA. Initially, MSC's were derived from bone marrow which is a complex process. However, Adipose- derived Stromal cells have the same properties and easy to obtain. Further studies related to intra-articular ADSC injection and OA showed promising result for the treatment of OA patients (MHJ, 2021). Mesenchymal stem cells can be derived

from bone marrow, synovial membrane, cord blood, periosteum and muscle etc. too., and with cell therapy these cells are expected to treat loss of articular cartilage. MSCs derived from different sources have different ways to differentiate into chondrocytes. However, MSC implantation may lead to excess production of cartilaginous and fibrous tissues which may not sustain in the long run and result in loss of repair tissue. Hence elaborate study on MSCs is required before it is clinically used as joint repairment (EV et al., 2018).

Platelet Rich Plasma

Autologous blood derive components has the potential to repair and regenerate tissue and have crucial roles to play in inflammation and regulatory metabolism. Platelet rich plasma (PRP) has shown promising healing property in tendon, ligament and skeletal muscle (B et al., 2019). Healing property of PRP has been proven consistently in early OA in recent years. The extended release of growth factors from PRP positively effects straight after inoculation and retains for about 3 weeks. Further research is ongoing for better therapeutic effect and effective way to administer PRP in OA patients (Dhillon et al., 2017).

Monoclonal antibody

Several mAbs i.e tanezumab, fluranumab, and fasinumab target the nerve growth factor for relieving chronic pain conditions. Among all the mAbs, most effective one is tanezumab as it improved physical function and stiffness scores. Although during phase 3 trial of tanezumab was halted due to some concerns over safety, later it was resumed in 2015 as the evidence supported its role in neuropathic pain mechanism. The monoclonal antibodies may have the potential to meet current treatment limitations. However, researchers are trying to

come up with better strategies to ensure its best outcome with a very few side effects and availability at an affordable price (JF et al., 2017).

Bone morphogenetic protein

The matrix production with the help of gene induction i.e., Bone morphogenetic proteins (BMPs) may show promising result in the field of long-term OA treatment. BMPs are thought to regenerate the loss of glycosaminoglycan (GAG) component which hampers biomechanical property of bone joints. A study found BMPs with the combinations of its heterodimers and homodimers induced proteoglycan, type I and type II collagen production (A et al., 2020). BMP-7 is found to reduce MMP-13 in chondrocytes which have been exposed to IL-1β. It can also induce anabolic activity of chondrocytes. The efficacy of the type BMP's and safe delivery to the target site and its stability is still being studied for utmost benefit of patients (Caron et al., 2021).

Chapter 5

Conclusion

As we age, we come up with many multimorbid conditions which drops the quality of life. To treat these multimorbid conditions, we are prescribed to intake many drugs. The point is, with the unpleasant symptoms of disease, many drug intake eventually leading to drug toxicity, organ failure etc. makes life more complicated to lead and function. Patients who have chronic illness, like osteo-arthritis, these patients are prescribed with prolonged intake of drugs. It is not necessary that these osteo-arthritic patients are suffering and will suffer from only one disease condition, as it is a chronic disease, many times in their life will come across with other disease conditions. Those other disease conditions will need different types of drugs which may react with the osteoarthritic drug or drug side-effects. This chronic drug usage side effects and drug reactions specifically on elder populations when their physical-body is already wearing off naturally, is one big problem in the long run which needs more attention. The best recommendation with the current available knowledge and resources can be drawn from prevention is better than cure. With early diagnosis, differentiation between necessary and unnecessary care, modified lifestyle may pave the way to well manage osteoarthritis.

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