**THE INVOLVEMENT OF T- AND B- LYMPHOCYTES IN THE PATHOGENESIS AND PROGRESSION OF OSTEOMYELITIS AND OSTEOARTHRITIS.**

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	5. **Osteomyelitis and Osteoarthritis**

Osteomyelitis is inflammation of the bone caused by an infecting organism. Although bone is normally resistant to bacterial colonization, events such as trauma, surgery, the presence of foreign bodies, or the placement of prostheses may disrupt bony integrity and lead to the onset of bone infection *(P. Wong et al.,* 2003). Osteomyelitis can also result from hematogenous spread after bacteremia. When prosthetic joints are associated with infection, microorganisms typically grow in biofilm, which protects bacteria from antimicrobial treatment and the host immune response. Symptoms may include pain in a specific bone with overlying redness, fever, and weakness. The long bones of the arms and legs are most commonly involved in children, while the feet, spine, and hips are most commonly involved in adults (Gentry L0., 1987).

The cause is usually a bacterial infection, but rarely can be a fungal infection. It may occur by spread from the blood or from surrounding tissue. (Schmitt SK *et al.,* 2017) Risks for developing osteomyelitis include diabetes, intravenous drug use, prior removal of the spleen, and trauma to the area. Diagnosis is typically suspected based on symptoms. This is then supported by blood tests, medical imaging, or bone biopsy (Li H,2010).

Treatment often involves both antimicrobials and surgery. In those with poor blood flow, amputation may be required. Treatment outcomes are generally good when the condition has only been present a short time. About 2.4 per 100,000 people are affected a year. The young and old are more commonly affected. Males are more commonly affected than females. (Ferri *et al.,* 2017). The condition was described at least as early as the 300s BC by Hippocrates. Before the availability of antibiotics, the risk of death was significant (Brackenridge *et al.,* 2016).

 Arthritis is the inflammation of joints. Osteoarthritis is a type of [joint disease](https://en.wikipedia.org/wiki/Joint_disease) that results from breakdown of [joint cartilage](https://en.wikipedia.org/wiki/Articular_cartilage) and underlying [bone](https://en.wikipedia.org/wiki/Bone). The most common symptoms are [joint pain](https://en.wikipedia.org/wiki/Joint_pain) and stiffness (Hatekar *et al*., 2015). It could be caused by previous joint injury, abnormal joint or limb development, and [inherited](https://en.wikipedia.org/wiki/Heredity) factors. The risk of having the disease is greater in those who are [overweight](https://en.wikipedia.org/wiki/Overweight), have legs of different lengths, or have jobs that result in high levels of joint stress (Glyn-Jones *et al*., 2015). The disease develops as cartilage is lost and the underlying bone becomes affected and as pain may make it difficult to exercise, [muscle loss](https://en.wikipedia.org/wiki/Atrophy) may occur (National, C. G. C. U, 2014). Diagnosis is typically based on signs and symptoms, with [medical imaging](https://en.wikipedia.org/wiki/Medical_imaging) and other tests used to support or rule out other problems (Hatekar *et al*., 2015).

**1.2 T- and B- Lymphocytes**

**1.2.1 T-lymphocytes (T-cells)**

A T cell is a type of [lymphocyte](https://en.wikipedia.org/wiki/Lymphocyte), which develops in the [thymus](https://en.wikipedia.org/wiki/Thymus) gland (hence the name) and plays a central role in the [immune response](https://en.wikipedia.org/wiki/Immune_response). T cells can be distinguished from other lymphocytes by the presence of a [T-cell receptor](https://en.wikipedia.org/wiki/T-cell_receptor) on the [cell surface](https://en.wikipedia.org/wiki/Cell_surface_receptor). These immune cells originate as [precursor cells](https://en.wikipedia.org/wiki/Precursor_cell), derived from [bone marrow](https://en.wikipedia.org/wiki/Bone_marrow) and develop into several distinct types of T cells once they have migrated to the thymus gland. T cell differentiation continues even after they have left the thymus (Alberts *et al*., 2002).

**1.2.2 B-lymphocytes (B-cells)**

**B cells**, also known as **B lymphocytes**, are a type of [white blood cell](https://en.wikipedia.org/wiki/White_blood_cell) of the [lymphocyte](https://en.wikipedia.org/wiki/Lymphocyte) subtype. They function in the [humoral immunity](https://en.wikipedia.org/wiki/Humoral_immunity) component of the [adaptive immune system](https://en.wikipedia.org/wiki/Adaptive_immune_system) by [secreting](https://en.wikipedia.org/wiki/Secretion) [antibodies](https://en.wikipedia.org/wiki/Antibody), Additionally, B cells [present antigens](https://en.wikipedia.org/wiki/Antigen_presentation) (they are also classified as professional [antigen-presenting cells (APCs)](https://en.wikipedia.org/wiki/Antigen-presenting_cell)) and secrete [cytokines](https://en.wikipedia.org/wiki/Cytokine) (Murphy, 2012). B-cells mature in the bone marrow (Cooper, 2015).

**1.3 The involvement of T- and B- lymphocytes in pathogenesis and progression of Osteoarthritis**

**1.3.1 T-lymphocytes.**

According to a study carried out in 2013, mononuclear cell infiltrates in synovial tissues have been reported in osteoarthritis and have been shown to contain primarily Cluster of differentiation (CD3) + T cells. Both CD4+ and CD8+ cells were found in osteoarthritis synovium at similar levels as in Rheumatoid arthritis (RA) synovium. The Th1 subset of T cells was found to be about 5 times more than Th2 cells and higher levels of Th1 cytokines, interleukin 2 (IL-2) and interferon gamma (IFNᵧ), were detected in most of the osteoarthritis patients. T-cells in lymphocytic aggregates in osteoarthritis synovium were shown to bear early (CD69), intermediate (CD25 and CD38) and late (CD45RO) activation markers (Hasseb and Haqqi, 2013). These observations suggest the presence of an active cell-mediated immune response in majority of osteoarthritis patients. Analysis of α/β T cell receptor diversity revealed the presence of oligoclonal populations of T cells in osteoarthritis patients. This suggested that those cells were undergoing clonal expansion in response to specific antigens within the synovium. Although there are no conclusive data on the antigens, which drive the immune response in osteoarthritis, several candidate antigens have been proposed. T cells derived from peripheral blood and synovial fluid of osteoarthritis patients showed a strong response to autologous chondrocyte and fibroblast membrane preparations (de Jong *et al*., 2010).

In another study osteoarthritis chondrocytes were shown to stimulate autologous T cell response in vitro. Cellular immunity to type III collagen and proteoglycan was detected after partial meniscectomy in rabbits. Higher cellular immunity was observed in osteoarthritis patients compared to normal subjects when their peripheral blood lymphocytes were stimulated with human cartilage link protein and G1 globular domain of proteoglycan. More specifically, peptides representing amino acid regions 16–31 and 263–280 located in G1 domain of proteoglycan were more frequently recognized by PBMCs isolated from osteoarthritis patients compared to healthy controls. These studies suggest a role for cartilage components as osteoarthritis antigens responsible for oligoclonal T cell response observed in osteoarthritis patients. The role of CD4+ T cells in osteoarthritis was highlighted by a recent study in anterior cruciate ligament-transection (ACLT)-induced osteoarthritis mice where these cells were found to be involved in increased production of macrophage inflammatory protein 1 gamma (MIP-1γ) followed by increased infiltration of macrophages in synovium and increased expression of Matrix metallopeptidase (MMP-9) (Haseeb and Haqqi, 2013).

**1.3.2 B-lymphocytes.**

Cellular infiltrates in the inflamed osteoarthritis synovium have been reported to contain activated B cells along with other cell types. A clonal analysis of B cells in osteoarthritis synovium revealed their oligoclonal nature suggesting an antigen driven (HasEEB and Haqqi, 2013). Moreover, several studies found antibodies against cartilage components highlighting the activation of humoral adaptive immune response in osteoarthritis. When cartilage cell surface proteins were used as substrate in an ELISA and sera from osteoarthritis patients were applied, an elevated antibody titer was detected compared to controls. Similarly, autoantibodies were found in osteoarthritis patients against cartilage derived proteins osteopontin, cartilage intermediate layer protein (CILP), YKL-39, fibulin-4 and collagen. Anti-cyclic citrullinated peptide antibodies were detected in 7 out of 136 osteoarthritis patients, while another group also detected them in osteoarthritis patients but at significantly lower levels compared to RA patients (Caspi et al, 2006). Antibodies against native G1 domain of aggrecan core protein were found in synovial fluid of osteoarthritis patients. Using proteomic approach, triosephosphate isomerase (TPI) was identified as an important antigen with autoantibodies present specifically in osteoarthritis but not in RA (Xiang *et al*., 2004). Other studies have reported autoantibodies in animal models of osteoarthritis including horses and dogs. The role of the autoantibodies against cartilage components in the development of osteoarthritis has been further highlighted by studies showing their deposition and cytotoxic effects on cartilage, which may be one of the mechanisms playing an important role in cartilage degeneration in osteoarthritis (Hasseb and Haqqi, 2013).

**1.4 The involvement of T- and B- lymphocytes in pathogenesis and progression of Osteomyelitis**

Chronic bone infection is associated with bone resorption. From animal studies, CD3/CD28-activated T cells are known to enhance osteoclastogenesis and bone resorption. Because CD28 is expressed constitutively on T cells and its expression is down-regulated by chronic exposure to the inflammatory environment, we characterized co-stimulatory molecule expression on T cells from chronically infected patients. Cytofluorometric techniques were used to phenotypically characterize T cells, its co-stimulatory molecules and perforin secretion from infected and non-infected human bones. Chronic bone infection was defined as infection lasting for more than a month... Chronically infected human bones are characterized by an increase of CD28-negative CD4+ T cells, indicating long-term activated cells with cytotoxic ability. Therefore, this alteration of co-stimulatory molecules may modify interactions with osteoclasts and impact bone resorption (Beck-Broichsitter, 2015).

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