Aetiopathogenesis of Knee Osteoarthritis

Raju Vaishya[1], Ashish Kumar Mishra[1], Abhishek Vaish[1]

Abstract

Knee Osteoarthritis is a common disease of the middle-aged and elderly population. It is slightly more frequent and severe in females than in males. Several modifiable and non-modifiable risk factors have been identified. Some genetic factors have been identified in the causation of OA. Obesity seems to be the most influential modifiable risk factor for knee OA. Dietary intake of non-nutritious food items, vitamin D deficiency, and several metabolic disorders are also responsible for the causation and progression of knee OA. Traumatic injuries of the knee joint and its malalignment cause harm to articular cartilage and lead to OA. Several occupations putting excessive loads on the knee joint and individual habits (like cross-legged sitting and using Indian toilets) are also critical factors for the causation of knee OA.

Keywords: Knee joint, Osteoarthritis, Obesity, Articular Cartilage, Aetiology.

Background

Osteoarthritis (OA)is a disease of synovial joints, characterized by progressive deterioration and loss of articular cartilage with simultaneous structural and functional changes in the entire joint, including the synovium, meniscus, periarticular ligaments, and subchondral bone [1,2]. Although all the joint tissues may be implicated in disease initiation and progression of OA, the articular cartilage is the crucial component in this context[2]. Articular cartilage is a flexible and mechanically compliant connective tissue found at the end of long bones in articulating joints and in the intervertebral disc [2]. Its principal function is to provide a smooth surface for articulation and to facilitate the transmission of loads with a low frictional coefficient[3]. OA is one of the most common and disabling forms of joint disease, far more common than rheumatoid arthritis (RA) and other forms of joint disease[4]. Studies have demonstrated that significant risk factors for the development of OA are age, obesity, and metabolic diseases[5,6]. Cartilage is continually remodeled as chondrocytes replace the degraded matrix macromolecules with newly synthesized components. Articular cartilage can tolerate a tremendous amount of intense and repetitive physical stress, but it is unable to heal even after a minor injury [2]. These facts make joints sensitive to degenerative processes and the development of OA. The biomechanical forces that place inappropriate levels of stress on the joints like excessive or abnormal load-bearing, postural or orthopedic abnormalities, and traumatic injuries, that destabilize the joint interact with other environmental, systemic and genetic factors contribute to the pathogenesis of OA.

Prevalence of OA

In the Global Burden of Disease 2010 study, hip and knee OA was ranked as the 11th highest contributor to global disability [4]. According to the World Health Organization (WHO), OA is the fourth leading global cause of years lived with disability [2]. In individuals older than 70 years, OA is the leading cause of chronic disability globally and has been designated as a 'priority disease' by the WHO (report WHO/ EDM/PAR/2004.7). In the United Kingdom, a third of people aged 45 and over (8.75 million people) have sought treatment for OA, and at least half of these individuals have knee OA. In India, it is the most frequent joint disease with a reported prevalence ranging from 22% to 39% [7].

Risk Factors

Several risk factors for knee OA have been identified. These may be classified into non-modifiable and modifiable factors (Table.1)

A) Non-Modifiable Risk Factors

Age:

The age of the patient is the most important of all etiological factors.[7] OA also progresses with age, and as specified earlier, radiological OA may be found in 80% of all people more than 75 years of age. With advancing age, morphological and structural changes like softening, fraying, and articular cartilage attrition in the knee cartilage can be seen. The aging process affects the cellular regenerative ability of chondrocytes, and with age, the apoptosis of chondrocytes increases, and both these factors cause a reduced ability for repair. Metabolic factors like diabetes, hyperuricemia also increase with age, and these, in turn, lead to increased incidence of OA of the knee as age progresses.

Gender:

Women are not only at higher risk of developing OA, but also they develop more severe OA, compared to males.[8]Among adults age 60 years or more, the prevalence of symptomatic OA is about 10% in males and 13% in females[9].

Genetic:

Genes coding for structural proteins of the extracellular matrix of the cartilage have a pivotal role, especially those coding for collagen type II (COL2A1). Other genes that code for the structural proteins of the

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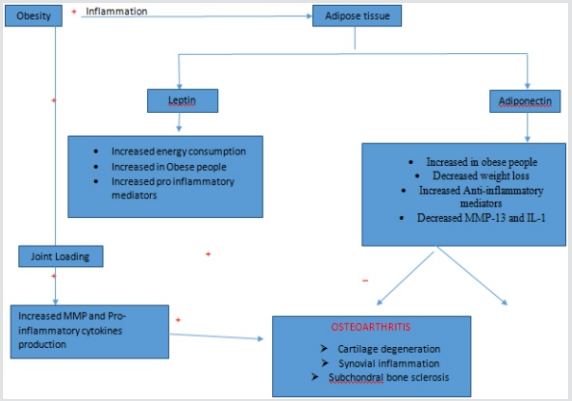

Figure 1: Influence of Obesity on the development of Osteoarthritis

Table 1: Risk factors for Osteoarthritis

NON- MODIFIABLE RISK FACTORS	MODIFIABLE RISK FACTORS
	• Obesity
• Age	• Trauma
	• Joint malalignment
• Gender	• Diet
	• Occupation
• Genetics	• Metabolic Disorders
	• Vitamin D deficiency

extracellular matrix, and can lead to increased susceptibility to developing the disease, includes COL9A2, COL11A1, COL11A2 or COMP (cartilage oligomeric matrix protein gene) [10]. As shown in the study by Lian et al. (2005), there is an association between specific mutations in the COL1A1 gene and the decreased probability of suffering hip OA in women [11]. Some other genes have also been implicated in the process of the OA. These include Estrogen Receptor α gene [12,13], Frizzled Related Protein gene [14], and Asporins [15].Apart from these genes, there has been the discovery of new genes related to OA, which carry out one of the below-mentioned mechanisms:

a) genes that code for structural proteins and proteins related to the loss of cartilage

b) genes related to the increase in the synthesis of the extracellular matrix

c) genes related to an adaptive response to the disintegration of cartilage.

B) Modifiable Risk Factors

Obesity:

The factors related to Obesity and their role and effect in the causation of OA are as follow (fig.1):

I) Dyslipidaemia:

Dyslipidaemia is one of the characteristic features of obese. Normally, HDL scavenges cholesterol and other lipids from the bloodstream and transports them to the liver, thereby maintaining lipid homeostasis, but this function is impaired in obesity[16,17,18].

ii) Oxidized -LDL:

There is an increased level of plasma ox-LDL in obesity due to an increased level of reactive oxygen species [19]. Ox-LDL induces cartilage degradation via VEGF release, causing secretion of cartilage-destructive factors. It also induces MMP-3 release [20], decreases chondrocyte cell viability and proteoglycan synthesis. In OA cartilage, LOX-1 expression and amount of ox-LDL-positive cells are increased compared with healthy cartilage. [21].

iii) Adipokine levels:

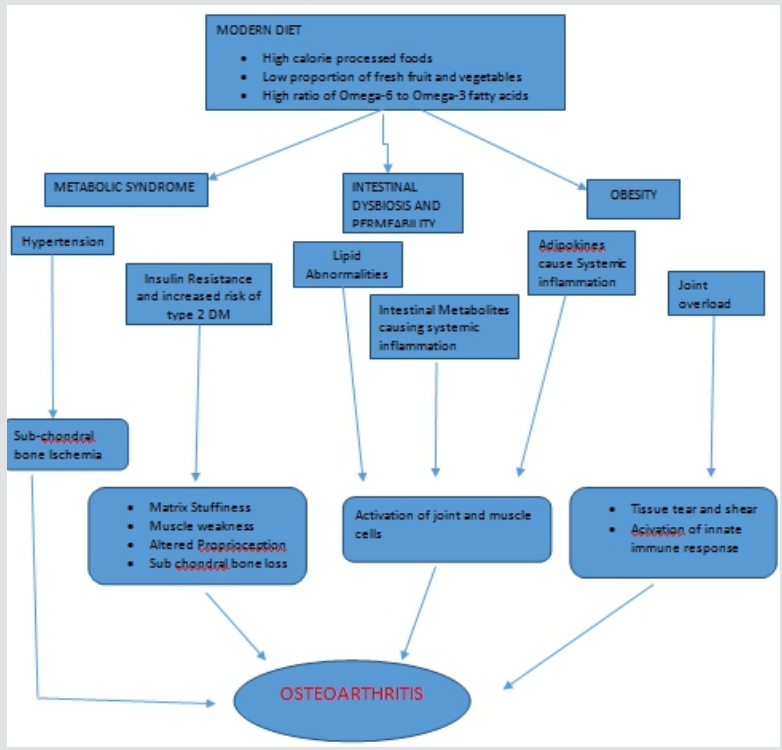

Figure 2: Effects of diet on Osteoarthritis

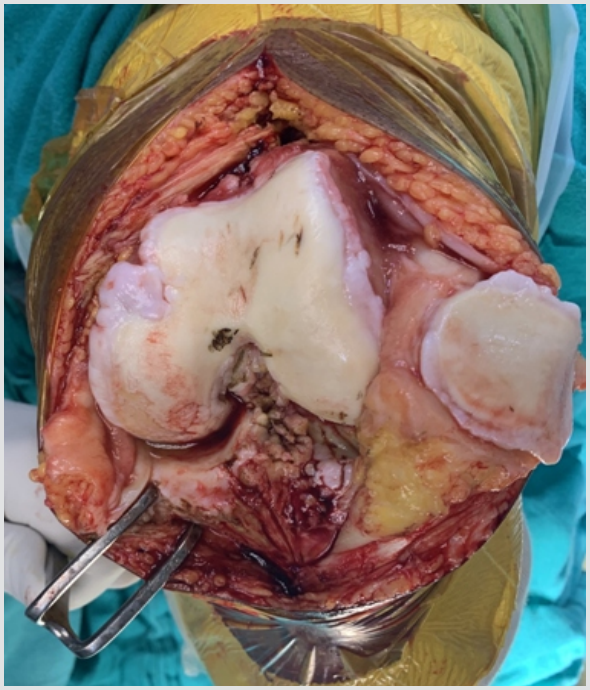

Figure 3: Intraoperative picture of the knee showing advanced stage of OA, with significant loss and damage of the articular cartilage on the femoral condyles and exposure of subchondral bone.

The secretory profile of adipose tissue changes in obesity. Most adipokine levels increase (e.g., leptin, resistin, visfatin, lipocalin-2, chemerin), but the level of one adipokine (adiponectin) decreases. The current observation is that these adipokines induce a state of low-grade systemic inflammation in obesity and, together with local adipokine production by the IPFP, have detrimental effects on joint tissues. Resistin, chemerin, lipocalin-2, and visfatin are newly identified adipokines implicated in OA development.

iv) Leptin:

Leptin has catabolic effects on the cartilage by causing proteoglycan depletion, synovial fibroblasts stimulation, and increased expression of cytokines IL-6 and IL-8 [22,23]. Thus leptin might be involved in the initiation and progression of the OA process.

v) Adiponectin:

It is produced by adipose tissue, which improves insulin sensitivity, increases fat oxidation, and is vasculature protective via its anti-inflammatory effects [24]. Plasma levels of adiponectin are decreased in obesity, whereas they are increased in OA [25]. Thus the deficiency of adiponectin might have a role in the pathogenesis of OA. [26].

Trauma and joint Malalignment

Trauma and joint malalignment are inextricably linked together. The younger patients and athletes are at the highest risk due to these factors. Trauma reduces periarticular blood flow and affects cartilage nutrition leading to OA. Remodeling of cartilage reduces and leads to further malalignment and further OA changes. For knee OA to happen in sportspersons, it has been shown that the injury rather than the sport itself,leads to the development of OA.

OA results from local mechanical factors, and studies have demonstrated that malalignment is a potent predictor of disease progression in patients with OA of the knee. Malalignment is influenced by certain local factors within the joint, such as tibiofemoral congruence, the integrity of the anterior cruciate ligament (ACL), and meniscal degeneration and position. Malalignment also accentuates the effects of other risk factors, including obesity, quadriceps strength, laxity, and stage of the disease.Thus, trauma and joint malalignment play an essential role in the pathogenesis of OA.

PEARLS OF WISDOM
• Knee osteoarthrosis is a very common cause of chronic disability in the elderly population and its incidence seems to be increasing, probably due to longer life spans.
• The aetiopathogenesis of knee OA is multifactorial with both, mechanical and biological factors playing a role. While some factors are modifiable, several others are not.
• A high body mass index is perhaps the most important modifiable risk factors. Besides obesity causes increased joint loading, cytokines released form adipose tissue are also detrimental to articular cartilage.
• Trauma to the cartilage due to sports or injury, instability and constitutional mal-alignment like tibia vara must all be sought and rectified early to prevent progressive degeneration of the joint.
• Where no apparent mechanical issues are incriminatory, biological therapy in the form of orthobiologics have an important role in patient management.

Occupation

Occupational activities that physically load the joint may lead to degenerative changes in the articular cartilage with time, which can lead to the development of OA later in life. People who have occupations in which there is - squatting and kneeling for substantial parts of the working day, regular heavy weight lifting, stair climbing. Crawling, bending, and whole-body vibration and repetitive movements and high physical workload are more susceptible to develop OA than normal persons.

Diet

Intake of high calorie processed foods along with a low proportion of fresh fruits and vegetables leads to metabolic syndrome, which leads to obesity, and further issues related to obesity ensues, as discussed earlier. Obese people have insulin resistance, and increased risk of Type 2 DM causes Matrix stiffness and subchondral bone loss. Thus, the modern unhealthy diet causes the problems above, which eventually makes the person susceptible to develop OA, and a schematic representation of how diet has a relation with the pathogenesis of OA is presented in (Fig.2).

Metabolic Disorders

The coexistence of OA with other metabolic disorders such as systemic arterial hypertension, cardiovascular disease, diabetes, and dyslipidemia is increasing. The majority of knee OA is associated with metabolic syndrome, which suggests that the chronic inflammation status existing in patients with Metabolic syndrome alters the metabolism of cartilage, regardless of excessive weight, and contributes to the development and progression of OA. It shows that the metabolic disorders, although most are associated with obesity but is an independent risk factor for development and progression of OA.

Vitamin D

Vitamin D is essential for the growth and maturation of cartilage and bone remodeling. Vitamin D act via Vitamin D receptors (VDRs), which are demonstrated in human chondrocytes and have a direct impact on cartilage by metabolic transformation, which stimulates proteoglycan synthesis in mature chondrocytes[27]. According to Tetlow and Woolley, V DR expression is increased in areas of erosion in patients with late-stage OA [28]. They demonstrated that when vitamin D binds to VDRs, a signaling cascade effect occurs, and chondrocytes expressed increased levels of MMPs 1, 3, and 9,which lead to degradation of bone at increased rates.[29,30] VDRs also signal an increase in fibroblast growth factor 23, caspase 9, and extracellular signal-regulated kinase 1/2. When VDR is inhibited, down regulation occurs[31]. In response to joint degeneration, there occurs upregulation of vitamin D signaling in an arthritic joint in an attempt to spread joint contact pressures through new bone formation in the form of osteophytes. Vitamin D deficiency inhibits bone remodeling, which affects the bone changes, which eventually evolve into OA. Thus, Vitamin D could help in the prevention of the progression of OA by enhancing bone remodeling [32,33,34,35].

Pathophysiology of OA

Recent studies in OA pathophysiology have established it to be more of a pan-articular disease. The macroscopic changes of an OA knee joint are as follow (fig. 3):

- Synovitis
- Cartilage degeneration
- Narrowing of joint space
- Sub-chondral bone sclerosis and
- Formation of osteophytes

Articular cartilage is the first tissue to be affected, in which degradation of the cartilage proteins causes an increased water content. Fraying of collagen fibres occurs within the hyaline cartilage, starting from periphery of the joint in the non-

weight bearing areas and gradually extends into deeper cartilage layers in the weight-bearing areas of the joint upto one-third of the cartilage thickness. It starts with formation of small defects between the fibres which gradually becomes vertical clefts. The degenerated part might break off and remain as loose bodies, causing sudden episodes of pain and locking of joint. Loose bodies and the by-products of cartilage destruction causes the synovium to inflame, at this stage NSAIDs can provide temporary relief.

Proteoglycan and collagen turnover increase but proteoglycan molecules near the fibrillated cartilage are smaller than normal. This altered cartilage is mechanically weaker. As the cartilage thins out the joint space is reduced, which is visible on X-ray.

Bone beneath this defective cartilage becomes shiny and this change is termed Eburnation. This eburnated area becomes osteoporotic and local avascular necrosis leads to cyst formation where ever there is complete bone loss. Osteophytes are formed at the periphery of the joint, which may protrude into the joint space. Thickening and increase in vascularity of synovial membrane occurs along with an inflammatory response.

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