# The Risk factors of Osteoarthritis

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**Abstract.** Osteoarthritis (OA) is the one type of arthritis which affects 7% of the population and is the 15th leading cause of disability. However, the etiology of this disease is complex and its pathogenesis is still under investigation. The pathological changes seen in OA most commonly include synovitis, osteophyte formation, cartilage degradation, thickening of the subchondral bone, etc. which may lead to symptoms such as stiffness, movement disorder and swelling. OA generally starts with the damage of the articular cartilage of the synovial joint which later leads to a cascade of effects that ultimately leads to joint destruction. Some of the identified risk factors of OA include old age, gender, genetics, obesity, and neurological disorder. However, even with these factors being identified, many of the mechanisms responsible for progression to OA behind these risk factors remain unclear. This paper reviews different articles regarding the risk factors of OA and summarizes the possible mechanisms behind each risk factor.

**Keywords:** Osteoarthritis, Risk Factors, Age, Female Fex, Obesity.

## 1. Introduction

Osteoarthritis (OA), the most common type of arthritis, affecting approximately 7% of the global population, or more than 500 million individuals [1]. This illness develops over time and is most prevalent on joints located in the hands, hips, and knees which hinders movement and adversely affects the overall health of the affected individual. Therefore, understanding its mechanisms and risk factors is essential to reduce and prevent the incidence of OA.

OA generally starts with the damage in the articular cartilage of synovial joints. The articular cartilage, including the synovium, plays a vital role in decreasing shock when stress is exerted on the joint and reducing friction when moving, by separating the two bones located in the joint, preventing them from physically contacting each other. However, when the articular cartilage starts to degrade, the joint space narrows, causing the bones to glide against each other, resulting in the generation of inflammation and the formation of osteophytes (overgrowth of bone) [2]. These are natural responses of the body in response to the damage of cartilage; however, it may further increase friction which worsens the condition and induces pain and stiffness. Although the intensity of symptoms varies among different patients, the severe symptoms of OA involve stiffness, pain, disorder of motion and swelling [2]. Currently, patients can only undergo arthroplasty, or joint replacement surgery, to be able to move freely without pain [2]. Arthrodesis, or joint fusion, is also another option; however, it can only reduce pain, and movement of the joint is difficult after the surgery. Although there are several other treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) [2]. However, it can only help in alleviating the symptoms. Therefore, it is very critical to comprehend the mechanisms, causes, and risk factors of OA to prevent and allow further development of treatments in the future to totally cure OA.

There are several types of cells involved in the initiation of OA, and understanding each type is beneficial for comprehending the pathogenesis of OA. These include the chondrocytes, a specialized cell that maintains the articular cartilage by maintaining a delicate balance between catabolic activity, which breaks down existing cartilage by synthesizing degradative enzymes, and anabolic activity, which produces new cartilage by synthesizing synthetic enzymes. An imbalance in the secretion of the degradative and synthetic enzymes may result in the degradation of cartilage. the osteoclasts are the second type of cell, responsible for the degradation of bone to initiate bone remodeling. Osteoclasts are suspected to make a difference in the onset of OA, especially after joint injuries, for they will be recruited to the joint which degrades the bone and articular cartilage [3]. The third type

of cell involved in OA is the osteoblasts which make a difference in synthesizing bone matrix and coordinating the mineralization of the skeleton. Several pieces of evidence, such as OPG and RANKL gene, whose abnormal expression were observed in the osteoblasts of osteoarthritic joints and the production of osteophytes by osteoblasts, suggest that osteoblasts participate in the pathophysiology of OA [4]. The fourth type of cell, osteocytes, which is the most abundant type of cell located in the bone, play a vital role in detecting mechanical loading and maintaining bone homeostasis by regulating bone formation by osteoblast and bone degradation by osteoclasts. Therefore, osteocyte dysfunction is linked to the structural and functional disturbance of the bone. Lastly, the synoviocytes, located along the synovium of the joints, also affect OA. The functions of synoviocytes are mainly to absorb debris in the joint and produce synovial fluid to lubricate the joint and reduce friction. However, when the articular cartilage starts to damage, synoviocytes may produce inflammatory regulators, such as proinflammatory cytokines, nitric oxide, and prostaglandin E2. The production of these pro-inflammatory factors will lead to inflammation which can exacerbate the condition of the disease [5].

OA was caused by several factors, which include the dysfunction or apoptosis of bone cells [5], cartilage thinning, joint injuries, decreased matrix mineralization, increase bone mineral density, excess stress exerted on the joint, neurological disorders, etc. Thence, those factors include age, gender, obesity, genetics, etc. This paper will discuss the possible explanations of each risk factor: age, female sex, obesity, joint injury, genetics, and neurological disease.

## 2. Pathogenesis of OA

Although OA is a very common disease, especially among elderlies, its pathogenesis is still not fully understood. Furthermore, since OA is a multifactorial disease, the molecular pathway of the disease differs according to different factors that have initiated it. Nevertheless, several studies provided insightful knowledge regarding the different pathways and the general progression of the disease.

(Figure 1.) Comparison of healthy joint and osteoarthritic joint. As seen in the figure, the layers of cartilage in OA are severely disrupted which narrows the joint space, causes apoptosis and hypertrophy of chondrocytes, and triggers inflammatory responses. Furthermore, vascular infiltration is happening which leads to the activation of osteoclast and osteoblast, increasing bone remodeling, leading to the formation of osteophyte [6].

Four layers of tissue cells make up healthy articular cartilage: the protective superficial layer that is adjacent to the synovium, the midzone layer, the deep zone layer, and the calcified cartilage, which is a border between the articular cartilage and the subchondral bone (see figure 1.) [7].

The protective surface layer begins to disintegrate at the beginning of OA, exposing the midzone layer to the synovium, which includes numerous substances that may induce chondrocyte proliferation and release of catabolic factors [7]. The loss of integrity of the interface leads to apoptosis of chondrocytes and, together with the proliferation of chondrocytes, leads to the formation of hypertrophic chondrocytes which generates matrix degradation products and pro-inflammatory mediators [6-7]. These pro-inflammatory mediators act directly on the adjacent synovium which stimulates proliferative and inflammatory responses [6]. The macrophages located along the synovium release pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α). In response to these pro-inflammatory stimuli, the chondrocytes decrease the production of cartilage matrix components and increase the production of degradative enzymes [7]. In addition to deregulating chondrocyte function, the production of cytokines by the macrophages may stimulate the nociceptors found in the joint which triggers pain. Lastly, the inflammatory biological factors and abnormal joint mechanics result in the reactivation of endochondral ossification which may lead to the formation of osteophytes [6].

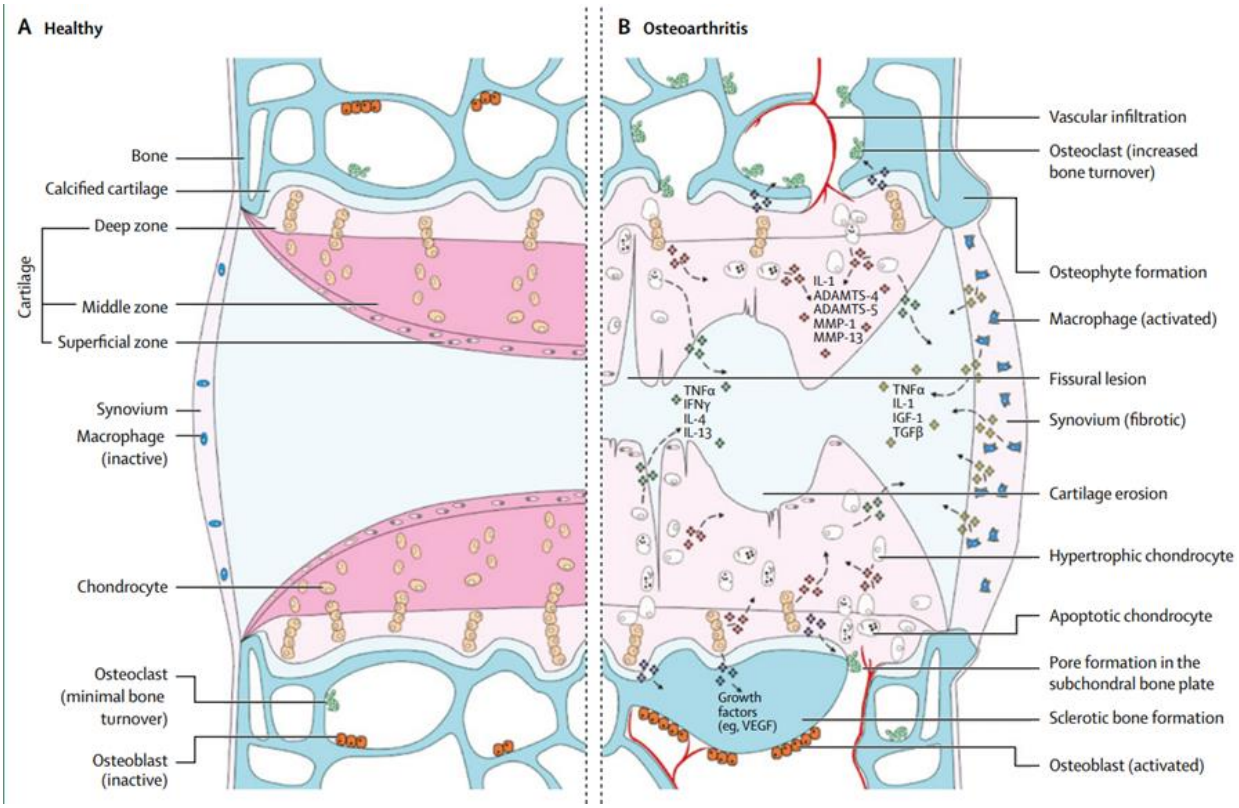



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Vascularization of the subchondral bone, cartilage, and synovium is also present in the pathology of OA. Subchondral bone vascularization may expose the cartilage to hormones, pro-inflammatory cytokines, and bone-derived anabolic and catabolic factors which results in chondrocyte hypertrophy and deregulation of chondrocyte function which may at last lead to further cartilage damage [7]. Furthermore, hypertrophic chondrocytes may also produce angiogenic factors which promote blood vessel growth in response to hypoxia [7]. The further growth of blood vessels will lead to further subchondral bone vascularization and vascular infiltration which permeabilize the calcified cartilage [6-7], leading to cartilage and synovial vascularization. Osteoclasts and osteoblasts enter through permeabilized cartilage, leading to subchondral bone remodeling, increased bone turnover and further cartilage degradation [7]. This results in a vicious cycle which worsens the condition of the disease as time progresses (see figure 2). However, it should be noted that OA is a multifactorial disease and different factors may lead to different mechanical pathways, but it all ends with joint destruction.

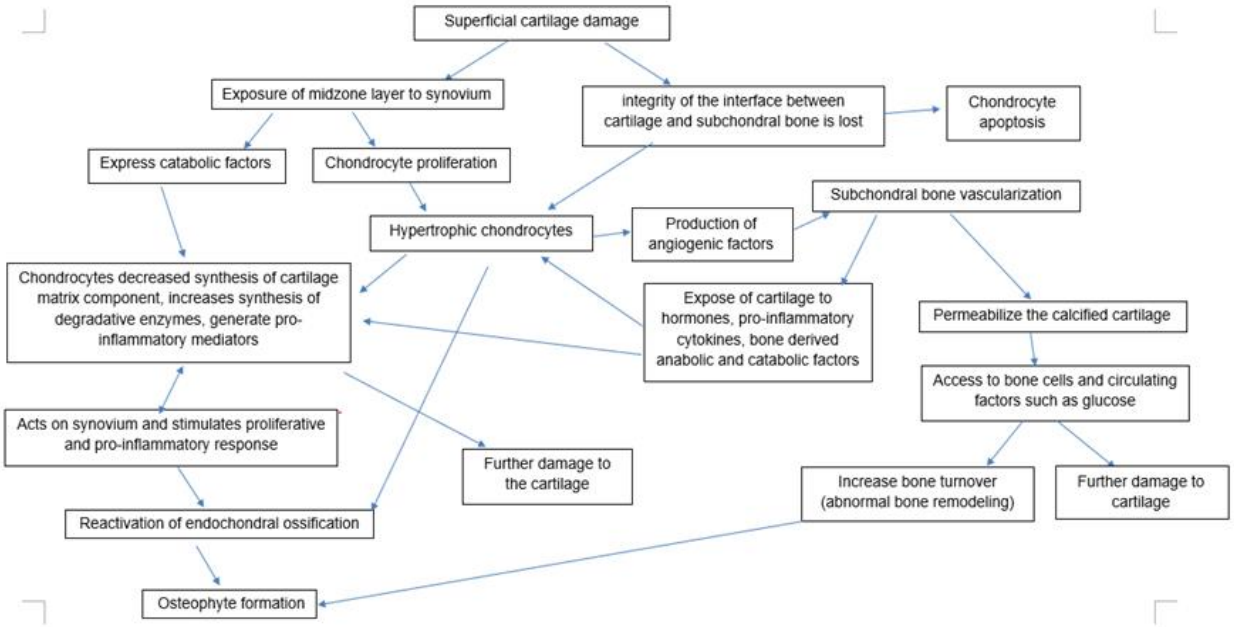



**Figure 2.** Summary of a pathway of OA progression. In general, the initiation of OA is the damage of the articular cartilage which leads to a cascade of events that at last results in joint damage. This is a vicious cycle that worsens the condition over time. Note that this is only one of the possible pathways of OA.

## 3. Risk factors of OA

### 3.1. Age

Age is one of the biggest risk factors for OA. As proven by data collected by Prieto-Alhambra et. al., the incidents of knee, hand, and hip OA increase significantly as age increases (see figure 3.). Furthermore, according to the findings of this study, the incidence of OA peaks at around the age of 75, with a frequency of 4-5 percent in hand, 16-17 percent in knee, and 6 percent in hip [8].

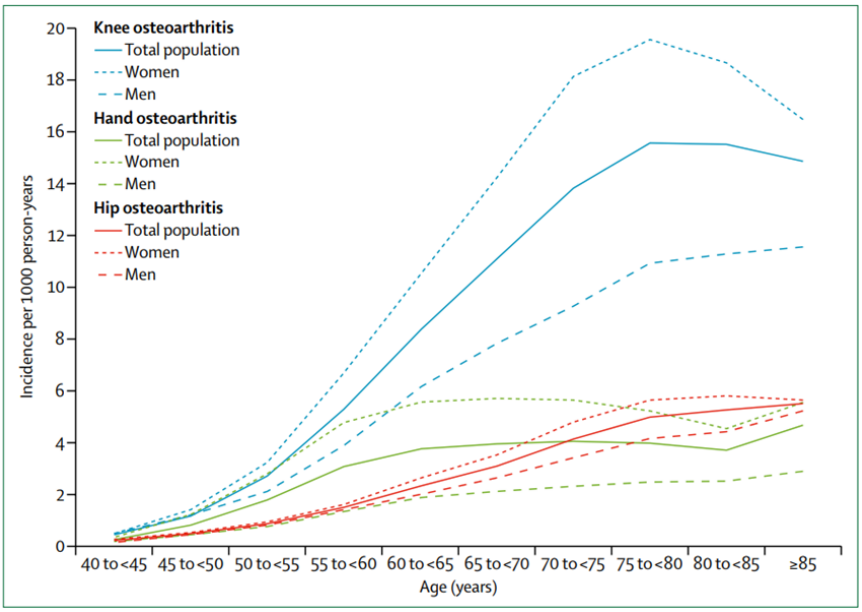



**Figure 3.** The figure illustrates the incidents of the knee, hand, and hip OA in different age groups and different sexes. It is observed that the incidents of OA, especially knee OA, peak at approximately the age of 70-75, and the incidents of women developing OA are generally higher compared to that of men [18].

Musculoskeletal aging can result in several consequences, such as sarcopenia, increased joint laxity, meniscal degeneration, damage of bone structure, etc. [9]. All of these added together deteriorates bone health and increase the risk of developing OA (see figure 4.). This section will mainly focus on the effects of meniscal degeneration, the inability of tissues and cells to maintain homeostasis, and the degradation of the cartilage matrix.

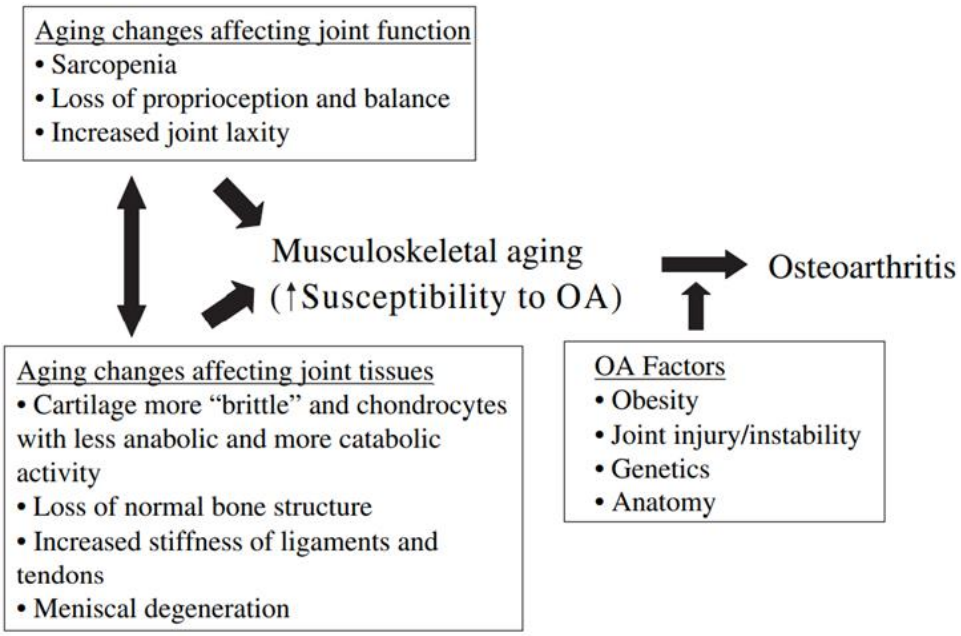



**Figure 4.** The relationship between musculoskeletal aging and the increase of susceptibility to OA. Changes in the joint due to aging may increase the susceptibility to OA; however, aging alone does not directly lead to OA; it is often accompanied by other risk factors of OA [8].

First, meniscal damage is very common in elderly people and is strongly associated with the increase in susceptibility to OA. The meniscus located in the joints plays a vital role in stabilizing the joint, reducing load, absorbing shock, and lubricating the joints in the knee for better movement. Hence, the degradation of the meniscus increases joint laxity, which will increase the risk of joint injuries and tissue damage, which ultimately increases the susceptibility to OA.

Second, OA can be caused by the loss of cells' or tissues' ability to maintain homeostasis, which is age-related [9]. In young and healthy individuals, the joint is able to handle stress and some degree of abnormal load distribution [9]; however, the responses to stress on joints are not adequate in older individuals. This is due to the deterioration of the fundamental biological systems that maintain tissue homeostasis. For instance, in the cartilage of a healthy individual, the chondrocytes maintain the balance. Growth factors, such as IGF-I and TGF-β, are critical anabolic factors [9]. However, studies have shown that as age increases, the response to IGF-I and the level of OP-1, TGF-β2 and TGF-β3 decreased [9]. A decrease in the response and level of these growth factors can lead to a decrease in anabolic activity which leads to cartilage degradation.

Third, a decrease in cartilage matrix is being observed in older individuals with the cartilage becoming thinner as age increases [9]. Because turnover rate of cartilage is slow, which is particularly vulnerable to advanced glycation end products (AGEs) [9], a harmful substance that is formed when proteins or fats combine with sugars in the bloodstream, a process called glycation. In young healthy individuals, the body can eliminate these substances; however, AGE naturally accumulates in the body as individual ages [9]. The cross-linking of the most abundant matrix protein in the cartilage, collagen II molecules, will be increased by AGE formation increases [9]. The increase in cross-linking of collagen molecules will then result in an increase in stiffness, increasing its susceptibility to fatigue failure [9]. Furthermore, an increase in AGE is related with a decrease in anabolic activity [9], which will eventually lead to cartilage degradation.

### 3.2. Female sex

Women in their 50s and 60s may be 3.5 times more vulnerable to hand OA than men in the same age range [8], women are 40% more susceptible to knee OA than men [10] and are 10% more susceptible to hip OA [11]. Furthermore, the severity of the condition is also higher in women. Though mounting evidence suggests that women are indeed more susceptible to OA compared to men. However, the reasons behind this are not entirely clear. There are several hypotheses regarding the reason behind this, which includes hormonal change, anatomy differences, and tendencies of carrying excess weight.

The first hypothesis is that because women's hips are wider than men's, and the quadriceps angle (Q-angle) is wider in women. Excess Q-angle adds more biomechanical stress when using the joint, which hastens cartilage damage, leading to OA [12].

Other studies have observed that there is an increase in joint laxity in women during menstruation which makes the joint weaker [13], increasing the possibility of getting injured in the knee which may damage the essential tissues located in the joint, and many postulates that this is due to the increase in estrogen level during menstruation because estrogen decreases the stiffness of the tendons and ligaments, making it weaker and more prone to injuries [14]. Hence, many experts believe that an increase in estrogen levels is to blame for athletes of female being more likely than males to suffer anterior cruciate ligament (ACL) injuries by 2 to 8 times [14].

However, some studies proven that women undergoing estrogen treatment have a reduced risk of developing OA, and the incidents of OA, especially knee OA, increase steeply as women enter the menopausal stage (see figure. 3) where a decline in the level of estrogen is happening. This is in contrast with the finding that an increase in estrogen level during menstruation can increase the risk of OA. Currently, there has been no clear consensus regarding how estrogen or the fluctuations of ovarian hormones affects the susceptibility of an individual to OA.

Lastly, according to the new research, women coming from the United States are more likely to be obese than males [15], and another major risk factor is obesity which will be discussed in the next section. Especially after menopause, women have a higher tendency of gaining weight. The reason behind this may be due to the decrease in estrogen level and physical inactivity. In addition to obesity, excess weight carried during pregnancy, fluctuations of hormones, and increased knee laxity during and after pregnancy may also be another reason for the increased incidents of OA among women.

### 3.3. Obesity

Several studies have revealed that the big body mass index (BMI) is associated with the vulnerability to OA. According to a study, obese individuals (BMI $\geq$ 30kg/m2) are more likely to develop OA compared to normal controls by 6.8 times [16]. Furthermore, according to Jiang et al., the results are consistent. These studies clearly show that there is indeed a positive correlation between an increase in BMI and susceptibility to OA.

One reason that obesity can lead to OA is that obesity can alter the biomechanics of the joint, for obesity adds weight to the joints, especially the weight-bearing joints located in the knees and hips. Furthermore, obese individuals have greater knee adduction moments and tend to walk slower with greater toe-out angles [17]. These factors added together increases the stress on the joint which alters the biomechanics and structure of the bone and will hasten cartilage damage, leading to joint destruction. This is also a reason why knee and hip OA are more common in obese individuals because these are the weight-bearing joints that are most heavily affected by an abnormal load distribution of the joint.

In addition to biomechanical factors, obesity can also create metabolic factors that may cause OA. Studies have shown that obesity leads to aberrant expression of adipokines [17], which are cell signaling molecules produced by the adipose (fat) tissue. Adipokines play a function in the body's metabolic condition, inflammation, obesity, etc. It has been discovered that two receptors, Leptins and Adiponectin, are present on the surface of synoviocytes and osteoblasts [17]; the aberrant expressions of adipokines in obesity will greatly increase the level of pro-inflammatory cytokines and

degradative enzymes, such as MMP and nitric oxide [17]. The biochemical environment produced due to obesity makes the chondrocytes unable to respond effectively, leading to the cartilage degradation which ultimately develop to OA.

### 3.4. Injury – Anterior Cruciate Ligament injury

Joint injuries increase the risk of developing post-traumatic osteoarthritis (PTOA), which result in the early onset of OA. In general, fractures or dislocations in the joints can lead to PTOA, and if not totally recovered, the abnormal structure of the joint may lead to increased stress which may hasten joint tissue damage, leading to OA.

The anterior cruciate ligament is an important tissue for joint stabilization. ACL injuries often happen in younger individuals and is the most common cause of PTOA. Data have shown that the occurrence of PTOA after experiencing ACL injury is as prevalent as 87% [18-19]. However, the mechanism responsible for the occurrence of OA followed by an ACL injury is multifactorial and is not totally understood.

It is suggested that ACL injuries lead to structural damage of the articular cartilage, for as measured on the magnetic resonance imaging (MRI), occult osteochondral lesion, or bone bruise, occurs in 80 to 90 percent of ACL injury patients, suggesting that the articular cartilage was subjected to a considerable amount of mechanical impact during the onset of the injury [20]. In addition, a damaged ACL would not be able to bear loads exerted on joints, leading to the increase in load on other structures such as the articular cartilage and meniscus which will lead to degradation of these tissues, resulting in OA [21]. Lastly, any injury in the synovial joint will alter the level of synovial fluid compounds, upregulating multiple proinflammatory cytokines (TNF-α, IL-1β, IL-6, etc.), which will lead to the degeneration of the joint, and may even persist for a long time. Especially after an ACL surgery, the joint is once again traumatized which can further increase the level of these pro-inflammatory factors [21], resulting in inflammation of the joint which make a difference in the progression of OA.

### 3.5. Genetics

According to the findings of a twin study, the influence of genetic factors on hand and knee OA in females ranges from 39% to 66%, independent of known environmental influences [22]. Another twin study discovered that narrow joint space of the hip is inheritable, about 60% [23]. All of these data taken together suggest that OA has a probability of inheritability of approximately 50% or more [24]. Genetics has numerous influences that can contribute to OA (see figure 5.). Genes, for example, can change the mechanism involving injury and its prevention and recovery, bone and cartilage structure, bone and cartilage turnover, etc. [24]. Female heritability appears to be higher, which should be emphasized.

Since OA is affected by several types of genes. Candidate genes include VDR, COL5A2, AGC1, AGF-1, ER-alpha, ER-beta and those encoding for the fibronectin and glycoproteins found in normal cartilage's extracellular matrix, the IL-8 receptor, and others. However, the findings of these association studies evaluating the genes linked to OA remain unclear and must be validated in future investigations.

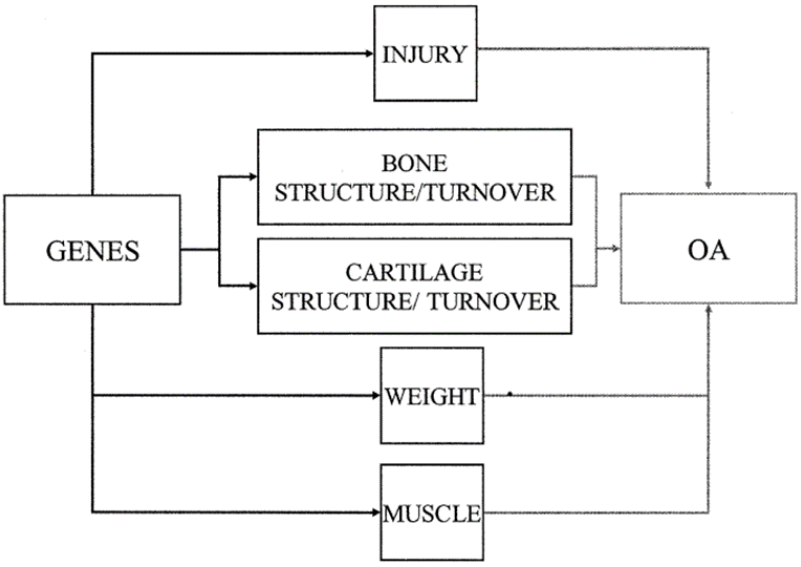



**Figure 5.** The role of genes in OA. Genes can influence how the body responds to and prevents damage, bone and cartilage structure, bone and cartilage turnover, weight, and muscles. All these are involved in OA and will affect the susceptibility of an individual to OA [24].

### 3.6. Neurological disease

Several studies have suggested that impairments of the nerves, especially those located in the joints, are also another factor that may lead to joint destruction and OA.

First, it is known that abnormal loading on the joints can lead to OA. This can be also caused by a deficiency in proprioception which can be caused by the decrease of proprioceptors. If there is a reduction or insensitivity of proprioceptors, then the central nervous system (CNS) will not be able to receive information regarding the position of the body, which can lead to abnormal gait and load distribution [25], ultimately resulting in joint destruction.

In addition to a lack of proprioception, the vasodilatory effects of different neurotransmitters are hampered in the early stages of OA joints, and vasoconstriction is eliminated in arthritic joints due to the loss of alpha-adrenoceptor activity [25], which are receptors that are involved in neurotransmission and are responsible for controlling blood pressure by inducing vasoconstriction. These observations suggest that an impaired neurovascular system in an arthritic joint will lead to decrease joint homeostasis which exacerbates the condition of the disease.

Furthermore, the mechano-gated ion channels of sensory nerves in the joints will open during movement, generating an action potential, which the CNS will interpret as normal movement; however, if the load distribution on the joint is aberrant, more mechano-gated ion channels open, resulting in the generation of more action potentials than normal. This time the CNS interprets it as pain [25]. This mechanism is beneficial, for it allows the body to correct any abnormal loading, preventing further damage to the joint. Hence, if such mechanism is altered, for instance, being insensitive, then it may lead to joint destruction. Interestingly, in OA patients, the activation threshold of these nerves is greatly reduced, leading to a bombardment of action potential even with normal movement. This results in the pain experienced by OA patients and leads to changes in brain morphology as observed in some OA patients [25]. Lastly, sensory nerves located in the joint may also fire the action potential in an antidromic direction (away from the axon terminal, towards the soma). This causes the nerve terminals to release pro-inflammatory neuropeptides [25], which can cause joint inflammation.

## 4. Conclusions

OA is a highly prevalent disease, especially in older individuals; however, the mechanism behind it is still poorly understood. Due to it being multifactorial, different factors can lead to different

pathways; hence, it is more complicated to fully understand the pathogenesis of the disease. Some of the risk factors of OA include old age, female sex, obesity, joint injury, genetics, and neurological disorders. These factors may lead to OA by degradation of integral tissues located in the joints, abnormal load distribution, loss of sense, altered biomechanics, production of pro-inflammatory factors, etc. After thoroughly reviewing the different risk factors and pathogenesis of OA, it is being suggested that further research regarding the pathogenesis of OA should be conducted, for this is not only beneficial for developing more efficient treatment but also allows people to understand the mechanism behind each risk factor, for it is being observed that even with identified risk factors, some of its mechanism is still not clear. With a clear understanding of the risk factors, individuals may prevent some of them, and if inevitable (ex. old age, female sex) people may develop practices to reduce the risk.

## References

[1] Hunter, D. J., March, L., et al. (2020). Osteoarthritis in 2020 and beyond: a Lancet Commission. The Lancet.

[2] Abramoff, B., & Caldera, F. E. (2019). Osteoarthritis. Medical Clinics of North America.

[3] Löfvall, H., Newbould, H., et al. et al. Osteoclasts degrade bone and cartilage knee joint compartments through different resorption processes. Arthritis Res Ther 20, 67 (2018).

[4] Maruotti, N., Corrado, A., et al. (2017). Osteoblast role in osteoarthritis pathogenesis. Journal of cellular physiology, 232 (11), 2957 – 2963.

[5] Han D, Fang Y, et al. The emerging role of fibroblast-like synoviocytes-mediated synovitis in osteoarthritis: An update. J Cell Mol Med. 2020 Sep; 24 (17): 9518 - 9532.

[6] Glyn-Jones S, Palmer AJR, et al. Osteoarthritis. Lancet 2015; 386: 376 – 87.

[7] Bay-Jensen AC, Slagboom E, et al. Role of hormones in cartilage and joint metabolism: understanding an unhealthy metabolic phenotype in osteoarthritis. Menopause. 2013 May; 20 (5):578 - 86.

[8] Prieto-Alhambra D, Judge A, et al. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. Ann Rheum Dis. 2014;73 (9): 1659 - 1664.

[9] Shane Anderson, A., & Loeser, R. F. (2010). Why is osteoarthritis an age-related disease?. Best practice & research. Clinical rheumatology, 24 (1), 15 – 26.

[10] Losina E, Weinstein AM, et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. Arthritis Care Res (Hoboken). 2013; 65 (5): 703 – 711.

[11] Murphy et. al, "One in four people may develop symptomatic hip osteoarthritis in his or her lifetime," Osteoarthritis and Cartilage 18 (2010): 1372 - 1379.

[12] Khasawneh RR, Allouh MZ, et al. Measurement of the quadriceps (Q) angle with respect to various body parameters in young Arab population. PLoS One. 2019 Jun 13; 14 (6): e0218387.

[13] Shultz SJ, Sander TC, Kirk SE, Perrin DH. Sex differences in knee joint laxity change across the female menstrual cycle. J Sports Med Phys Fitness. 2005 Dec; 45 (4): 594 - 603.

[14] Chidi-Ogbolu N, Baar K. Effect of Estrogen on Musculoskeletal Performance and Injury Risk. Front Physiol. 2019 Jan 15; 9: 1834.

[15] National Association of Diabetes and Digestive and Kidney Diseases. Overweight & Obesity Statistics. Last Updated August, 2017. Accessed October 30, 2020.

[16] Coggon D, Reading I, et al. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord. 2001 May; 25 (5): 622 - 7.

[17] King LK, March L, et al. Obesity & osteoarthritis. Indian J Med Res. 2013; 138 (2): 185 - 93.

[18] Shelbourne KD, Stube KC. Anterior cruciate ligament (ACL)-deficient knee with degenerative arthrosis: treatment with an isolated autogenous patellar tendon ACL reconstruction. Knee Surg Sports Traumatol Arthrosc 1997; 5: 150 – 6.

[19] Nakata K, Shino K, et al. Arthroscopic anterior cruciate ligament reconstruction using fresh-frozen bone plug-free allogeneic tendons: 10-year followup. Arthroscopy 2008; 24: 285 – 91.

[20] Potter HG, Jain SK, et al. Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up. Am J Sports Med 2012; 40: 276 – 85.

[21] Friel, N. A., & Chu, C. R. (2013). The role of ACL injury in the development of posttraumatic knee osteoarthritis. Clinics in sports medicine, 32(1), 1–12.

[22] Spector TD, Cicuttini F, et al. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996;312: 940 – 3.

[23] MacGregor AJ, Antoniadis L, et al. The genetic contribution to radiographic hip osteoarthritis in women: results of a classic twin study. Arthritis Rheum 2000; 43: 2410 – 6.

[24] Spector TD, MacGregor AJ. Risk factors for osteoarthritis: genetics. Osteoarthritis Cartilage. 2004; 12 Suppl A: S39 - 44.

[25] McDougall, J. J. (2019). Osteoarthritis is a neurological disease – a hypothesis. Osteoarthritis and Cartilage Open, 100005.