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Risk factors and molecular entities of the etiopathogenesis of the knee osteoarthritis (literature review)

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Introduction Osteoarthritis (OA) is a heterogenic group of disorders of different etiology with similar biological, morphological and clinical manifestations and outcomes. OA is now considered a disease of the whole joint, including alterations in the articular cartilage, subchondral bone, synovial membrane, ligaments, capsule and periarticular muscles. OA of the knee as the most commonly affected joint accounts for the great medical, medical, social and economic impact. **Material and methods** A literature review assessing Russian and foreign studies on molecular mechanisms of etiology and pathogenesis of knee OA identified a set of factors for which there was consistent evidence for their association with onset of knee OA. A search of studies published in Russian and in English for the last ten years was conducted using bibliographic databases, including PubMed, PubMedCentral, GoogleScholar, eLIBRARY. Search terms included 'knee osteoarthritis', 'etiology', 'pathogenesis', 'risk factors'. **Results** Review of the literature showed that patients with knee OA are characterized by changes in cartilage, subchondral bone, synovium, suggesting common mechanisms of joint degeneration during OA development. Osteoarthritis (OA) is multifactorial in origin and closely associated with a wide spectrum of local (previous injury, muscle weakness, knee malalignment, knee surgeries, abnormal mechanical loading, excessive high impact sports, occupational physical activities) and systemic risk factors (advanced age, female sex, height, greater body mass index and obesity, hormone status, family history, mineral bone density, vitamin D deficiency, ethnicity). The prevalence of the knee OA and patterns of joint involvement vary among different racial and ethnic groups. **Conclusion** The literature review allowed us to identify the molecular mechanisms of etiopathogenesis of knee OA and the major risk factors for the pathology.
Keywords: knee osteoarthritis, etiology, pathogenesis, risk factors

INTRODUCTION

Osteoarthritis (OA) is a heterogenic group of disorders of different etiology with similar biological, morphological and clinical manifestations and outcomes. OA is now considered a disease of the whole joint, including alterations in the articular cartilage, subchondral bone, synovial membrane, ligaments, capsule and periarticular muscles [1]. OA of the knee as the most commonly affected joint accounts for the great medical, medical, social and economic impact [2]. The World Health Organization estimates are that 9.6 % of men and 18.0 % of women > 60 years of age have symptomatic OA. [3]. Radiological signs of OA are normally observed in the population over 65 years old. Knee OA is the most common form of osteoarthritis [4]. Among the adult population of Russia, rheumatoid patients include mostly OA cases with more than 4 million registered in 2012–2013, and more than half of them (about 2.5 million) are individuals older than the working age [5]. Eighty percent of patients with OA have limitations in movement and 25 % cannot perform their major daily activities [3]. Knee OA leads to a significant decrease in working capacity and disability of people of working age [2]. It should also be noted that patients with progressive OA of the knee joint are at risk of total knee replacement (TKR) which is an effective method of treatment but rather expensive [6, 7]. Patients < 55 years of age represent the fastest growing group of TKR recipients according to the joint replacement registry of the R.R. Vreden RNIITO [8]. With the great medical, social and economic impact of the condition, the underlying mechanisms associating knee OA onset, progression and risk factors are not yet understood, but their identification would provide novel targets for the management and prevention of the disease in adults. The review is aimed at the analysis of the Russian and foreign publications on the etiology and pathogenesis of knee OA, as well as the major risk factors for the disease.

MATERIAL AND METHODS

A literature review assessing Russian and foreign studies on molecular mechanisms of etiology and pathogenesis of knee OA identified a set of factors for which there was consistent evidence for their association with onset of knee OA. A search of studies published in Russian and in English for the last ten years was conducted using bibliographic databases, including PubMed, PubMedCentral, GoogleScholar, eLIBRARY.

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Search terms included 'knee osteoarthritis', 'etiology', 'pathogenesis', 'risk factors'. Earlier papers describing important aspects of etiology and pathogenesis of knee OA, risk factors for the condition were added, if needed.

RESULTS AND DISCUSSION

Molecular mechanisms of etiology and pathogenesis of knee OA have been explored by international and Russian researchers for many decades [9–22]. It should be noted that in recent years, the understanding of the etiopathogenesis of OA of the knee joint has undergone significant changes. Knowledge about the pathogenesis of the disease has evolved from being presented as age-related wear and tear of the joint to recognizing the involvement of all the structures into the pathological process, immune and genetic aspects of the disease, and neurogenic mechanisms of pain [9–11]. There are strong associations of the condition with disorders in the metabolism of articular cartilage and subchondral bone in addition to synovial inflammation [11–14]. T.P. Andriacchi et al. (2015) reported the role of biological, mechanical and structural factors in the pathogenesis of OA in the systematic review [15]. The authors noted that a failure in one of the factors (for example, mechanical) led to changes in other factors (for example, biological and/or structural) with resultant destruction of articular cartilage and the development of OA [15]. S. Glyn-Jones et al. (2015) described OA as a multifactorial disease with genetic, biological and biomechanical factors playing an important role in the pathogenesis of the disease [13]. A.I. Dyadyk et al. (2012) presented OA pathogenesis as shown in the diagram [16] (Fig. 1). Articular cartilage degradation and synovial inflammation were seen as major factors in the development of the disease. Cartilage degradation leads to the synthesis of proinflammatory cytokines, "defective" collagens and proteoglycans by chondrocytes, sclerosis, micro-fractures and cysts in the subchondral bone, osteophytes, softening, fissuring and loss of hydrophilicity of the cartilage tissue. Synovial inflammation contributes to joint dysfunction, pain and progression of cartilage degradation.

It should be noted that the inflammatory process affects almost all structures of the joint with resultant synovitis, chondritis, osteitis [11, 17–18]. A long-term chronic inflammatory process in the synovial membrane results in changes in the metabolism of chondrocytes and impaired biosynthetic balance with catabolism prevailing over anabolism [19].

A role of cytokines in the pathogenesis of knee OA is reported by many researchers [16, 20–22]. It is worth noting that the synthesis of cytokines is dependent on the duration and severity of OA, can change significantly with evident immune response involved in the inflammatory process.

Among cytokines, the most important are interleukin 1β, tumor necrosis factor α, interleukins 6, 15, 17 and 18, with increased levels in the synovium, the fluid, and cartilage seen in OA patients [21]. These cytokines lead to increased synthesis of metalloproteinases (MMP) in chondrocytes, decreased synthesis of proteoglycans, tissue inhibitor of MMP contributing to producton of oxygen radicals, nitric oxide with the latter facilitating progression of catabolism in cartilage [22–23].

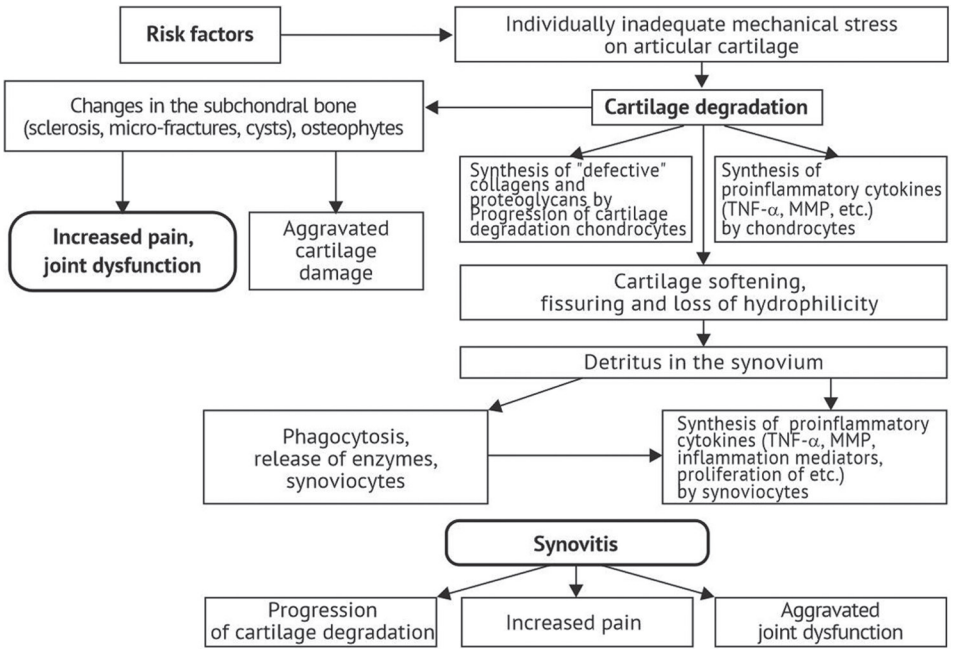

Fig. 1 Diagram of OA pathogenesis [16]. TNF-α, tumor necrosis factor α, IL-1, interleukin 1, MMP, matrix metalloproteinases

Destructive changes in the joints in OA are also associated with increased expression of isoform of nitric oxide synthase (NOS). This enzyme is capable of regulating interleukin 1 induced formation of nitric oxide. An increased level of nitric oxide results in chondrocyte resistance to growth factors with the synthesis in the cartilage matrix being suppressed and apoptosis of chondrocytes induced [12].

L.T. Nguyen et al. (2017) presented molecular mechanism of OA pathogenesis in the form of sequential and interrelated links (Fig. 2) [24]. The first stage was characterized by proteolytic destruction of the cartilage matrix resulting from impaired metabolism of chondrocytes, increased secretion of such degradative enzymes as collagenases and aggrecanases. The second stage involved fibrillation and erosion of the cartilage surface, followed by release of debris products into synovial fluid. At the third stage, inflammation of the synovial membrane resulted from the debris penetrating into synovial cells that facilitated production of pro-inflammatory cytokines and proteases leading to destruction of the cartilage matrix [24].

G. Musumeci et al. (2015) reported the OA-associated molecules, including IL-1β, TNF-α, RAGE, leptin, IGF-1, TGFβ1, iNOS, MMP13, laminin, fibronectin, integrin and collagen as being involved in chondrocyte activation contributing to the pathogenesis of OA by destroying the cartilage in the joints or serving as the substrates for extracellular matrix destruction [25]. There are a number of other inflammatory mediators that also contribute to OA pathogenesis. The biological activity of prostoglandins, leukotrienes, protease-activated receptors (PARs) is known to play a role in tissue degradation and reparation, angiogenesis, nociception, and neurogenic inflammation [26]. Immune factors play a significant role in the pathogenesis of knee OA. Circulating autoantibodies to proteinglycans are detected in the blood of patients with early OA [27]. The resulting antigen-antibody complex leads to the destruction of macrophages in the synovial membrane facilitating release of inflammatory mediators with a damaging effect on chondrocytes and causing synovitis [26]. Meanwhile, the synovial membrane releases biological mediators of inflammation that contribute to destructive processes in the cartilage forming a vicious circle [17, 28].

In recent years, views on causal aspects in OA pathogenesis have undergone significant changes. In the first instance, there was cartilage damage, which also affected articular space and subchondral bone at a secondary phase [24]. To date, there is evidence of subchondral bone changes playing a key role in the disease pathogenesis [18, 20]. Normal bone structure is ensured by a balance between bone formation and resorption. Many hormones, growth factors, and cytokines are involved in the regulation of these processes. According to modern literature [29, 30], a key role in the regulation of bone cell metabolism is assigned to the molecular triad: osteoprotegerin; receptor activating transcription factor NFkB; ligand of this receptor (OPG/RANK/RANKL). The level of sex hormones is one of the factors that regulates functioning of this triad [20].

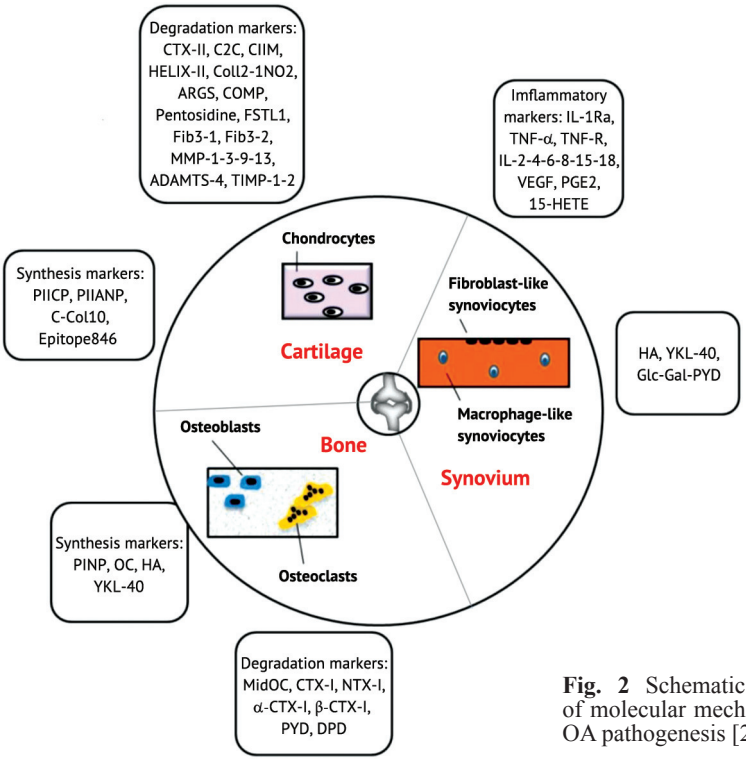

Fig. 2 Schematic diagram of molecular mechanisms of OA pathogenesis [24]

Deficiency of female sex hormones is known to lead to an increase in the expression of RANKL by stromal cells. RANKL binding to RANK, which is expressed on osteoclast progenitors stimulates their differentiation and functional activity of mature cells [19]. At the same time, there is a decrease in RANK – OPG antagonist expression in stromal cells and osteoblasts [29]. These processes lead to changes in the subchondral bone, slowing down bone formation with resultant decrease in the proliferation of osteoblasts and their functional activity.

O.V. Sinyachenko et al. (2016) reported a role of bone metabolism in the pathogenesis of gonarthrosis in patients with knee OA showing significant changes in blood markers of bone metabolism with imbalance of osteoassociated macronutrients (calcium, magnesium, phosphorus), the development of hypocalcemia observed in 98 %, high activity of alkaline phosphatase (in 47 % of cases), signs of hyperparathyroidism and hyperosteocalcemia [31]. The main etiological factors of knee OA include micro-and macro-injuries to the joint that occur as a result of intense physical stress including sports, overweight, etc. [17, 22]. In this case, the unevenly distributed load on the surface of the articular cartilage and the maximum pressure are concentrated over a small area, at the site of the greatest convergence of the articular surfaces, leading to cartilage dystrophy and degeneration [12, 32]. These negative processes are associated with impaired cartilage metabolism and decreased level of proteoglycans and collagen fiber tears.

There is evidence of a role of cartilage erosion in the medial knee in OA pathogenesis [33, 34]. S. R. Lyu et al. (2015) revealed higher concentrations of total protein, TNF-α, IL-1β and MMP-3 in the medial part of the knee joint in patients with the disease [33]. A. Heijink et al. (2012) focused on biomechanical aspects of pathogenesis of knee OA including meniscal damage, cartilage defects and joint instability [35].

Osteoarthritis of the knee joint is a multifactorial disease [36]. There are a number of risk factors for the development of knee OA [22, 37, 38]. The current understanding of the origin of OA is that this disease occurs due to the interaction of many local and systemic risk factors [25, 38, 39]. Systemic risk factors for knee OA include older age, female gender, tall height, overweight and obesity, hormonal status, hereditary predisposition, bone mineral density, vitamin D deficiency, and ethnicity [23, 25, 39, 40]. Local risk factors for OA are history of joint injury, muscle weakness, limb malalignment, surgical interventions on the joint, strenuous physical activity including sports and occupational activity [25, 40-41]. Risk factors such as age, gender, ethnicity, and genetic factors are classified as non-modifiable risk factors for the disease (Fig. 3) [25], and overweight, squatting, and cycling are included in the group of modifiable risk factors for knee OA [42]. G. Musumeci et al. (2015) emphasized the role of local risk factors in the development of OA (Fig. 3).

Age is one of the most important risk factors for knee OA [10, 22, 43]. The prevalence of knee OA increases indefinitely with age [2, 19, 44]. Aging can be associated with a decreased ability of chondrocytes to restore the articular cartilage matrix which inevitably leads to a deficiency of interstitial matter. The cartilage matrix is likely to be more sensitive to micro-damage in old age with cell repairation mechanisms failing to compensate for this increasing sensitivity.

Female sex is an important risk factor for knee OA . There is a higher incidence of knee joint OA in women than in men [19, 38]. Moreover, the risk of knee OA in menopausal women is higher [25] and associated with estradiol deficiency. Sex hormones are known to modify the metabolism of cartilage tissue [19, 20]. A reduced level of estrogen in menopausal women causes an increased level of metabolism in the subchondral bone, decreased muscle strength and mass and chondrocyte destruction. Hormone replacement therapy with estrogens in postmenopausal women is associated with a lower risk of knee and hip OA [45].

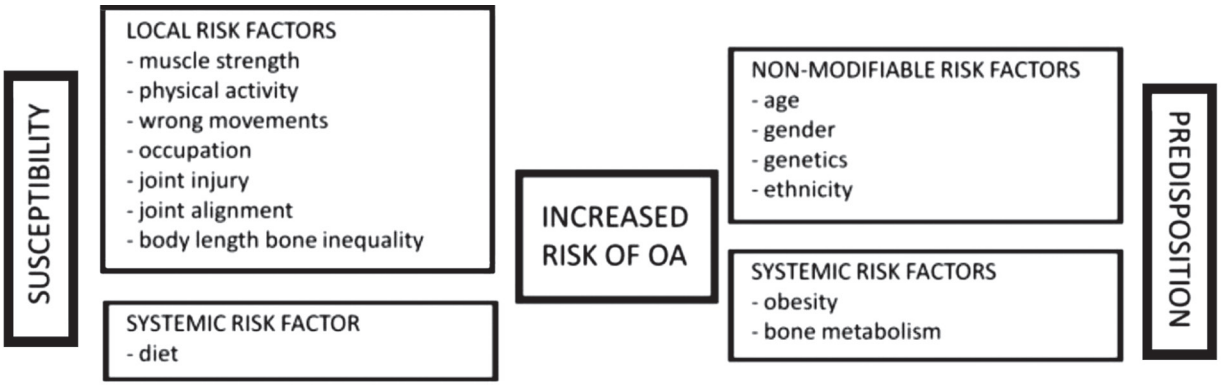

Fig. 3 Schematic diagram of risk factors for OA [25]

S. Lee et al. (2017) estimated the national prevalence of knee OA in the Korean population and found the condition being 2.1 times higher in women than in men (43.8 % and 21.1 %, respectively) [46]. S. Muraki et al. (2012) also reported the incidence of radiological knee OA grade 3 or higher according to the Kellgren/Lawrence classification (K/L) in Japanese women being 13.9 %, which is 1.7 times higher than in men (8.4 %, OR 1.34 95 % CI 1.15-1.58) [47]. This group of researchers detected that knee pain was not only an important risk factor for the occurrence, but also for the progression of knee OA [47].

High bone mineral density (BMD) is known as an increased risk factor for OA, with low bone mineral density being a protective factor [22, 48-49]. No data describing the influence of molecular mechanisms of BMD on the risk of developing OA could be found in modern literature [48]. K. N. Linde et al. (2017) reported the level of P1NP (N-terminal propeptide procollagen type 1) as a marker of bone metabolism, being significantly higher in patients with knee Kellgren/Lawrence grade IV OA than in patients with Kellgren/Lawrence grade III OA (45.9 mg/l and 41.9 mg/L, respectively, p = 0.03) [50].

Osteoarthritis is a comorbid disease often combined with cardiovascular pathology, obesity, diabetes mellitus, osteoporosis, etc. [51, 52]. H.S. Kim et al. (2016) reported the prevalence of knee OA in patients with diabetes mellitus being 2.4 times higher than in patients without diabetes, adjusted for age and gender (OR 1.19 95 % CI 1.00-1.41; p = 0.04) [53]. F. Eymard et al. (2015) explored the influence of metabolic factors (obesity, diabetes, hypertension and dyslipidemia) on the rate of progression of knee OA and found that the width of the articular space was significantly less in patients with knee OA without type 2 diabetes than in patients with diabetes mellitus (p = 0.018) [52]. Type 2 diabetes mellitus in patients with knee OA joint can be considered a risk factor for the disease [25, 54]. Niu et al. (2017) detected neither metabolic syndrome nor its components being associated with radiographic and symptomatic knee OA with no statistical significance after adjustment for body mass [55].

Obesity and excessive body weight have been associated with the development and progression of knee OA [10, 40, 56–58]. Jiang et al. (2012) reported a direct relationship between obesity and the risk of OA in patients with knee OA with the relationship being significantly stronger in women than in men [59]. The authors found that an increase in body mass index by 5 kg/m2 increases the risk of knee OA by 35 % (OR 1.35 95 % Cl 1.21–1.51) [59]. Weight loss is recognized as an effective measure for the prevention and treatment of gonarthrosis [60]. Several studies and meta-analyses of the relationship between weight loss and clinical outcomes of OA demonstrate the important role of diet therapy as a major factor in the prevention of knee OA [61–62]. S. P. Messier et al. (2013) reported a 9.5 % reduction in body weight induced by diet after 18 months among overweight and obese adults, and participants in the diet + exercise groups had a significantly lower level of pain than those in the exercise group [61]. Overweight and obesity are risk factors for knee OA and for the progression of the disease [40, 62–64]. Arthroscopic evidence indicates to the negative role of synovial inflammation in the progression of cartilage degradation in gonarthrosis [65]. D.T. Felson et al. (2016) reported synovitis as an independent cause of OA in the review of 239 patients with knee OA and 731 controls (OR 1.1 95 % Cl 1.0-1.2, p = 0.02) [66].

Vitamins and other micronutrients are involved in the pathogenesis of OA with vitamin D deficiency being a risk factor fo knee OA [9, 67–69]. Higher circulating serum levels of 25(OH)D is associated with less cartilage loss in the knee joint [70], and reduced vitamin D intake and low serum vitamin D levels are associated with a higher risk of progression of gonarthrosis [71]. Race differences in experimental pain are shown to be mediated by differences in the vitamin D level. T. L. Glover. et al. (2012) reported vitamin D deficiency as a risk factor for increased knee OA pain in black Americans [72]. There is evidence of vitamin K's role in regulating skeletal mineralization [19, 73]. In the longitudinal study, D. Misra et al. (2013) reported subclinical vitamin K deficiency being associated with increased risk of developing radiographic knee OA (OR 1.56; 95 % CI 1.08–2.25) [73].

There are controversies regarding prevalence of knee OA in different ethnic groups. African Americans had slightly higher prevalence of radiographic knee OA defined as Kellgren-Lawrence radiographic grades 3 and 4 compared to Caucasians [74]. B.R. Deshpande et al. (2016) estimated that in the United States in 2007–08, 13.7 million had symptomatic knee OA, with 10.4 million persons among non-Hispanic whites and 3.4 million persons among non-Hispanic blacks and Hispanics and other racial/ethnic minorities [4]. Y. Cruz-Almeida et al. (2014) detected that African American subjects with knee OA displayed increased pain sensitivity when compared to non-Hispanic white subjects with knee OA [75].

Genetic influences are mostly revealed in generalized OA. Assessment of hip and knee joints in 992 monozygotic and dizygotic female twin participants from the TwinsUK Registry showed the contribution of hereditary factors to the development of knee OA that accounted for 37 % [76]. S.G. Skousgaard et al. explored sex differences in risk and heritability estimates on primary knee osteoarthritis leading to total knee arthroplasty and found 18 % of the variation being attributable to genetic factors and 82 % of the variation being attributable to common and unique environmental factors [77].

Muscle weakness is known to be associated with an increased risk of developing knee OA [18, 78–79]. S. Muraki reported quadriceps muscle weakness being significantly associated with knee pain in knee OA [80]. The systematic review and meta-analysis conducted by B.E. Oiestad et al. (2015) showed that knee extensor muscle weakness was associated with an increased risk of developing knee OA in both men and women [81].

Local risk factors for knee OA include increased physical activity. Regular moderate physical activity has well-known effects on lower-limb OA, decreasing pain and improving function. Y. Wang et al. reported increasing levels of total physical activity being positively associated with the risk of primary knee replacement due to OA [82]. C. Gay C. et al. (2018) reviewed interviews of 548 people with knee OA with 42.6 % of patients reported high, 38.6 % moderate, and 18.8 % low physical activity level [83]. Variables significantly related to inactive or minimally active PA levels were BMI ($p = 0.03$) and sex ($p = 0.0008$), and biomedical barriers, related to self-efficacy ($p = 0.0118$) [83]. The study performed by J. Gholami did not show any significant association between knee OA and daily occupational and non-occupational activities like squatting, climbing, kneeling, lifting and carrying weights [84].

Knee OA was also shown to be associated with occupational factor and sport loads. Occupational activity associated with performing repetitive movements can lead to overloading the joints and fatigue muscles and increase the risk of developing OA in the joints [25]. In this case, the risk of OA is doubled compared to people whose activities do not require physical activity and repetition of movements [85]. Exposure to physical work activities can aggravate knee OA. There is evidence that work performed on the knees when the joint is bent for a long time increases the risk of developing knee OA [19, 86]. Increased risk of developing knee OA was found among those who work with the knee joint being bent for a long time [19, 86].

A higher incidence of knee OA was reported in high-impact sports (football, baseball, runners) players due to greater stress on the joint, a wrong movement during performance resulting in injury to articular cartilage, subchondral bone, collateral ligament and meniscus [25] that can often cause secondary or posttraumatic OA. K.A. Timmins et al. (2017) performed a systematic review and determined no significant association between running and the development of knee OA [88]. S. Mat et al. (2015) reported strength training and aerobics exercises improving balance and falls risk in older individuals with knee OA [89]. Traumatic injuries play a significant role in the etiopathogenesis of knee OA but the condition cannot be unequivocally recognized as a posttraumatic disease [25]. S. Muraki et al. (2012) reported a previous knee injury being a risk factor for knee pain but not for radiographic knee OA [90].

CONCLUSION

The literature review demonstrated a diversity of molecular mechanisms in the etiology and pathogenesis of knee OA. First, mechanisms associated with impaired cartilage metabolism, inflammation, changes in the subchondral bone, and pathological processes in the synovium were shown to play a significant role in the development of knee OA. Second, knee OA appeared to be a heterogeneous disease with a range of risk factors including local (history of knee injury, muscle weakness, joint malalignment, surgical interventions on the joint, increased physical activity) and systemic (older age, female gender, high height, overweight and obesity, hereditary predisposition, bone mineral density, vitamin D deficiency, ethnicity) aspects. The risk factors are essential for genetic and epidemiological studies of knee OA.

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