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AUTHOR'S AFFILIATIONS

Universitas Pembangunan
 Nasional Veteran Jakarta^{1, 2}

CORRESPONDING AUTHOR

Basuki Supartono
 Jalan RS. Fatmawati Raya, Pd.
 Labu, Kec. Cilandak, Kota Depok,
 Jawa Barat 12450

E-mail: basuki@upnvj.ac.id

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The Role of Cytokines in Inflammatory Process of Knee Osteoarthritis: Systematic Review

Florencia Christofora Ngantung¹, Basuki Supartono², Hikmah Muktamiroh³

Abstract

Osteoarthritis (OA) is a degenerative joint disorder that occurs in cartilage. OA is the main cause of disability in adults and generally characterized by pain to the joints that got pressured. Based on several previous studies, it is known that the incidence of osteoarthritis is correlated with synovial inflammation and that inflammatory cytokines play an important role in the expansion of osteoarthritis. Based on these things, the author intends to conduct a literature study with the aim of knowing the role of cytokines on inflammation in knee osteoarthritis. The research was conducted through PubMed and Science Direct databases. The results of the study showed that cytokines played negative different roles depending on the type of cytokines such as those found in knee OA inflammation. Conclusion: Cytokines have a negative effect because they can disrupt synovial tissue balance, induce catabolic processes, and induce osteoclast differentiation and subchondral bone resorption.

Keywords: Osteoarthritis, Cytokines, Inflammation, Synovial

Review Article

Pengaruh Sitokin dalam Proses Inflamasi pada Penyakit Osteoarthritis Lutut: Systematic Review

Abstrak

Osteoarthritis (OA) adalah kelainan degenerasi sendi yang terjadi pada kartilago. OA merupakan penyebab utama disabilitas pada orang dewasa dan umumnya ditandai dengan nyeri saat adanya tekanan pada sendi. Berdasarkan beberapa penelitian yang telah dilakukan diketahui bahwa kejadian osteoarthritis berkorelasi dengan inflamasi sinovial dan sitokin ada inflamasi berperan penting dalam perkembangan

osteoarthritis. Berdasarkan hal-hal tersebut, penulis ingin melakukan studi literatur dengan tujuan mengetahui peran sitokin pada inflamasi pasien osteoarthritis lutut. Penelitian dilakukan melalui database PubMed dan Science Direct. Hasil dari penelitian didapatkan bahwa sitokin memainkan peran negatif yang berbeda-beda tergantung dari jenis sitokin seperti yang terdapat pada inflamasi OA lutut. Kesimpulan: Sitokin berpengaruh negatif karena dapat mengganggu keseimbangan jaringan sinovial, menginduksi proses katabolik, dan menginduksi diferensiasi osteoklas serta resorpsi tulang subkondral.

Kata Kunci: Osteoarthritis, Sitokin, Inflamasi, Sinovial

INTRODUCTION

Osteoarthritis (OA) is a disorder characterized by the gradual degradation of cartilage tissue that lines joints, subchondral

bone, and synovium, along with pain, immobility, muscular weakness, and reduction in the ability to perform daily activities (Newberry et al., 2017).

Osteoarthritis (OA) is the most prevalent degenerative joint condition that affects one or more diarthrodial joints, including small joints such as hands and larger joints like the knee or hip (Martel-Pelletier et al., 2016). Osteoarthritis is characterized by pain when the afflicted joint is pressed, joint swelling, crepitus, and decreased joint motion. Age, genetics, gender, and obesity are factors that affect the likelihood of developing osteoarthritis (Abramoff & Caldera, 2020). The osteoarthritis starts with subchondral pressure, deterioration of the surface of cartilage, cartilage layers breakdown and finally osteochodral defects on trochlear region of the knee joint (Supartono et al., 2018).

Several studies have shown that symptoms such as pain, and the severity of osteoarthritis, are associated with synovial inflammation. Synovial tissue inflammation occurs as a result of cartilage fragments being released due to a range of factors, including joint trauma, which triggers synovial cells to create proinflammatory substances, accelerating cartilage deterioration (van den Bosch, 2019). Another research used an ELISA (Enzyme-linked immunosorbent Assay) test to discover three synovial fluid compounds in patients with severe knee osteoarthritis. It was shown that synovial fluid has a stronger ability to induce the production of cytokines/chemokines and MMPs (Matrix Metalloproteinases) to prevent collagen and aggregation synthesis (van den Bosch, 2019). This shows that cytokines in inflammation play a vital role in osteoarthritis development (van den Bosch, 2019). The researchers, on the other hand, wanted to study more about the role of cytokines in inflammation in knee osteoarthritis patients.

Symptomatic osteoarthritis affects 9.6% of men and 18% of women over the age of 60 globally (van den Bosch, 2019). Around 303 million people in the world have osteoarthritis (Kolasinski et al., 2020). Osteoarthritis affects up to 4% of the global population, with knee osteoarthritis contributing to 83% of cases (Kohn

et al., 2016). The prevalence of osteoarthritis increased with age, reaching 18.6 % in people over 65 and 18.9 % in people over 75. (Riskseddas, 2018).

Proinflammatory cytokines plays important role in the start and/or development of osteoarthritis (Bastiaansen-Jenniskens et al., 2017). The rise in proinflammatory cytokines in peripheral blood and fluid samples is induced by mononuclear cells infiltrating the synovial membrane, such as T cells and macrophages. Increased inflammatory mediator release, such as interleukin (IL) IL-1beta, IL-15, IL-8, IL-6, and TNF-alpha, will increase the development of proteolytic enzymes such as matrix metalloproteinases (MMPs), which cause cartilage damage (Nees et al., 2019).

In osteoarthritis, secreted inflammatory factors such as proinflammatory cytokines are significant mediators of impaired metabolism, particularly those that induce increased joint tissue catabolism. TNF-alpha, IL-1, IL-6, as well as other gamma-chain cytokines including IL-2, IL-7, IL-15, IL-21, and chemokines, are cytokines strongly implicated in the pathogenesis of OA (Mabey & Honsawek, 2015).

Proinflammatory cytokines, particularly IL-1, TNF, and IL-6, were increased, and these three cytokines contributed to the pathogenesis of OA through the mechanisms including anabolic downregulation and upregulation of catabolic and inflammatory responses, which influence the outcome of structural damage in knee osteoarthritis. Various studies have found that an increase in inflammatory cytokines in cartilage, synovial membrane, and subchondral bone is associated with the development and structural changes in OA joints (Kapoor et al, 2011).

METHOD

The literature search was performed using the PRISMA-P method systematically, using the type of systematic review method from the literature review. The researchers also reviewed the PubMed and Science Direct databases for relevant articles using keywords and subjects such as inflammation, osteoarthritis, and cytokines.

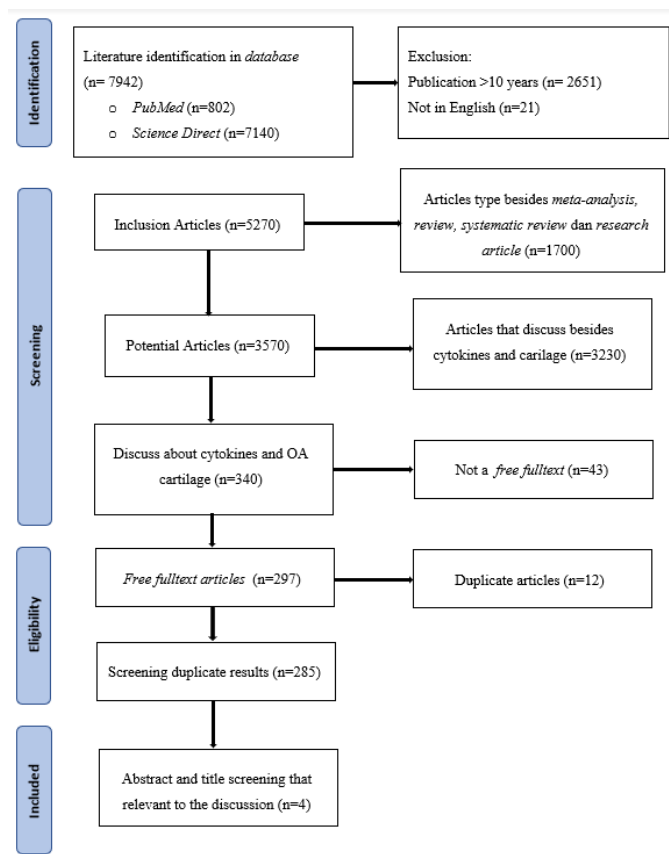


Figure 1. PRISMA- P methods of the study

RESULT

The imbalance of cytokines in the body, which favors proinflammatory cytokines, is one of the significant factors in OA pathogenesis. These cytokines cause catabolic enzymes like MMPs and ADAMTS to be activated, which in turn damages cartilage and other intra-articular structures (Molnar et al., 2021). IL-1, TNF, and IL-6 are the most significant inflammatory mediators in the OA pathogenesis. These mediators are signaling pathway activators that stimulate other cytokines and pathological processes (Molnar et al., 2021).

In this research, IL-1 and TNF-Alpha were both proinflammatory cytokines that were often found in studies. Similarly, various additional proinflammatory and anti-inflammatory cytokines, including IL-1 β , TNF-38 Alpha, IFN-gamma, IL2, IL-4, IL-6, IL-8, IL-18, and TGF (Transforming growth factors), have been investigated in OA. IFN-gamma was discovered using immunohistochemistry (IHC), and another study found that when stimulated ex vivo, T cells from synovial tissue in OA may release IFN-gamma, IL10, and IL-4. Ex vivo induces T cells from OA synovial tissue and is known to release IL-2, however, IHC cannot detect this cytokine in

synovial tissue. Another cytokine related to these cells and identified to be released in OA synovial tissue by IHC and ELISA experiments is IL-8. Only a few studies have shown that inflammation has a significant role in the course and development of OA (de Lange-Brokaar et al., 2012).

DISCUSSION

According to Hosnijeh et al. (2019) discovered that IL-6, IL-8, and TNF-alpha had a function in pain during movement, however, TNF-alpha alone contributed to pain during rest. TNF- α may stimulate the production of cytokines such as IL-6 and IL-8, along with activating iNOS, COX-2, and PGE-2, and all have the impact of activating catabolic processes in one tissue. The IL-6 and IL-8 proteins in late-stage OA tissue are equivalent to those in early-stage OA. In particular, the protein was generated mostly by self-cultured synovium, with co-cultured IL-8 being statistically significant when compared to cultured meniscus alone. Our findings indicate that the synovium plays an essential role in the expression of IL-6 and IL-8 genes, indicating that it serves as a source of inflammatory molecules that impact the surrounding joint tissue (Favero et al., 2019). In osteoarthritis, IL-8 in the synovial

fluid has a function in neutrophil recruitment and activation. To break down cross-linked type II collagen and proteoglycans in articular cartilage, activated cells will produce the enzyme elastase (Chow & Chin, 2020). IL-1 β plays a vital role in modulating the signaling of other cytokines, which when activated, inhibit type II collagen expression, increase MMP production, disturb synovial tissue balance, and induce cartilage damage.

Several studies have found that IL-6, with or without IL-6R, stimulates type 2 collagen expression, whilst others found that IL-6 or IL-6 + sIL-6R treatment can suppress type 2 collagen formation through transcriptional control. MMP-1, 3, and 13 as well as ADAMTS-4, and 5/11 were all induced by the combination of IL-6 and IL-6R. Patients with end-stage OA showed in synovial fluid there's significantly higher concentrations of IL-6 as compared to a healthy control group, and the higher concentrations of IL-6 were known to correspond with pain experienced by OA patients (Favero et al., 2019).

IL-6 functions by attaching to the membrane-bound IL-6R or sIL-6R associated with gp130. Gp130 generates intracellular signaling that can affect inflammation and enzyme, collagen, and proteoglycan expression. Alternative splicing or sgp130 membrane-bound IL-6R release can generate and suppress IL-6 signaling. IL-6 stimulates the PI3K, JAK/STAT, and MAPK signaling pathways, which control the production of enzymes (TIMP, MMPs, and ADAMTS) along with proteoglycan synthesis and type II collagen. So that IL-6 balances anti-inflammatory and pro-inflammatory actions, and the latter predominates, eventually leading to osteoarthritis (Molnar et al., 2021).

Deligne et al. (2015) discovered that both inflamed and non-inflamed tissues produced the same IL-17 and IL-22 mRNA, however, IL-17 and IL-22 mRNA expression was stronger in inflamed tissue. Furthermore, according to (Zhu et al., 2017), IL-17 is a proinflammatory cytokine that acts a regular function in chronic inflammation. According to (Chow & Chin, 2020), IL-17 may drive synovial fibroblasts and chondrocytes to secrete IL-6, IL-8, and TNF- α , resulting in inflammation and cartilage damage. Furthermore, IL-17 has been found in the synovial fluid of a subgroup of patients with end-stage osteoarthritis. Increased levels of IL-17 and IL-22 were also seen in the synovial fluid of

osteoarthritis patients. An increase in these two cytokines is connected to an increase in nuclear factor kappa-ligand activator receptor (RANKL), which promotes osteoclast formation and the resorption of subchondral bone, the layer of bone underneath cartilage in joints.

CONCLUSION

Cytokines are essential in inflammatory knee osteoarthritis; however, each cytokine has a negative varied role depending on the kind of cytokine present in knee OA inflammation. Cytokine concentrations in OA patients are higher in late-stage OA than in early-stage OA. In addition, several other types of cytokines related to the major cytokines mentioned above might affect the balance of tissue cells causing tissue damage depending on their roles.

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