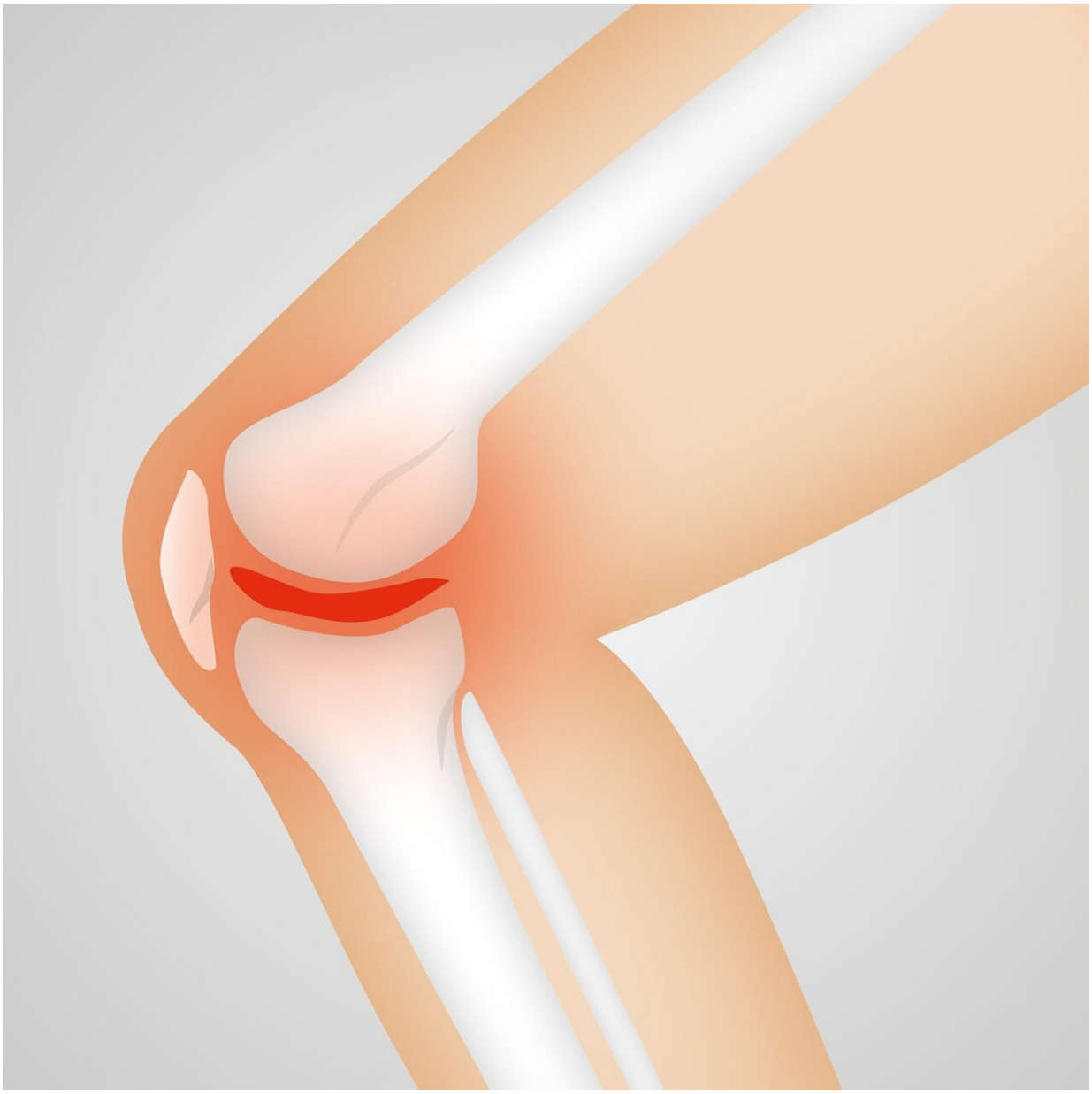
Osteoarthritis: Unveiling complex mechanisms and immune influences

November 24 2023



Credit: Pixabay/CC0 Public Domain

According to the World Health Organization (WHO), this musculoskeletal disorder affects approximately 1.71 billion people globally. Osteoarthritis is a condition where cartilage gradually breaks down, and joint bones are exposed to each other. This leads to pain and reduced joint function.

Osteoarthritis is a burdensome disease, both for the individual patient and for society. Currently, there is no curative treatment. Treatment is limited to lifestyle changes, pain relief, and in some cases, surgical interventions.

However, by better understanding the mechanisms behind this condition, new treatment strategies may be discovered in the future. Randi Krog Eftedal has done just that. In her doctoral thesis at the Faculty of Dentistry, she has examined the immunological processes that may help explain why osteoarthritis may occur and how it develops.

Genetics is a risk factor

"Approximately 12% of osteoarthritis cases have a known triggering factor, such as an injury to the joint, but in most cases, we do not know the cause of the disease," says Krog Eftedal. However, what we do know is that genetics is an important risk factor.

There is a hereditary component when it comes to osteoarthritis, with heritability rates of 70% in the spine and 30% in the knees. This means that genes can influence the shape and musculature surrounding and stabilizing the joints. Genetic factors also affect cellular mechanisms, including those in the immune system.

"In our studies, we could see at an immunological level that mutations in the promoter region or the part of the gene that codes for important immune components may play a role in the development of the disease, says Krog Eftedal.

The promoter region is an area of DNA that precedes the actual gene and is important for the gene to be read. A mutation in this area can alter how strongly a gene is expressed or its characteristics.

Vulnerability to osteoarthritis: Genetic and epigenetic factors

Krog Eftedal and her research colleagues examined osteoarthritis in both knee and hip joints. DNA was isolated from patients suffering from severe idiopathic osteoarthritis in knee or hip joints.

"These DNA samples were compared to DNA from healthy individuals to look for any genetic differences between the two groups," explains Krog Eftedal.

At the same time, cell lines were studied in the laboratory to examine the epigenetic regulation of inflammation.

"The results of the study suggest that there are differences in genetic predisposition between primary osteoarthritis in knee and hip joints, and mutations in or near genes coding for important immunological components may have an impact on vulnerability to developing osteoarthritis," says Krog Eftedal.

Vulnerability is not only about having the gene but how it is activated or expressed, meaning whether there are point mutations in genes coding for inflammation factors or not.

Understanding the interaction between joints and immune reactions

"But it is also important to understand how the interaction between the joint and the immune mechanisms works if we are to find new treatment methods," says Krog Eftedal. "We need to know something about how the joint functions."

The cartilage in the joint does not have its own blood supply, so it depends on surrounding tissues, such as bone or synovial membrane, to receive necessary nutrients and eliminate waste products.

"The joint relies on a certain physiological movement to function optimally," explains Krog Eftedal.

Physical activity is beneficial for the whole body and is essential for maintaining healthy and functional joints. Mechanical loading contributes to the distribution of substances to and from areas in the cartilage. If the cartilage is subjected to too much or improper use, causing mechanical stress that exceeds the joint's ability to regenerate, this can disrupt the joint's interaction and lead to disease development. Immune cells in the joint also play a role in this breakdown process.

"When an immune reaction occurs, it can worsen the condition and lead to further cartilage breakdown," says Krog Eftedal. "The immune reaction can also attract more immune cells to the area, which in turn contributes to cartilage degradation."

Changing function

"The immune system activates cells in the joint, such as chondrocytes (cartilage cells), bone cells, and fibroblasts, to release enzymes and

cytokines that contribute to cartilage breakdown. These cells then shift from their normal 'caretaker' role, or homeostasis, to actively participating in the inflammatory reaction."

"For example, fibroblast cells are normally responsible for producing synovial fluid that lubricates the joint. But in an inflammatory situation, they change their function from maintenance cells to become sentinel cells with immune properties and start producing other substances, tipping the delicate balance in the joint from maintenance to breakdown and inflammation," says Krog Eftedal.

"This leads to a change in their normal functions, and they become 'drivers' in inflammatory reactions that contribute to disease development."

"By studying fibroblast cells in the laboratory, we found that the amount of interleukin-6 produced by the fibroblasts can be reduced by introducing a specific microRNA, miR-149-5p. MicroRNAs are short RNA molecules that are important in regulating gene expression."

Differences between knee and hip joints

"In our studies of various point mutations, we found differences in genetic vulnerability between knee and hip joints. The most significant differences were observed in hip joints, where point mutations in or near genes coding for TNF-α, Interleukin-6, Interleukin-17, and Toll-like receptor 10 seemed to affect vulnerability to developing osteoarthritis," says Krog Eftedal.

"This suggests that it is important to distinguish between different joints when studying genetic risk factors."

Important to use the term osteoarthritis

"I would also like to emphasize the importance of using the term 'osteoarthritis' rather than just 'arthrosis' to recognize that it is not just a matter of pure mechanical wear and tear but a disease process involving the immune system."

"The 'itis' ending acknowledges the immunological process occurring in the joint. Osteoarthritis also affects the entire joint organ and is not limited to the cartilage. Inflammation may come and go during the disease process, but when it is present, it plays a crucial role in disease development."

"In addition, I would also suggest that osteoarthritis should possibly be seen as an umbrella diagnosis for several diseases with similar courses. It is important to look at each joint separately and examine the interaction between the immune processes to understand both the causal relationship and how the disease develops."

"Although more research is needed, the results from this doctoral work point to the possibility of developing new treatment methods aimed at influencing epigenetic regulations and thereby reducing inflammatory reactions in osteoarthritis. This opens up exciting perspectives in future research on osteoarthritis and other genetically related diseases," says Krog Eftedal.

More information: Randi Krog Eftedal et al, Interleukin(IL)-6 Gene rs1800795 (-174G>C) Polymorphism is Associated with Increased Risk to Hip but not Knee Osteoarthritis. Manuscript submitted for publication.

Provided by DIFFER