****Discuss the involvement of T- and B-lymphocytes in the pathogenesis and progression of osteomyelitis and osteoarthritis.****

**BY**

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16/MHS01/196

ANA 404

HISTOPATHOLOGY

AN ASSIGNMENT SUBMITTED TO THE

DEPARTMENT OF ANATOMY,

FACULTY OF BASIC MEDICAL SCIENCES,

COLLEGE OF MEDICINE AND HEALTH SCIENCES,

AFE BABALOLA UNIVERSITY,ADO-EKITI,

EKITI STATE,NIGERIA

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE AWARD OF THE DEGREE OF

BACHELOR OF SCIENCE (B.Sc)

IN ANATOMY

**Osteomyelitis**

Osteomyelitis (OM) is an [infection](https://en.wikipedia.org/wiki/Infection%22%20%5Co%20%22Infection) of [bone](https://en.wikipedia.org/wiki/Bone_tissue%22%20%5Co%20%22) .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. 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](https://en.wikipedia.org/wiki/Fever%22%20%5Co%20%22Fever), and weakness. The long bones of the arms and legs are usually affected in children, while the feet, spine, and hips are mostly affected in adults.The cause is commonly a [bacterial infection](https://en.wikipedia.org/wiki/Bacterial_infection%22%20%5Co%20%22Bacterial%20infection), but not normally a [fungal infection](https://en.wikipedia.org/wiki/Fungal_infection%22%20%5Co%20%22Fungal%20infection). It may occur by spread from the blood or from surrounding tissue.Risks for developing osteomyelitis include [diabetes](https://en.wikipedia.org/wiki/Diabetes%22%20%5Co%20%22Diabetes), [intravenous drug use](https://en.wikipedia.org/wiki/Intravenous_drug_use%22%20%5Co%20%22Intravenous%20drug%20use), prior [removal of the spleen](https://en.wikipedia.org/wiki/Splenectomy%22%20%5Co%20%22Splenectomy), and trauma to the area.Diagnosis is typically suspected based on symptoms.This is then supported by [blood tests](https://en.wikipedia.org/wiki/Blood_test%22%20%5Co%20%22Blood%20test), [medical imaging](https://en.wikipedia.org/wiki/Medical_imaging%22%20%5Co%20%22Medical%20imaging)(Radiography), or bone [biopsy](https://en.wikipedia.org/wiki/Biopsy%22%20%5Co%20%22Biopsy).Early and specific treatment is important in osteomyelitis, and identification of the causative microorganisms is essential for antibiotic therapy. The major cause of bone infections is Staphylococcus aureus

Treatment often involves both [antimicrobials](https://en.wikipedia.org/wiki/Antimicrobials%22%20%5Co%20%22Antimicrobials) and surgery.In those with poor blood flow, [amputation](https://en.wikipedia.org/wiki/Amputation%22%20%5Co%20%22Amputation) 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 (Hochberg *et al*., 2016). The young and old are more commonly affected.Males are more commonly affected than females.The condition was described at least as early as the 300s BC by [Hippocrates](https://en.wikipedia.org/wiki/Hippocrates%22%20%5Co%20%22Hippocrates).Before the availability of antibiotics the risk of death was significant (Brackenridge *et al*.,2016).



Chronic osteomyelitis of the long bones

**Signs and symptom**

Symptoms may include pain in a specific bone with overlying redness, [fever](https://en.wikipedia.org/wiki/Fever%22%20%5Co%20%22Fever), and weakness.Onset may be sudden or gradual.[Enlarged lymph nodes](https://en.wikipedia.org/wiki/Enlarged_lymph_nodes%22%20%5Co%20%22Enlarged%20lymph%20nodes) may be present (Root *et al*.,1999).

In children, the [long bones](https://en.wikipedia.org/wiki/Long_bone%22%20%5Co%20%22Long%20bone) are usually affected. In adults, the vertebrae and the [pelvis](https://en.wikipedia.org/wiki/Pelvis%22%20%5Co%20%22Pelvis) are most commonly affected.

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](https://en.wikipedia.org/wiki/Intravenous%22%20%5Co%20%22Intravenous) drug abuse, infectious root-canaled teeth, or other disease or drugs (e.g., [immunosuppressive](https://en.wikipedia.org/wiki/Immunosuppressive%22%20%5Co%20%22Immunosuppressive) therapy).

Osteomyelitis is a secondary [complication](https://en.wikipedia.org/wiki/Complication_%28medicine%29%22%20%5Co%20%22Complication%20%28medicine%29) in 1–3% of patients with pulmonary [tuberculosis](https://en.wikipedia.org/wiki/Tuberculosis%22%20%5Co%20%22Tuberculosis).In this case, the bacteria, in general, spread to the bone through the [circulatory system](https://en.wikipedia.org/wiki/Circulatory_system%22%20%5Co%20%22Circulatory%20system), first infecting the [synovium](https://en.wikipedia.org/wiki/Synovium%22%20%5Co%20%22Synovium) (due to its higher [oxygen](https://en.wikipedia.org/wiki/Oxygen%22%20%5Co%20%22Oxygen) concentration) before spreading to the adjacent bone (Kumar *et al*., 2007).Tubercular osteomyelitis, the long bones and vertebrae are the ones that tend to be affected.

**Pathogenesis of Osteomyelitis**

In general, microorganisms may infect bone through one or more of three basic methods

* Via the [bloodstream](https://en.wikipedia.org/wiki/Bloodstream%22%20%5Co%20%22Bloodstream) (*haematogeneously*) – the most common method
* From nearby areas of infection (as in [cellulitis](https://en.wikipedia.org/wiki/Cellulitis%22%20%5Co%20%22Cellulitis)), or
* Penetrating [trauma](https://en.wikipedia.org/wiki/Physical_trauma%22%20%5Co%20%22Physical%20trauma), including [iatrogenic](https://en.wikipedia.org/wiki/Iatrogenic%22%20%5Co%20%22Iatrogenic) causes such as [joint replacements](https://en.wikipedia.org/wiki/Joint_replacement%22%20%5Co%20%22Joint%20replacement) or internal fixation of [fractures](https://en.wikipedia.org/wiki/Bone_fracture%22%20%5Co%20%22Bone%20fracture) or secondary [periapical periodontitis](https://en.wikipedia.org/wiki/Periapical_periodontitis%22%20%5Co%20%22Periapical%20periodontitis) in teeth.

The area usually affected when the infection is contracted through the bloodstream is the [metaphysis](https://en.wikipedia.org/wiki/Metaphysis%22%20%5Co%20%22Metaphysis) of the bone (Luqmani *et al*., 2013) the bone is infected, [leukocytes](https://en.wikipedia.org/wiki/Leukocyte%22%20%5Co%20%22Leukocyte) enter the infected area, and, in their attempt to mop up the infectious organisms, releasing  [enzymes](https://en.wikipedia.org/wiki/Enzyme%22%20%5Co%20%22Enzyme) that break down the bone. [Pus](https://en.wikipedia.org/wiki/Pus%22%20%5Co%20%22Pus) spreads into the bone's blood vessels, damage their flow, and areas of devitalized infected bone, known as [sequestra](https://en.wikipedia.org/wiki/Sequestra%22%20%5Co%20%22Sequestra), form the basis of a chronic infection.Often, the body will try to create new bone around the area of [necrosis](https://en.wikipedia.org/wiki/Necrosis%22%20%5Co%20%22Necrosis). The resulting new bone is often called an [involucrum](https://en.wikipedia.org/wiki/Involucrum%22%20%5Co%20%22Involucrum).On [histologic](https://en.wikipedia.org/wiki/Histology%22%20%5Co%20%22Histology) examination, these areas of necrotic bone are the basis for distinguishing between [acute](https://en.wikipedia.org/wiki/Acute_%28medicine%29%22%20%5Co%20%22Acute%20%28medicine%29) osteomyelitis and [chronic](https://en.wiktionary.org/wiki/chronic%22%20%5Co%20%22wikt%3Achronic) osteomyelitis. Osteomyelitis is an infective process that encompasses all of the bone ([osseous](https://en.wiktionary.org/wiki/osseous%22%20%5Co%20%22wikt%3Aosseous)) components, including the bone marrow. When it is chronic, it can lead to bone [sclerosis](https://en.wikipedia.org/wiki/Sclerosis_%28medicine%29%22%20%5Co%20%22Sclerosis%20%28medicine%29) 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. At this point, the bacteria may be resistant to some antibiotics.These combined facts may explain the chronicity and difficult eradication of this disease, resulting in significant costs and disability, potentially leading to amputation. Intracellular existence of bacteria in osteomyelitis is likely an unrecognized contributing factor to its chronic form.

In [infants](https://en.wikipedia.org/wiki/Infant%22%20%5Co%20%22Infant), the infection can spread to a [joint](https://en.wikipedia.org/wiki/Joint%22%20%5Co%20%22Joint) and cause [arthritis](https://en.wikipedia.org/wiki/Arthritis%22%20%5Co%20%22Arthritis). In [children](https://en.wikipedia.org/wiki/Child%22%20%5Co%20%22Child), large [subperiosteal](https://en.wikipedia.org/wiki/Subperiosteal%22%20%5Co%20%22Subperiosteal) [abscesses](https://en.wikipedia.org/wiki/Abscess%22%20%5Co%20%22Abscess) can form because the [periosteum](https://en.wikipedia.org/wiki/Periosteum%22%20%5Co%20%22Periosteum) is loosely attached to the surface of the bone.

Because of the particulars of their blood supply, the [tibia](https://en.wikipedia.org/wiki/Tibia%22%20%5Co%20%22Tibia), [femur](https://en.wikipedia.org/wiki/Femur%22%20%5Co%20%22Femur), [humerus](https://en.wikipedia.org/wiki/Humerus%22%20%5Co%20%22Humerus), [vertebra](https://en.wikipedia.org/wiki/Vertebra%22%20%5Co%20%22Vertebra), the [maxilla](https://en.wikipedia.org/wiki/Maxilla%22%20%5Co%20%22Maxilla), and the [mandibular bodies](https://en.wikipedia.org/wiki/Human_mandible%22%20%5Co%20%22Human%20mandible) are especially susceptible to osteomyelitis (King MD *et al*.,2006). However, may be precipitated by trauma to the affected area. Many infections are caused by [Staphylococcus aureus](https://en.wikipedia.org/wiki/Staphylococcus_aureus%22%20%5Co%20%22Staphylococcus%20aureus), a member of the normal [flora](https://en.wikipedia.org/wiki/Flora_%28microbiology%29%22%20%5Co%20%22Flora%20%28microbiology%29) found on the [skin](https://en.wikipedia.org/wiki/Skin%22%20%5Co%20%22Skin) and [mucous membranes](https://en.wikipedia.org/wiki/Mucous_membrane%22%20%5Co%20%22Mucous%20membrane). In patients with [sickle](https://en.wikipedia.org/wiki/Sickle_cell%22%20%5Co%20%22Sickle%20cell)

[cell](https://en.wikipedia.org/wiki/Sickle_cell%22%20%5Co%20%22Sickle%20cell) disease, the most common causative agent is *[Salmonella](https://en.wikipedia.org/wiki/Salmonella%22%20%5Co%20%22Salmonella)*, with a relative incidence more than twice that of S. aureus (Burnett *et al*., 1998).Osteomyelitis complications may include:

Bone death (osteonecrosis). An infection in your bone can impede blood circulation within the bone, leading to bone death. Areas where bone has died need to be surgically removed for antibiotics to be effective.

Septic arthritis. Sometimes, infection within bones can spread into a nearby joint.

Impaired growth. Normal growth in bones or joints in children may be affected if osteomyelitis occurs in the softer areas, called growth plates, at either end of the long bones of the arms and legs.

Skin cancer. If your osteomyelitis has resulted in an open sore that is draining pus, the surrounding skin is at higher risk of developing squamous cell cancer.

**Progression of O**steomyelitis****

Osteomyelitis often requires prolonged [antibiotic](https://en.wikipedia.org/wiki/Antibiotic%22%20%5Co%20%22Antibiotic) therapy for weeks or months. A [PICC line](https://en.wikipedia.org/wiki/PICC_line%22%20%5Co%20%22PICC%20line) or [central venous catheter](https://en.wikipedia.org/wiki/Central_venous_catheter%22%20%5Co%20%22Central%20venous%20catheter) can be placed for long-term [intravenous](https://en.wikipedia.org/wiki/Intravenous%22%20%5Co%20%22Intravenous) medication administration. Some studies of children with acute osteomyelitis report that antibiotic by mouth may be justified due to PICC-related complications.It may require surgical [debridement](https://en.wikipedia.org/wiki/Debridement%22%20%5Co%20%22Debridement) in severe cases, or even amputation. Antibiotics by mouth and by intravenous appear similar (Stengel *et al*., 2001).

Due to insufficient evidence it is unclear what the best antibiotic treatment is for osteomyelitis in people with sickle cell disease as of 2019 (Martí-Carvaja *et al*., 2019).

Initial first-line antibiotic choice is determined by the patient's history and regional differences in common infective organisms. A treatment lasting 42 days is practiced in a number of facilities.Local and sustained availability of drugs have proven to be more effective in achieving prophylactic and therapeutic outcomes (Soundrapandian *et al*., 2007). Open surgery is needed for chronic osteomyelitis, whereby the involucrum is opened and the sequestrum is removed or sometimes saucerization can be done. [Hyperbaric oxygen therapy](https://en.wikipedia.org/wiki/Hyperbaric_oxygen_therapy%22%20%5Co%20%22Hyperbaric%20oxygen%20therapy) has been shown to be a useful [adjunct](https://en.wiktionary.org/wiki/adjunct%22%20%5Co%20%22wikt%3Aadjunct) to the treatment of [refractory](https://en.wiktionary.org/wiki/refractory%22%20%5Co%20%22wikt%3Arefractory) osteomyelitis.

Before the widespread availability and use of antibiotics, [blow fly larvae](https://en.wikipedia.org/wiki/Maggot%22%20%5Co%20%22Maggot) were sometimes [deliberately introduced](https://en.wikipedia.org/wiki/Maggot_therapy%22%20%5Co%20%22Maggot%20therapy) to the wounds to feed on the infected material, effectively scouring them clean.

There is tentative evidence that [bioactive glass](https://en.wikipedia.org/wiki/Bioactive_glass%22%20%5Co%20%22Bioactive%20glass) may also be useful in long bone infections.(Aurégan *et al*., 2015).

**Osteoarthritis**

Although osteoarthritis (OA) has been originally regarded as a non-inflammatory disease, reports increasingly suggest that it is inflammatory, at least in specific patients. OA patients often exhibit inflammatory infiltration of synovial membranes by macrophages, T cells, mast cells, B cells, plasma cells, natural killer cells, dendritic cells, granulocytes, etc. Although previous reviews have summarized the knowledge of inflammation in the pathogenesis of OA, as far as we know, no report review our current understanding about T cells, especially, each T cell subtype, in the biology of OA. This review highlights the current understanding of the role of T cells in the pathogenesis of OA, with attention to Th1 cells, Th2 cells, Th9 cells, Th17 cells, Th22 cells, regulatory T cells, follicular helper T cells, cytotoxic T cells, T memory cells, and even unconventional T cells (e.g., γδ T cells and cluster of differentiation 1 restricted T cells). The findings highlight the importance of T cells to the development and progression of OA and suggest new therapeutic approaches for OA patients based on the manipulation of T-cell responses.

Affecting approximately 3.8% (95% CI: 3.6–4.1) of the global population, osteoarthritis (OA) is regarded as a prevalent cause of morbidity and disability worldwide (Williams S *et al.,* 2010*)*. OA shows many disease characteristics, such as cartilage degradation, moderate synovial inflammation, pain, alteration of bony structure, and impaired mobility. However, despite the severity of the disease, relatively little is known about its exact etiology. Recent compelling investigations have attributed the onset of OA to various person-level factors such as age, sex, obesity, and diet and joint-level factors such as injury, malalignment, and abnormal joint loading. Although more and more researchers have recently presented hypotheses concerning the involvement of these factors in OA, especially for person-level factors, few of their hypotheses have been demonstrated experimentally, and some have even been challenged by the latest observational studies and clinical trials (Li Y*, et al.,* 2016).

Of the several factors potentially involved in the pathogenesis of OA, T cell-mediated immune responses and their influence on the biology of OA are the focus of this review (Saito I *et al.,* 2002*)*. The scientific community once understood OA to be induced by mechanical stress in the form of cartilage destruction, with minimal if any involvement of immune responses. Thus, OA was regarded as a non-inflammatory disease, in contrast with rheumatoid arthritis (RA), an inflammatory disease. However, recent studies suggest that at least in certain patients, OA is an inflammatory disease; patients have frequently been found to exhibit inflammatory infiltration of synovial membranes. Most recent studies have shown that the number of inflammatory cells in the synovial tissue is lower in patients with OA than in patients with RA, but higher than that in healthy subjects. Indeed, little difference has been found in the percentages of T cells, B cells, and natural killer cells in the peripheral blood between patients with OA and RA (Leheita *O et al.,* 2005*)*. Further experiments indicated that inflammation in OA is anatomically restricted and varies in intensity. The synovial membranes in regions rimming the cartilage of OA patients, which contain T cells bordered by B lymphocytes and plasma cells, showed a pronounced inflammatory response. In contrast, only a few infiltrating lymphocytes were observed in the synovial membranes taken from macroscopically non-inflamed areas in OA patients (Lindblad *S et al.,* 1987*).*This may explain the suggestion made by some researchers that immune responses are not involved in the pathogenesis of OA. When synovial samples from patients with knee OA were analyzed, the synovial lining cells showed strong immunoreactivity and phagocytic potential with cluster of differentiation (CD) 68 antibodies (Saito*et al.,* 2002*).*These findings suggested that macrophages may be associated with the pathogenesis of knee OA. Of 20 osteoarthritic synovial membranes, 5 showed lymphoid follicles containing T cells, B cells, and macrophages, and 10 (including the latter five) displayed a diffuse cellular infiltrate containing T and B cells, macrophages, and granulocytes (Revell PA *et al.,* 1988*).Th*ese results suggested that B cells and granulocytes may also be involved in the pathogenesis of knee OA.

**Pathogenesis of Osteoarthritis**

In this view, analyze literature data concerning participation of synovial inflammation, subchondral bone, humoral and cellular immune responses towards various cartilage autoantigens in the initiation and progression of primary osteoarthritis (OA). The vast majority of studies showed that the synovial inaflammation in OA is less pronounced than in RA but is more pronounced than in healthy people. In OA synovial tissue, macrophages and T-cells predominate in the inflammatory infiltrate. Some authors detected mast cells in the OA synovium in quantities higher than in healthy control and significantly higher than in RA patients. Most of researchers found many cytokines related to innate and adaptive immune cells in the OA synovial tissue, while in some studies the cells producing those cytokines were not identified. Among the cytokines there were both pro-inflammatory and anti-inflammatory ones: IL-1b, TNFα, IFNγ, IL-4, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18. In addition, some authors detected IL-5, IL-13, IL-19, IL-21, IL-26, IL-32, and TGFb. A role of adaptive immune response in OA is supported by the presence of autoantibodies against antigen determinants of collagens type II, IX, XI, aggrecan, fibronectin fragments, in the synovial tissue, synovium fluid, and peripheral blood serum. The research data clearly support a role of chronic inflammation and changes in innate and adaptive immune response in the pathogenesis of OA thus justifying the change of the disease name from “osteoarthrosis” to “osteoarthritis”. This novel understanding of OA pathogenesis is paramount as it provides a rationale for modern anti-inflammatory treatments and discovery of new therapeutic targets. We discuss the results of studies evaluating efficacy and safety of some types of anti-inflammatory treatment of OA. Until now, treatment of OA directed on inflammation control was not successful. Thus, clinical trials of anti-TNFα anti-IL-1b strategies for the treatment of OA did not show clinically significant improvement in spite of multiple studies demonstrating elevated concentrations of TNFα and IL-1bin synovial fluid and subchondral bone in OA thus suggesting the role of these cytokines in the OA pathogenesis. On the other side, treatment with IL-1 inhibitor diacerein was found to be effective which can be explained by pleiotropic effects of this drug. It should be stressed out that in order to increase the efficacy of anti-inflammatory treatments of OA they should be initiated at early disease stages, thus necessitating the use of new informative biormarkers of early OA.

**Progression of Osteoarthritis**

Osteoarthritis (OA) is a chronic degenerative disease. It causes damage to your joints, including those in your:

* hands and fingers
* knees
* hips
* lower back
* neck

Treatment for OA focuses on managing your symptoms. The disease can’t be reversed.

The progressive degeneration of OA has been classified into four stages. The first stage, with no joint damage, is called Stage 0.

Stage 4 is the most advanced and severe stage of OA. Here are some signs of stage 4 OA:

* your cartilage is worn away
* the space between the bones in your joint is greatly reduced
* your joint is warm and inflamed
* the normal lubricating fluid of your joint is decreased, although the joint may be swollen
* you have more bone spurs and bone rubbing against bone at the joint

People with advanced OA have pain and discomfort moving the joint. The pain is often severe. It can be debilitating and prevent you from carrying out your daily activities.

The progression of OA depends on the severity of the disease at your diagnosis, the joints involved, and your general health. There aren't any drugs yet that can stop the deterioration. However, following a therapy regimen early in the disease can help slow the rate of degeneration.

Progression to stage 4 can take years or even decades. For very advanced OA, pain management and surgery or joint replacement may be recommended.

The cause of osteoarthritis progressin is now thought to be a combination of these factors:

### **Genetics**

Your genes may be involved in the development of osteoarthritis, though [researchers](http://jmg.bmj.com/content/50/11/715.full%22%20%5Ct%20%22https%3A//www.healthline.com/health/osteoarthritis/_blank) are still working to fully understand this connection. It may be that you have an abnormality in the makeup of your cartilage, or that your bones fit together abnormally at the joint.

### **Weight**

Extra weight can put pressure on your hips and knees, which can cause the cartilage in your joints to deteriorate faster. The [Arthritis Foundation](http://www.arthritis.org/about-arthritis/types/osteoarthritis/causes.php%22%20%5Ct%20%22https%3A//www.healthline.com/health/osteoarthritis/_blank)reports a link between being overweight and an increased risk of OA of the hand. Excess fat tissue is thought to produce chemicals that inflame and damage your joints.

### **Past injuries**

Joint injuries or repetitive motion can lead to cartilage breakdown and OA. If the muscles supporting your joints are imbalanced or weak, this can also lead to cartilage breakdown.

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Medically reviewed by [William A. Morrison, MD](https://www.healthline.com/medical-team) on March 27, 2017 — Written by Marjorie Hecht.

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