**A TERM PAPER**

**ON**

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

**BY**

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**INTRODUCTION**

**What is Osteomyelitis?**

Osteomyelitis is an infection in a bone. Infections can reach a bone by passing through the bloodstream or spreading from nearby tissue. Infections can also begin in the bone itself if an injury exposes the bone to germs.

Smokers and people with chronic health conditions, such as diabetes or kidney failure, are more at risk of developing osteomyelitis. People who have diabetes may develop osteomyelitis in their feet if they have foot ulcers (Lalani, 2018).

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.

Although it was once seen as an incurable disease, osteomyelitis can now be successfully treated. Most people need surgery to remove areas of the bone that have died.

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, 2017)

Most cases of osteomyelitis are caused by staphylococcus bacteria, types of germs commonly found on the skin or in the nose of even healthy individuals. Germs can enter a bone through different ways, including:

* The bloodstream. Germs in other parts of your body — for example, in the lungs from pneumonia or in the bladder from a urinary tract infection — can travel through your bloodstream to a weakened spot in a bone.
* Injuries. Severe puncture wounds can carry germs deep inside your body. If such an injury becomes infected, the germs can spread into a nearby bone. Germs can also enter the body if you have broken a bone so severely that part of it is sticking out through your skin.
* Surgery. Direct contamination with germs can occur during surgeries to replace joints or repair fractures.

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, 2017). Risks for developing osteomyelitis include diabetes, intravenous drug use, prior removal of the spleen, and trauma to the area.

Acute osteomyelitis almost invariably occurs in children because of rich blood supply to the growing bones. When adults are affected, it may be because of compromised host resistance due to debilitation, intravenous drug abuse, infectious root-canaled teeth, or other disease or drugs. (Kumar *et al.,* 2007)

In this case, the bacteria, in general, spread to the bone through the circulatory system, first infecting the synovium (due to its higher oxygen concentration) before spreading to the adjacent bone. In tubercular osteomyelitis, the long bones and vertebrae are the ones that tend to be affected (Kumar *et al.,* 2007). Staphylococcus aureus is the organism most commonly isolated from all forms of osteomyelitis (Kumar *et al.,* 2007).

Bloodstream-sourced osteomyelitis is seen most frequently in children, and nearly 90% of cases are caused by Staphylococcus aureus. In infants, S. aureus, Group B streptococci (most common (Haggerty, 2002) and Escherichia coli are commonly isolated; in children from one to 16 years of age, S. aureus, Streptococcus pyogenes, and Haemophilus influenza are common. In some subpopulations, including intravenous drug users and splenectomised patients, Gram-negative bacteria, including enteric bacteria, are significant pathogens (Carek et al., 2001).

The most common form of the disease in adults is caused by injury exposing the bone to local infection. Staphylococcus aureus is the most common organism seen in osteomyelitis, seeded from areas of contiguous infection (Carek et al., 2001).

Signs and symptoms of osteomyelitis include:

* Fever
* Swelling, warmth and redness over the area of the infection
* Pain in the area of the infection
* Fatigue

Sometimes osteomyelitis causes no signs and symptoms, or the signs and symptoms are hard to distinguish from other problems. This may be especially true for infants, older adults and people whose immune systems are compromised.

**PATHOGENESIS OF OSTEOMYELITIS**

Microorganisms may infect the bone through one or more of these basic methods;

Via the bloodstream which is the most common method; From nearby areas of infection (as in cellulitis); or Penetrating trauma (Luqmani *et al.,* 2013).

The area usually affected when the infection is contracted through the bloodstream is the metaphysis of the bone (Luqmani *et al.,* 2013). Once the bone is infected, leukocytes enter the infected area, and, in their attempt to engulf the infectious organisms, release enzymes that lyse the bone. Pus spreads into the bone's blood vessels, impairing their flow, and areas of devitalized infected bone, known as sequestra, form the basis of a chronic infection. Often, the body will try to create new bone around the area of necrosis. The resulting new bone is often called an involucrum (Kumar *et al.,* 2007). On histologic examination, these areas of necrotic bone are the basis for distinguishing between acute osteomyelitis and chronic osteomyelitis. Osteomyelitis is an infective process that encompasses all of the bone (osseous) components, including the bone marrow. When it is chronic, it can lead to bone sclerosis and deformity.

Chronic osteomyelitis may be due to the presence of intracellular bacteria (inside bone cells) (Ellington, 1999). Also, once intracellular, the bacteria are able to escape and invade other bone cells (Ellington, 2003).

In infants, the infection can spread to a joint and cause arthritis. In children, large subperiosteal abscesses can form because the periosteum is loosely attached to the surface of the bone (Kumar *et al.,* 2007).

Because of the particulars of their blood supply, the tibia, femur, humerus, vertebra, the maxilla, and the mandibular bodies are especially susceptible to osteomyelitis (King *et al.,* 2006).

In patients with sickle cell disease, the most common causative agent is Salmonella, with a relative incidence more than twice that of S. aureus (Burnett, 1998)

**What is Osteoarthritis?**

Osteoarthritis is a type of joint disease that results from breakdown of joint cartilage and underlying bone (Arden *et al.,* 2015). The most commonly involved joints are the two near the ends of the fingers and the joint at the base of the thumbs; the knee and hip joints; and the joints of the neck and lower back. Joints on one side of the body are often more affected than those on the other. Unlike some other types if arthritis, only the joints are affected here and not internal organs.

Osteoarthritis can also be referred to as, degenerative arthritis, degenerative joint disease or osteoarthrosis. The formation of hard knobs at the middle finger joints (known as Bouchard's nodes) and at the farthest joints of the fingers (known as Heberden's nodes) are a common feature of osteoarthritis in the hands.

Osteoarthritis is the most common form of arthritis, affecting about 237 million people, or 3.3% of the world's population (March *et al.,* 2014). In the United States, 30 to 53 million people are affected, and in Australia, about 1.9 million people are affected (Elsternwick, 2013). It becomes more common as people become older. Among those over 60 years old, about 10% of males and 18% of females are affected (Glyn-Jones *et al.,*2015). Osteoarthritis is the cause of about 2% of years lived with disability.

The primary cause of osteoarthritis is believed to be damage from mechanical stress with insufficient self-repair by joints. Sources of this stress may include misalignments of bones caused by congenital or pathogenic causes; mechanical injury; excess body weight; loss of strength in the muscles supporting a joint; and impairment of peripheral nerves, leading to sudden or uncoordinated movements (Brandt *et al.,* 2009).

The development of osteoarthritis is correlated with a history of previous joint injury and with obesity, especially with respect to knees (Coggon *et al.,* 2001) Changes in sex hormone levels may play a role in the development of osteoarthritis, as it is more prevalent among post-menopausal women than among men of the same age (Tanamas *et al.,* 2011).

Increased risk of developing knee and hip osteoarthritis is also found among those who work with manual handling (e.g. lifting), have physically demanding work, walk at work, and have climbing tasks at work (e.g. climb stairs or ladders).

Osteoarthritis can also be caused by other factors like; alkaptonuria, Ehlers-Danlos syndrome, hemochromatosis, Marfan syndrome and Wilson's disease.

The main symptom is pain, causing loss of ability and often stiffness. The pain is typically made worse by prolonged activity and relieved by rest. Stiffness is most common in the morning, and typically lasts less than thirty minutes after beginning daily activities but may return after periods of inactivity. Osteoarthritis can cause a crackling noise known as "crepitus" when the affected joint is moved, especially shoulder and knee joint. A person may also complain of joint locking and joint instability. These symptoms would affect their daily activities due to pain and stiffness (Sinusas, 2012). Some people report increased pain associated with cold temperature, high humidity, or a drop in barometric pressure (Figueiredo *et al.,* 2011). Osteoarthritis of the toes may be a factor causing formation of bunions, rendering them red or swollen.

**PATHOGENESIS OF OSTEOARTHRITIS**

Understanding of changes early in the development of osteoarthritis is important, since these changes could still be reversible, and therefore, preventive treatment could be initiated to slow or reverse further progression of the disease (Dieppe, 2011).

Initially, osteoarthritis has been considered to be a disease of articular cartilage, but recent research has indicated that the condition involves the entire joint (Abramson & Attur, 2009). The loss of articular cartilage has been thought to be the primary change, but a combination of cellular changes and biomechanical stresses causes several secondary changes, including subchondral bone remodelling, the formation of osteophytes, the development of bone marrow lesions, change in the synovium, joint capsule, ligaments and periarticular muscles, and meniscal tears and extrusion (Dequeker, 2008).

**Articular Cartilage**

Normal adult articular cartilage is made up of extracellular matrix (water, collagen, proteoglycans and a very small component of calcium salt) and chondrocytes (Goldring & Marcu, 2009). The turnover rate of collagen is relatively slow, whereas proteoglycan turnover is rapid. The normal turnover of this matrix components is mediated by the chondrocytes, which synthetize these components and the proteolytic enzymes responsible for their breakdown. Chondrocytes are, in turn, influenced by a number of factors, including polypeptide growth factors and cytokines, structural and physical stimuli and even the components of the matrix itself (Wise, 2010).

Osteoarthritis result from failure of chondrocytes to maintain homeostasis between synthesis and degradation of these extracellular matrix components. It is not known what initiates the imbalance between the degradation and the repair of cartilage. Trauma causing a micro fracture or inflammation causing a slight increase in enzymatic activity may allow the formation of “wear” particles, which could be then engulfed by resident macrophages (Wang *et al.,*2013). At some point in time, the production of these “wear” particles overwhelms the ability of the system to eliminate them and they become mediators of inflammation, stimulating the chondrocyte to release degradative enzymes.

Molecules from breakdown of collagen and proteoglycan, also taken up by synovial macrophages, cause release of proinflammatory cytokines, like TNFα, IL-1 and IL-6. These cytokines can bind to chondrocyte receptors leading to further release of metalloproteinase and inhibition of type II collagen production, thus increasing cartilage degradation (Stannus *et al.,* 2010). This disruption of homeostasis results in increased water content and decreased proteoglycan content of the extracellular matrix, weakening of the collagen network due to decreased synthesis of type II collagen and increased breakdown of pre-existing collagen (Buckwalter *et al.,* 2005). Furthermore, there is increased apoptosis of chondrocytes.

Osteoarthritic cartilage is characterized by an increase in anabolic and catabolic activity. At first, compensatory mechanisms such as increased synthesis of matrix molecules (collagen, proteoglycans and hyaluronate) (Goldring & Goldring, 2007) and proliferation of chondrocytes in the deeper layers of the cartilage, are able to maintain the integrity of the articular cartilage, but in the end loss of chondrocytes and changes in extracellular matrix predominate and osteoarthritic changes develop.

**Subchondral Bone**

It is not yet clear whether changes within subchondral bone precede changes in the articular cartilage or whether they occur in the disease progression, secondary to adaptation processes after changes in the biomechanical properties of the overlying articular cartilage. However, the two processes are closely related, as suggested by the concomitant increase in the levels of cartilage oligomeric matrix protein (COMP) and bone sialoprotein (BSP) in people with early osteoarthritis (Aigner &Schmitz, 2011).

Subchondral bone consists of the subchondral bone plate and the underlying trabecular bone and bone marrow space. The subchondral bone plate consists of cortical bone and is separated from the articular cartilage by the zone of calcified cartilage.

Changes in the bone include sclerotic changes and the development of bone marrow lesions that can be visualized by magnetic resonance imaging (MRI), and which seem to precede temporally and spatially, bone cysts in the subchondral compartment (Findlay, 2012). Thus, there is a progressive increase in the subchondral bone plate thickness, a modification in the architecture of subchondral trabecular bone, formation of new bone at the joint margins – osteophytes (Madry, 2010). In subsets of patients with osteoarthritis, the indices of bone resorption showing loss of trabecular tissue indicated by the increase in cross-linked N-telopeptide of type I collagen (NTx) and C-telopeptide (CTx), suggest a progressive loss of trabecular bone, not specifically of subchondral bone (Davis *et al.,*2007).

In osteoarthritic subchondral bone, type I of collagen is elevated, but this collagen content is abnormal, and this leads to abnormal mineralization. In normal bone, type I collagen is composed of a heterotrimer of α1 and α2 chains at an average ratio of 2.4:1. In osteoarthritic bone tissue this ratio varied between 4:1 and 17:1 (26), and this appears to be responsible for the abnormal mineralization pattern. Elevated TGF β1 levels in osteoarthritic osteoblast are responsible, in part, for the abnormal ratio of collagen I α1 to collagen I α2 and for the abnormal production of mature type I collagen. Thus, osteoarthritic subchondral bone has an increased osteoid collagen matrix and an abnormal mineralization resulting in a hypo-mineralization of this tissue. With alteration in its properties, subchondral bone may be less able to absorb and dissipate energy, thereby increasing forces transmitted through the joint and predisposing the articular surface to deformation (Neogi, 2012).

**Synovial Membrane**

It remains unclear whether the morphological changes that occur in the osteoarthritic synovial membrane are primary or whether they are the result of joint inflammation, cartilage degradation and lesions of the subchondral bone (Sutton *et al.,* 2009). Histologically, the synovial membrane of osteoarthritic joints commonly exhibits hyperplasia of the lining cell layer occasionally accompanied by focal infiltration of lymphocytes and monocytes in sub-lining layers (Brandt *et al.,* 2009).

Patients with osteoarthritis experience thickening of the synovial lining cell layer, increased vascularity and inflammatory cell infiltration of the synovial membranes, with the most marked changes occurring in advanced osteoarthritis. Angiogenesis in the synovium is closely associated with chronic synovitis and may occur at all stages of osteoarthritis (Haywood *et al.,* 2003).

**Menisci**

Meniscal degeneration is commonly seen in osteoarthritis, where menisci appear torn, fissured, fragmented, macerated or completely destroyed (Englund, 2009). Degeneration of menisci initiates within the substance of the tissue rather than surface. Tissue fibrillation and disruption is first seen at the inner rim, which spreads to the articular surfaces of the meniscus over time and progresses to total disruption or loss of meniscus tissue mainly in the avascular zone. Type I collagen content decrease gradually from the surface zone to the middle and the deep zone of osteoarthritic meniscus.

All these intra-meniscal changes correlated with peri-meniscal synovitis, calcification not limited to the outer, peripheral portion of the menisci contribute to meniscal degeneration and reduced meniscal tensile strength. The meniscus is less able to withstand loading and force transmission during normal movements of the joint, further leading to degenerative tears. Meniscal tears are often accompanied by varying degrees of meniscal extrusion. The tear might be a preceding feature of incipient osteoarthritis, and meniscus damage and extrusion often have a key role in the structural progression of the disease (Grainger *et al.,* 2007).

**What is T-Lymphocytes?**

A T cell is a type of lymphocyte, which develops in the thymus gland (hence the name) and plays a central role in the immune response. T cells can be distinguished from other lymphocytes by the presence of a T-cell receptor on the cell surface. These immune cells originate as precursor cells, derived from bone marrow, (Albert et *al.,* 2002) 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.

Groups of specific, differentiated T cells have an important role in controlling and shaping the immune response by providing a variety of immune-related functions. One of these functions is immune-mediated cell death, and it is carried out by T cells in several ways: CD8+ T cells, also known as "killer cells", are cytotoxic - this means that they are able to directly kill virus-infected cells as well as cancer cells. CD8+ T cells are also able to utilize small signalling proteins, known as cytokines, to recruit other cells when mounting an immune response. A different population of T cells, the CD4+ T cells, function as "helper cells". Unlike CD8+ killer T cells, these CD4+ helper T cells function by indirectly killing cells identified as foreign: they determine if and how other parts of the immune system respond to a specific, perceived threat. Helper T cells also use cytokine signalling to influence regulatory B cells directly, and other cell populations indirectly. Regulatory T cells are yet another distinct population of these cells that provide the critical mechanism of tolerance, whereby immune cells are able to distinguish invading cells from "self" - thus preventing immune cells from inappropriately mounting a response against oneself (which would by definition be an "autoimmune" response). For this reason, these regulatory T cells have also been called "suppressor" T cells. These same self-tolerant cells are co-opted by cancer cells to prevent the recognition of, and an immune response against, tumour cells.

**What are B-lymphocytes?**

B cells, also known as B lymphocytes, are a type of white blood cell of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigens (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines (Murphy, 2012). In mammals, B cells mature in the bone marrow, which is at the core of most bones (Cooper, 2105).

B cells, unlike the other two classes of lymphocytes, T cells and natural killer cells, express B cell receptors (BCRs) on their cell membrane. BCRs allow the B cell to bind to a specific antigen, against which it will initiate an antibody response (Murphy, 2012).

B cells develop from hematopoietic stem cells (HSCs) that originate from bone marrow. HSCs first differentiate into multipotent progenitor (MPP) cells, then common lymphoid progenitor (CLP) cells (Kondo, 2010).

B cells undergo two types of selection while developing in the bone marrow to ensure proper development. Positive selection occurs through antigen-independent signalling involving both the pre-BCR and the BCR (Martensson *et al.,* 2010). If these receptors do not bind to their ligand, B cells do not receive the proper signals and cease to develop (LeBien & Thomas, 2008). Negative selection occurs through the binding of self-antigen with the BCR; If the BCR can bind strongly to self-antigen, then the B cell undergoes one of four fates: clonal deletion, receptor editing, energy, or ignorance (B cell ignores signal and continues development). This negative selection process leads to a state of central tolerance, in which the mature B cells don't bind with self antigens present in the bone marrow (Pelanda & Torres,2012).

To complete development, immature B cells migrate from the bone marrow into the spleen as transitional B cells, passing through two transitional stages: T1 and T2 (Loder *et al.,* 1999) Throughout their migration to the spleen and after spleen entry, they are considered T1 B cells. Within the spleen, T1 B cells transition to T2 B cells (Chung *et al.,* 2003). T2 B cells differentiate into either follicular (FO) B cells or marginal zone (MZ) B cells depending on signals received through the BCR and other receptors (Cerutti *et al.,* 2013). Once differentiated, they are now considered mature B cells, or naive B cells.

B cells represent mainly the humoral immunity. Nevertheless, their role as a cell itself is equally relevant. B cells also serve as APCs. They have a transmembrane receptor, called BCR (a surface immunoglobulin), which enables them to identify specific antigens, against which they initiate an immune response and synthesize antibodies, and present fragments of these antigens to CD4+ T cells using MHC class II molecules (Ramos-Levi *et al.,* 2016). When the antigen is uncommon, B cells may be the dominant APCs as they have an ability of up-concentration antigens on the cell due to the presence of BCR in the cell membrane (Kambayashi & Laufer, 2014). T helper (Th) cells reciprocally support activation of B cells (Kristensen, 2016).

B cells exert their activity of antibody synthesis in the thyroid gland. It means that the thyroid may be a major place for thyroid antibody secretion and presents a significant role in promoting persistence of autoimmune thyroid diseases (AITD). They also play a role in regulation of immune responses. B cells are important in preventing the disease onset and also in suppressing the symptoms.

Osteoblasts are responsible for the deposition of bone matrix; they are found on bone surfaces and are derived from mesenchymal osteoprogenitor cells. These cells secrete osteoid, a mixture of bone matrix proteins primarily made up of type I collagen (over 90%), proteoglycans such as decorin and biglycan, glycoproteins such as fibronectin, osteonectin and tenascin C, osteopontin, osteocalcin and bone sialoprotein, oriented along stress lines (Mackie, 2003). The opposing action of bone matrix removal is performed by osteoclasts, multinucleate cells that are derived from the macrophage-monocyte lineage. These cells express large quantities of a vacuolar-type H (+)-ATPase on their cell surface, along with chloride channel 7 (ClC 7) enabling localized hydrochloric acid secretion into a closed compartment, known as the resorption lacuna, and subsequent solubilization of bone mineral (Blair et al., 1989). The balance of activity between these two cell types is crucial to maintaining the proper homeostasis of bone turnover, and any shift in the relative levels of osteoblast and osteoclast activity can result in bone pathology (Henderson & Nair, 2003). Infection with a pathogen such as S. aureus is capable of stimulating such a shift, mediated in part by induction of an inflammatory response. There is an intimate interaction between the two cell types, with osteoblasts interpreting the majority of extracellular signals and subsequently modulating osteoclast differentiation and function (Henderson & Nair, 2003; Matsuo & Irie, 2008).

Internalization of bacteria required live osteoblasts, but not live S. aureus, indicating osteoblasts are active in ingesting the organisms. The bacteria were not killed by the osteoblasts, since viable bacteria were cultured several hours after ingestion. From a clinical standpoint, it has become clear that patients can have recurrent attacks of osteomyelitis after completion of therapy even when causative organisms cannot be isolated (Craigen et al., 1992).

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