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Effect of cold on knee osteoarthritis: Recent research status

Haile Pan[#], Zilong Shen[#], Qi Chen, Rui Jiang, Yongchen Wang*

Abstract

Osteoarthritis is a common chronic irreversible joint disease characterized by degenerative changes of articular cartilage and secondary hyper osteogeny. Knee osteoarthritis(KOA) affects not only the articular cartilage, but also the entire joint, including subchondral bone, joint capsule, synovial membrane, meniscus, ligaments, periarticular muscles, and tendons. The primary aim of treatment is to relieve symptoms, delay joint degeneration, and maximally maintain patient's quality of life. There are many risk factors contributing to the development of KOA, including climate. This review will discuss the relationship between climate in cold region and KOA and the possibility of modifying risk factors such as the environment for the prevention and treatment of KOA.

Keywords

effect, knee, osteoarthritis, cold region, climate

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The Second Affiliated Hospital of Harbin Medical University, Harbin 150081, China

**Corresponding authors Yongchen Wang, E-mail: yongchenwang@163.com*

[#]These authors contributed equally to this work

1 Introduction

Osteoarthritis (OA) is the most common disease involving multiple anatomical and pathophysiological changes in joint tissue. Its pathogenesis and etiology are complex, and it has long been regarded as an overall joint disease or a collection of degenerative diseases including cartilage degeneration, bone remodeling, and osteophyte formation, *etc*[1-2]. The main clinical manifestations of OA include joint pain, stiffness, swelling, limited joint function and even deformity. OA is one of the main causes of disability in the elderly. In a large investigation of people over 50 in England, about half of the respondents said they had OA in at least one of the joints of the hands, elbows, hips, knees or feet[3].

The prevalence of knee osteoarthritis (KOA) has been more extensively studied compared to other joints[4-7]. Risk factors for KOA have been predicted by multiple groups. A retrospective study by Black *et al*.[8] predicted age, sex, body mass index, trauma, and osteoporosis to be the risk factors of KOA. It is also believed that genetic factors, metabolism, inflammation, diet and other factors have important impacts on the development of OA[9]. In addition, climate is also associated with the incidence of OA, since the prevalence of KOA in residents in cold regions is higher than in warm areas[10]. An investigation in Germany and Canada reported that about 40% of the subjects felt that the climate, especially temperature and humidity, affected the onset of their OA symptoms[11]. Therefore, this review summarizes the research status of KOA in cold regions.

2 Research Status

2.1 Impact of cold on joint bones

The specific mechanism of KOA is still inconclusive, but it is likely related to factors such as bone, cartilage and subchondral bone marrow lesions[12]. Studies have reported the effect of temperature on bone, indicating that local hypothermia above 0°C can cause chronic tissue damage[13-14]. Joint injuries were found in nearly 40 percent of 76 workers in a cold-storage facility after 20 years of occupational exposure. It is reported that found that these patients had typical clinical manifestations such as pain, soft tissue swelling, and limited joint motion. Imaging showed irregular articular surfaces and subchondral border osteophytes. In severe frostbite (grades II, III, and IV), there are radiographic changes in bone tissue after 4 to 10 weeks: the initial presentation is osteoporosis, similar to reflex dystrophy. As the disease progresses, osteonecrosis can be detected by imaging. In more severe cases, patients can develop joint dislocations and subluxations. The bone and joint changes caused by this severe frostbite are different from those of rheumatoid arthritis (RA). The proximal interphalangeal joints of these patients are rarely affected, and the rheumatoid factor test is also negative. Additional studies have shown that chronic cold injury can lead to destructive joint pathology with erosions, marginal osteophyte formation, and minor subluxation[15]. Chen

et al.[16] also found in rat models that cold stress can lead to increased expression of inflammatory factors such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and increased level of transient receptor potential vanilloid 1 and ankyrin 1 (TRPA1) and tetrahydrobiopterin (BH4). These factors can aggravate the pathological changes of OA. It has been shown that cold stimulation can constrict peripheral blood vessels and reduce circulating blood volume, resulting in cartilage cells in a state of hypoxia. Anaerobic respiration leads to accumulation of acidic substances and a decrease in the pH value of the surrounding environment, thereby causing damage to the surrounding bones[17].

2.2 Impact of cold on cartilage of knee joint

In addition to bone-damaging changes, all cartilages are highly susceptible to cold environments. Temperature can significantly affect the metabolism and phenotype of articular cartilage[18]. Low temperature inhibits chondrocyte metabolism and interferes with chondrocyte synthesis[19]. Animal studies have been conducted to explore the effect of hypothermia on the progression of OA in cold environment. Kocaoglu *et al*.[20] confirmed that low temperature environment can inhibit the synthesis of RNA, lactate, and proteoglycans in chondrocytes, thereby promoting the degradation of extracellular matrix (ECM). This inhibition can be weakened with the increase of temperature. Ainola *et al*.[21] found that the transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8) protein can be opened under cold stimulation, causing intracellular Ca^{2+} overload and cartilage necrosis, ultimately leading to OA pain and increased level of inflammatory factors. Chen *et al*.[22] compared the progression of KOA between two groups of rats at 25±2°C and 15±2°C. Their X-ray results showed that under low temperature, the knee joint space and joint surface were narrowed. There is decreased smoothness along with osteophyte formation. HE staining showed collapse of articular cartilage with necrosis of chondrocytes, disordered cartilage arrangement, and vascular invasion in the cartilage layer. Synovial fluid ELISA and immunohistochemical staining showed increased protein expression of IL-1β, TNF-α, vascular endothelial growth factor (VEGF), and matrix metalloproteinase-13 (MMP-13). These can cause the loss of articular cartilage and increase the prevalence of arthritis. MMP-13 is the most studied MMP in cartilage pathology. It is considered to be one of the key enzymes in the development of KOA. The ability of MMP-13 to decompose type II collagen is 5-10 times higher than that of MMP-1[23]. Due to its strong ability to decompose type II collagen in articular cartilage, MMP-13 is considered the main catabolic factor of OA[23]. MMP-13 also degrades other ECM molecules that play an important role in healthy cartilage metabolism, such as collagen types IV and IX, holo-proteoglycans, osteonectin, and proteoglycans[24]. In OA, MMP-13 expression is significantly increased, resulting in a greater degree of degeneration of articular cartilage[25]. Study has found that low-temperature environment can increase the death rate of chondrocytes[26]. Dying chondrocytes eventually release the cellular contents such as MMP-13, further impairing ECM[27]. In addition, studies have found that epiphyseal cartilage is susceptible to cold, which can lead to growth restriction and even bone deformities[28]. A study induced metatarsal head cartilage necrosis by cryoprobe Segmental loss of nuclear staining was present at 1 week, followed by loss of chondroitin sulfate (toluidine blue discoloration and safranin staining) a few days later. But not until 6 months later did significant degenerative arthritis begin. Moreover, studies have found that in addition to the death of cartilage cells, externally applied pressure is an important factor necessary for destroying the collagen skeleton and initiating degenerative arthritis[29].

2.3 Impact of cold on knee pain symptom

The most common clinical manifestation of KOA is knee pain. In the cold regions of northern China, senile knee pain is commonly called “old cold legs”, and most of the so-called “old cold legs” end up with clinical diagnosis of KOA[30]. “Old Cold Legs” reflects that, firstly, patients attribute the cause of the disease to cold; secondly, patients believe that cold can aggravate pain symptoms, and most patients believe that cold is closely related to the development and symptoms of their disease. Medically, this kind of cold-induced knee pain is also called “cold knee pain”[31]. There is also growing evidence indicating that climate is closely related to the degree of symptoms of OA patients. According to the statistics of an epidemiological survey, 33 percent to 66 percent of OA patients believed that their symptoms were significantly affected by the low ambient temperature, and nearly half (49.2%) reported that the weather could aggravate their joint pain[11]. Although no differences were found in the involvement of pathological arthritis between cold and warm regions, studies have shown that arthritis patients living in colder regions (55”N) have more joint pain complaints than those living in warmer regions (18”N) [32]. It has been suggested that, for people with arthritis living in warm climates, their joints are not sufficiently sensitive to temperature changes that can cause spontaneous pain[33]. Other studies also pointed out that KOA patients are more susceptible to cold pain than normal people[34].

Attention has been paid to the effect of temperature on OA, but the effect of ambient temperature on OA has not been commonly recognized. Most researchers believe that temperature can affect the pathological changes or pain in OA patients[35]. McAlindon *et al*.[36] studied 200 patients with KOA and found that changes in

air pressure and ambient temperature affect pain symptom. Yet different opinions exist. Zhao *et al*.[37] showed that temperature reduction increased hospital admissions in patients with RA, but there was no significant correlation between admissions and OA patients. The auhors believe that the effect of temperature on OA is due to wrong attribution. It is assumed that because of the strong believe that cold can cause joint pain in OA patients and the decrease of outdoor temperature will increase the pain in patients, the number of patients who rush into the hospital for OA will go up. However, clinical statistics did not reach a common conclusion[38]. Similarly, Dorleijn *et al*.[36,39] found that a 0.5-point increase in the knee pain score was not clinically significant after a 28°C decrease in temperature (from 38°C to 10°C). Ferreira *et al*.[40] indicated that weather factors did not trigger the onset of increased pain in patients with KOA. Therefore, the current research results on the effect of temperature on pain symptoms in OA patients and the relationship between the two are still inconsistent. Thus, a large sample size, multi-center study is required to confirm the effect of temperature on pain symptoms in OA patients.

2.4 Impact of cold combined with humidity on knee joint

In addition to the influence of temperature as single factor on OA as described in the aforementioned studies, greater impacts on OA imposed by the combination of low temperature with other factors have been proposed. One such example is the so-called “trench foot” that soldiers often suffer following standing in cold water or mud with wet boots for a long period of time, as well as some shipwreck survivors[15]. It is proposed that in low-temperature environment above 0°C, tissue damage is more likely to be aggravated with humidity and inactivity[15]. Subcutaneous fibrosis may sustain a long-lasting impairment of joint mobility for years. Hollander and colleagues found that 5 of the 24 patients with arthritis included in their study developed more severe joint stiffness after exposure to cold temperatures and 10 had increased joint stiffness after exposure to reduced air pressure and elevated humidity[6]. Erik *et al*.[41] found that the effect of humidity on pain was stronger in cold weather conditions. Humidity and temperature may affect the expansion and contraction of various tissues in affected joint, which may cause pain symptoms[42-44]. In addition, low temperature may increase the viscosity of synovial fluid, which can make joints stiffer resulting in greater sensitivity to pain with mechanical stress. The effect of relative humidity on OA joint pain was stronger in cold weather than in warmer one. This finding supports the popular view that joint pain in elderly OA patients is affected by both wet and cold weather conditions. Cold can increase the viscosity of synovial fluid, which may lead to joint stiffness and increased friction between the tissues within the joint resulting in a potentially more intense pain[43-45]. Additionally, at lower temperatures, the average daily humidity has a stronger effect on joint pain. Weather conditions may have transient causal effects limited to the same day on OA joint pain[46].

2.5 Impact of cold on the knee joint due to vitamin D deficiency

In addition to the direct effects of temperature and humidity on cartilage and synovial fluid, the climate in cold regions also has many indirect effects on KOA. Although the pathological mechanisms of osteoporosis and OA are different, the association between OA and bone mass is still controversial today. Some researches even report a negative correlation between these two[46]. But there are some common mechanisms for both[47]. Some studies also believe that osteoporosis and OA are closely related[8]. The subchondral trabecular bone in patients with osteoporosis becomes thinner and stiffer, and the ability to withstand pressure decreases, leading to an increased risk of OA. Preclinical studies have shown that vitamin D has a positive effect on articular cartilage. In rats, a diet deficient in vitamin D aggravates cartilage erosion and increases the expression of MMP-9 and MMP-13, whereas vitamin D supplementation counteracts this effect by regulating collagen II turnover through transforming growth factor-β1[48]. Cold and warm regions are mainly divided by latitude. The latitude difference has a lower impact on solar energy in summer. In winter, due to the sharp reductions of sunshine duration and solar altitude angle in the cold region, solar energy is far below the level in warm regions[49]. In addition, research has shown that below the -7°C line, the lower the temperature, the fewer the people who do outdoor exercises[45]. Sunshine is closely related to the production of vitamin D in the human body, and shorter sunshine duration can increase the prevalence of vitamin D deficiency and osteoporosis in residents of cold regions, which can in turn increases the prevalence of OA[50].

2.6 Impact of trauma on KOA under cold conditions

The risk of KOA increases following traumatic knee injury. Anterior cruciate ligament (ACL) and meniscus tears are among the most common forms of the sports-related knee injuries[51]. Therefore, better understanding of ACL, meniscus and other tissues is crucial for elucidating the phenotypes and mechanisms of KOA[52]. Cartilage strain was higher in the medial intercondylar notch and tibial plateau region in ACL defects (6% *vs*. 2%). This suggests that ACL injury changes the mechanical loading patterns or increases the sensitivity to cartilage loading[53]. The meniscus has the ability to load transmission, absorb shock energy, increase joint stability, lubricate and nourish joints, and maintain proprioception, *etc*[54-55]. ACL and meniscus injuries may promote the early onset of OA[56-57]. It is reported that individuals with ACL tears or ACL

dysfunction have more pronounced cartilage degeneration and a higher risk of severe KOA, severe knee pain, and poorer function[58-59]. Since the role of the hamstrings is to protect ACL from being overloaded, cold exposure of legs and knee joints in winter can simultaneously weaken the function of hamstrings and the elasticity of other ligaments, making the joints stiffer. Degradation of tissue elasticity can facilitate the development of knee injuries[49]. As a result, tissues such as ACL and meniscus are more easily to be injured during physical activity in the cold. Based on the significant increase in the incidence of wrist and hip fractures in winter, it is also reasonable to speculate that the incidence of joint trauma may be higher in cold regions under hypothermia[60]. Winter ice and snow sports unique to cold regions can cause ligament and meniscus damage[61].

In addition, the influence of low temperature on blood vessels, synovium, and nerve conduction velocity around the knee joint has been confirmed by accumulating evidence, but whether these factors are related to the occurrence and progression of KOA disease needs to be further elucidated[49].

3 Discussion

Based on the basic and epidemiological studies, it has proved that cold is closely related to the etiology and symptoms of KOA. Yet controversies remain on OA caused by pure hypothermia or the aggravation of pain symptoms in OA patients.

It has been reported that laser and infrared isothermal irradiation has positive effects on pain, stiffness, and limited mobility in patients with KOA[62]. On the contrary, ice compress, as another cold stimulus, does not increase the prevalence of KOA and it is widely used in the treatment of KOA. At the same time, cold water immersion does not increase the incidence of sports injuries[63]. Studies have found that local cold therapy can reduce synovial IL-6, IL-1β, VEGF, prostaglandin-E2 and nuclear factor kappa B p65 in human knee arthritis, which is beneficial to KOA treatment and symptom relief [64]. However, Aciksoz *et al*.[65] reported that both cold therapy patches and hyperthermia can mildly relieve symptoms in patients with primary KOA. These studies suggest that the influence of cold, as an independent factor, on KOA may have a complex mechanism and is largely affected by changes in other environmental factors.

To date the studies on low temperature and OA is still scanty. There are even fewer basic studies on the pathological mechanism and related pathways of KOA in the context of low temperature, despite that KOA in cold-area residents is more sensitive to temperature, humidity, light, daily activities, and many other factors than in warm-area habitants. There are obvious differences between these factors, and these factors may affect the occurrence and progression of the disease to varying degrees. The impacts of cold region on KOA are showed in Fig. 1. Clearly, the impact of climate on KOA in cold regions and the related hypotheses require more rigorous studies with larger sample size to verify in order to reach valid conclusions.

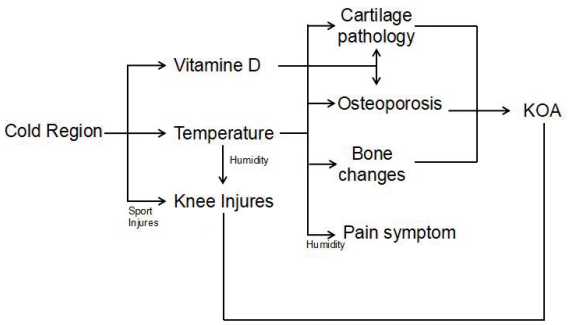

Fig. 1 Impacts of cold region on knee osteoarthritis

Although the pathogenesis of OA of other joints resembles that of KOA, certain differences exist in terms of the structural and functional alterations.

In summary, available studies indicate that OA is not only a disease characterized by cartilage loss due to mechanical load, but also one involving all different types of tissues in the joint such as cartilage, subchondral bone, joint capsule, synovium, and surrounding muscles. It can cause changes in tissue structure, metabolism, and function. The pathological development of OA is mediated by complex and yet-to-be-fully-understood interactions of pro-inflammatory cytokines, anti-inflammatory cytokines, chemokines, growth factors, and adipokines. It can be used as a biomarker for disease staging and progression[66]. However, efficacious medicines forcuring or even just for improving the main conditions of OA are not yet available, and difficulties in effective control and management of OA risk factors remain an important obstacle. Therefore, interfering with modifiable risk factors such as nutrition and the environment are the only viable and safe strategies for the prevention and treatment of OA[9].

Author contributions

Yongchen Wang conceived the present idea and was in charge of overall direction and planning. Haile Pan and Zilong Shen helped supervise the project. Qi Chen and Rui Jiang carried

out the literature search and screen. Zilong Shen wrote the manuscript with support from Haile Pan. All authors provided critical feedback and helped shape the analysis and manuscript.

Conflict of interests

Yongchen Wang is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and the research groups.

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