Rheumatoid Arthritis

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Objectives

1. To develop a basic knowledge about Rheumatoid Arthritis
2. To understand how joints work and move in the body
3. To identify the signs and symptoms of Rheumatoid Arthritis
4. To understand how to properly diagnose Rheumatoid Arthritis
5. To understand the treatment options for Rheumatoid Arthritis

Almost everyone has heard of arthritis, or they at least know a little about it. When asked about arthritis, most people know that it is common in the elderly population and relate it to their grandparents. The elderly population is often characterized as being slower, weaker, and having less range of motion. These traits can be common with increasing age. Any amount of exercise or activity can be beneficial to everyone, but especially the elderly population.

What most people do not know about arthritis is that there are many different types and that it can affect anyone from the middle aged population to the elderly population. Arthritis is an inflammation of one or more joints, which usually causes swelling and stiffening of the joints.[1] There are over 100 different types of arthritis and related diseases. The most common types include osteoarthritis, psoriatic arthritis, rheumatoid arthritis, fibromyalgia, and gout.

Rheumatoid arthritis, also known as RA, is a severe form of arthritis. Not only does rheumatoid arthritis cause swelling, but it also affects the lining of the joints, causing bone erosion and joint deformity over time. With rheumatoid arthritis, the immune system attacks the synovium, which then thickens and destroys cartilage. Synovium is connective tissue that lines the inside of a joint capsule. A joint capsule is a structure that surrounds joints. With this damage, tendons and ligaments stretch and weaken.[2] [Image 1][3] The picture provided shows the anatomy of a joint and how a healthy joint appears versus a joint with osteoarthritis or rheumatoid arthritis.Whether treatment is involved or not, rheumatoid arthritis can affect the entire body.

Joints are moveable connections between two bones. There is cartilage present on the end of both bones to prevent the bones from rubbing against each other. There is a joint cavity and a joint capsule. The joint capsule is composed of two layers: an inner and an outer layer. The inner layer is composed of blood vessels and nerves that send impulses to the brain. The outer layer is composed of a firm, fibrous tissue. It is important to stay mobile or active to make sure that joints do not shrink or shorten. Synovial fluid is produced by the inner layer of the joint capsule. Synovial fluid insures smooth gliding and works as a shock absorber. Some joint movement depends on tendons, ligaments, muscles and the type of joint.[4]

There are three different categories of joints: synarthrodial, amphiarthrodial, and diarthrodial. [Image 2][5] Synarthrodial is known as a fibrous or immovable joint. This is because

it is composed of fibrous connective tissue that has little to no movement. This joint has no cavity, or space, between the two bones. An example of this joint would be the sutures of the skull. Amphiarthrodial is known as a cartilaginous joint, which allows slight movement between the bones. The bones are connected by cartilage. Diarthrodial joints, or synovial joints, are freely movable joints. Synovial joints are the only type of joint that has a space between the bones. There are six types of synovial joints: hinge, gliding, ball and socket, condylar, pivot, and saddle.[6] [Image 3][7]

Range of motion is defined as the free movement of joints. Exercises can be performed daily to assure range of motion is not lost. There are three types of range of motion: passive, active-assisted, and active. Passive range of motion is when assistance is needed to move a joint because movement may be restricted or limited. Active-assisted range of motion is the ability to move a body part, but assistance may be needed in moving that body part to assure damage does not occur. It may also relieve some stress on the joint. Active range of motion is when no assistance is required in moving a body part or joint. Range of motion can be assessed by a series of exercises, physical therapy, or occupational therapy.[8]

Rheumatoid arthritis is categorized as an autoimmune disorder. Rheumatoid arthritis is not only a type of autoimmune disorder, but it is the most common autoimmune disorder. An autoimmune disorder is when the immune system is overactive and is attacking its own healthy tissues. This will also cause the person to become more susceptible or immunosuppressed to infections. Normally, the immune system can tell the difference between foreign cells and its own cells to release autoimmune antibodies.[9] Types of autoimmune disorders include: rheumatoid arthritis, lupus, type 1 diabetes, inflammatory bowel disease, multiple sclerosis (MS), Guillain Barre syndrome, psoriasis, and Graves disease. These are just the most common, or known diseases, as there are over eighty types of autoimmune disorders.[10]

In 1500 B.C., Eber Papyrus was credited with the first reference of rheumatoid arthritis because he described a condition that was similar to the disease.[11] Augustin Jacob Landre-Beauvais made the first description of RA in 1800, when he was a resident physician at Saltpetriere asylum in France. Beauvais treated patients with severe joint pain and patients that were ignored by other physicians. Often times, physicians would rather treat easier patients to

keep a better reputation and make an earning for their work. Since Beauvais was the physician taking care of these patients, he originally identified rheumatoid arthritis as a type of gout, which was inaccurate. It was not until the late 19th century that Alfred Garrod, an English physician, distinguished the difference between gout and arthritis through blood tests. In Garrod's observations, rheumatoid arthritis was known as "rheumatic gout". He described his findings and observations in his *Treatise on Nature of Gout and Rheumatic Gout,* which he published in 1859. He is now credited with laying a foundation to discover the etiology of rheumatoid arthritis.1[2]

Alfred Garrod's fourth son, Archibald Garrod, coined the term Rheumatoid Arthritis because it described the disease's actions on the body. Archibald Garrod authored the *Treatise of Rheumatism and Rheumatoid Arthritis* where he discussed bones and skeletal remains from around the world. This work also talks about how the remains displayed damage or evidence of rheumatoid arthritis but had no actual evidence or proof. His treatise serves as a backbone of Ancient Origin.[12]

There is some discussion about descriptions from ancient texts regarding rheumatoid arthritis. Some believe that these texts are evidence that rheumatoid arthritis existed long ago by the descriptions of the signs and symptoms. Others believe that is is not sufficient evidence and that the descriptions are too vague. One ancient text from Greek philosopher Hippocrates stated "In the arthritis which generally shows itself about age thirty-five there is frequently no great interval between the affection of hands and feet; both becoming similar in nature, slender, with little flesh… For the most part their arthritis passeth from feet to hands, next the elbows and knees, after these the hip joint. It is incredible how fast the mischief spreads." [12]

Besides these ancient texts, there are artwork pieces that show that rheumatoid arthritis may have been present. There is one piece that showcases possible RA more than others named "*The Three Graces*" from 1638. [Image 4][13] In this piece, one of the ladies, or Graces', hand is of an unnatural way and is deformed. Although this piece is the most pronounced, the most convincing painting is from the mid 15th to early 16th century. [Image 5][13] It is named "*The Temptation of St. Anthony*". Evidence for this is the beggar in the painting having a deformed wrist and hand. Paintings are not 100% evidence though because it is the artist's work and preferences. Some researchers studied these paintings and realized that there were other diseases

present such as rheumatic fever or gout. All of these diseases may look similar in artistic paintings which makes it extremely difficult to depict which one it may be, or to make a diagnosis.[12]

While there are ancient texts and paintings, researchers also participated in paleopathological studies known as post-mortem studies. Two studies were done before the development of paleopathological methods by Professor Flinders Petrie and Sir Armand Ruffer. Several sites of skeletal remains of many different ethnicities were examined only to find lesions and eburnation (degeneration/ cartilage erosion) of joints. However, in the 1970s, it was discovered that ankylosis spondylitis was present in these remains instead of rheumatoid arthritis. Although there was no evidence of rheumatoid arthritis in those remains, the discovery made by the two professors made it possible to believe that there is evidence of rheumatic diseases in human remains.[12]

In the mid-20th century, x-ray was integrated into the studies of rheumatoid arthritis, differentiating between skeletal remains and living patients. Observations were made between the two subjects and it was believed that the soft tissue of living patients may shift the study to be inaccurate compared to the skeletal remains. One variable was the preservation of the skeletal remains and how eroded bones were before finding/discovering them. There is a list of features that may indicate some forms of arthritis or other diseases, but no one certain feature for rheumatoid arthritis. Out of all these studies that were conducted, there is not one that diagnoses rheumatoid arthritis. They all suggest rheumatoid arthritis was present even if the case was not convincing.[12]

There are many symptoms involved in diagnosing rheumatoid arthritis. The main symptoms include tender, warm, swollen joints that are worse in the morning or after long periods of inactivity. Fatigue, fever, and loss of appetite are not uncommon. Small joints are usually affected first, such as in the hands and feet. Then it spreads to the major joints including the hip, shoulder, ankle, and spine. Rheumatoid arthritis can also affect the skin, eyes, mouth, lungs, heart, kidneys, and blood vessels.[2] Signs of these include: bumps on the skin, dry and sensitive eyes, dry and irritated mouth, shortness of breath with inflammation of the lungs,

inflammation of blood vessels that may cause nerve damage, and anemia. These symptoms are common in many other diseases and that is why it is difficult to diagnose rheumatoid arthritis.[1]

Rheumatoid arthritis is a systemic disease that affects about 1.5 million people in the United States, which is equivalent to 1% of the population. This disease is affected by age, race, sex, environmental factors, smoking, and family history.[2] If someone is diagnosed with rheumatoid arthritis, he/she has an increased risk for developing osteoporosis, rheumatoid nodules, dry eyes, dry mouth, infections, carpal tunnel syndrome, heart problems, lung disease, and lymphoma.[2] Statistics show that women are at a higher risk than men for developing rheumatoid arthritis.[2] Rheumatoid arthritis can start affecting an individual anywhere from age fifteen to forty-four, but starting at the age of fifty, women are more at risk, with diagnosis at an average age of sixty years old.[14] About 6.7% of women are affected versus only 2.7% of men.[9] Since more women are affected, some believe that the disease is triggered when estrogen and progesterone decrease. Smoking can increase the risk by 2.4%. If someone has a parent or sibling with rheumatoid arthritis, there is a four times greater risk of developing rheumatoid arthritis in his/her lifetime. Pollution, chemicals, secondhand smoke, or even traumatic events can trigger rheumatoid arthritis symptoms.[14]

Unfortunately, those living with rheumatoid arthritis have a shorter life expectancy, as much as ten to fifteen years shorter. With treatment, it is not uncommon to live to the age of eighty or ninety. Since rheumatoid arthritis can affect other organs, complications can arise, which causes half of rheumatoid arthritis related deaths.[14] The main organ that rheumatoid arthritis affects is the heart and cardiovascular system. If someone is diagnosed with rheumatoid arthritis, the chance of developing heart problems doubles compared to someone who does not have rheumatoid arthritis. Heart attacks, strokes, or atherosclerosis are the most common diseases or complications associated with the heart and cardiovascular system. This is because the endothelium, or the inner layer of the blood vessels, can get damaged due to the inflammation. The damage can cause plaque or fatty deposits to build up in the arteries, which can lead to future blockages and narrowing of the arteries. Rheumatoid arthritis can also affect the veins, and those diagnosed have a three times greater risk of developing deep vein thrombosis or pulmonary embolisms. An increased risk for atrial fibrillation, or irregular heart

rhythm, and diastolic dysfunction, or an abnormality in filling of the heart with blood, is not uncommon either.[15]

Rheumatoid arthritis is not uncommon in children, but if present, it is known as juvenile arthritis. The main symptoms of juvenile arthritis include fevers, loss of appetite, anemia, rashes and joint swelling. Children's joints will be uncomfortable for at least forty-five minutes at a time and they will experience eye pain or vision problems. Children will also have stunted growth or some limbs may be unequal. Over 300,000 children are diagnosed every year. Sometimes symptoms will persist, but in length, symptoms will disappear with age.[14] When studies are conducted, twins are preferred because rheumatologists can observe their genetic and environmental influences.[16]

Diagnosing rheumatoid arthritis is not easy due to there being no specific cause, but blood tests can help with the diagnosis. In the blood, if elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-cyclic citrullinated peptide antibodies (anti-CCP), or the rheumatoid factor are present, this will indicate that the inflammatory process is present. Also, if the antinuclear antibody test, or ANA, is positive, it will indicate that an autoimmune disorder is present, but it will be unable to tell which one.[2] Eighty percent of patients will test positive for the rheumatoid factor which is an antibody in the blood.[1] Sixty percent are seropositive, which means they have the anti-CCP and rheumatoid factor. The other forty percent test negative for both and are seronegative.[14]

Often times lupus and rheumatoid arthritis are misdiagnosed because of their similarities. Similarities between the two diseases include joint pain, joint swelling, fatigue, weakness, and fever, but fever is more common with lupus. The main difference between the two diseases is that lupus affects more of the internal organs and skin with persistent symptoms. Rheumatoid arthritis affects more of the joints and causes deformities or bone erosion within the joints, usually with worsening pain in the morning. Lupus can be a life threatening condition because it usually affects the kidneys the most. Treatment for lupus includes corticosteroids such as prednisone or hydrocortisone. If someone is diagnosed with an autoimmune disease, he/she is more prone to developing another autoimmune disease. When someone is diagnosed with lupus, it is not uncommon to develop scleroderma, Sjogren syndrome, polymyositis dermatomyositis,

autoimmune thyroid, or mixed connective tissue disease. With rheumatoid arthritis, it is not uncommon to develop Sjogren syndrome or autoimmune thyroid disease.[17]

Some genes and genetic markers have been common in people with RA that could aid in the diagnosis of the disease. The only issue is that not all people have these genes, nor do they develop these genes. There are over 22,000 genes, but only some will be used in diagnosing rheumatoid arthritis.[16] These genes include the STAT4, TRAF1, C5, and PTPN22. The STAT4 gene attaches itself to DNA and controls other genes and regulates the immune system. TRAF1 and C5 are associated with chronic inflammation. PTPN22 relays signals from outside of the cell to the cell nucleus. These signals influence the development and progression of rheumatoid arthritis.[18] The HLA gene, human leukocyte antigen, produces proteins that help the immune system distinguish between its own proteins versus foreign proteins or invaders. If the HLA gene is present, there is a five times greater chance of developing rheumatoid arthritis than those who do not have this genetic marker.[1]

Imaging modalities play a significant role in diagnosing rheumatoid arthritis. Rheumatoid arthritis can be diagnosed utilizing multiple imaging modalities and monitoring the progression. Imaging modalities include x-rays, CT (computed tomography), MRI (magnetic resonance imaging), and ultrasound. Each imaging modality is used to view different parts of the anatomy.[10] X-rays are utilized the most to follow the progression of rheumatoid arthritis. X-rays show if there is any bone erosion or joint damage. The only disadvantage of x-rays is that it is unable to detect the early signs and symptoms of rheumatoid arthritis.[19] [Image 6 and 7][20] Radiographs show the difference between a healthy joint and one with rheumatoid arthritis. The deformities and erosion are evident and appear to be painful. CT, or computed tomography, looks at the bone and soft tissue of the anatomy being imaged. MRI, or magnetic resonance imaging, is good at detecting early signs of rheumatoid arthritis because it focuses on the soft tissue, muscles, tendons, and joint capsules. MRI is able to detect the inflammation before damage occurs. MRI can also detect fluid build up in the bone marrow, which is a sign of deterioration. The last imaging modality is ultrasound. Ultrasound uses high frequency sound waves to form an image. Ultrasound also helps to detect the early signs of rheumatoid arthritis by finding the inflammation of the bursae or fluid build up in the joints.[10]

There is no cure for rheumatoid arthritis, but medication can be taken to help alleviate the symptoms. Participation in therapy to stay active can help, or in some extreme cases, surgery may be the only option for pain relief. Treatment for rheumatoid arthritis has developed over time as more is learned about this disease. Historical treatments included bloodletting and leeching, acupuncture, acupressure, heat, and cupping. Heavy metals found within the environment have had some success in treatments. One heavy metal, gold, has shown the best treatment and is still used today with DMARDs or disease modifying antirheumatic drugs. Gold injections are from sodium aurothiomalate, which is a component in DMARDs. It was believed that pain relief could come from plant extracts of willow bark and leaves that contained salicin.[11]

Starting in 1853, acetylsalicylic acid, or aspirin, was synthesized by neutralizing salicylic acid. This was performed by French chemist Charles Frederic Gerhardt. It was not until 1929, that salicylic acid was identified as the active substance that eased pain. Salicylic acid is obtained from willow bark or wintergreen leaves and it is used as a topical treatment. The chemical name for salicylic acid is orthohydroxybenzoic acid. Starting in the 1940s, sulphasalazine was developed to alleviate the symptoms of rheumatoid arthritis and was categorized as a DMARD. In 1949, the start of NSAIDs, or nonsteroidal anti-inflammatory drugs, became present in the treatment of rheumatoid arthritis. Also in 1949, cortisone was trialed in a treatment regime by Philip Hench and Edward Kendalland with successful results for autoimmune diseases.[14] Methotrexate was originally used for leukemia in the 1950's, but in the 1980's, it was used for the treatment of rheumatoid arthritis. In 1975, tumour necrosis factor (TNF) was identified in the development of rheumatoid arthritis and the anti-TNF antibodies became effective in the treatment against rheumatoid arthritis in 1993. Tumour necrosis factor is a multifunctional cytokine that plays an important role in diverse cellular events and is usually secreted by inflammatory cells. Anti-TNF antibodies or TNF blockers are biosimilar drugs.[11]

Current treatment for rheumatoid arthritis has progressed quite extensively since treatments first started. Many different drugs are used to either slow the progression or stop the progression of rheumatoid arthritis and to help alleviate pain from inflammation. Corticosteroids are used as anti-inflammatory medications to reduce inflammation and joint swelling. Some types of corticosteroids include prednisone, prednisolone and methyprednisolone. DMARDs

(disease modifying antirheumatic drugs) and NSAIDs (nonsteroidal anti-inflammatory drugs) are also used in the treatment of rheumatoid arthritis. DMARDs treat the underlying disease rather than treating the symptoms. They help with the progression and the pain or swelling associated with rheumatoid arthritis. Types of DMARDs include methotrexate, hydroxycholorquine, sulfasalazine, leflunomide, cyclophosphamide, and azathioprine.[1] Methotrexate is one of the most common DMARDs that are prescribed, but this medication can come with some side effects such as folic acid deficiency, mouth sores, ulcers, and headaches. Folic acid is a B vitamin that is prescribed by a doctor when methotrexate is prescribed to help prevent those side effects. NSAIDs block COX enzymes, cyclooxygenase, and reduce prostaglandins throughout the body. COX enzymes produce prostaglandins which cause inflammation and fever.[21] Examples of NSAIDs are Tylenol and aspirin.[1]

Biologics are new for the treatment of rheumatoid arthritis. Biologics can be used for those with rheumatoid arthritis when other treatments have not been effective. Biologics target individual molecules and will work faster than DMARDs. Biologics are also used because they do not wipe out the immune system. Biologics were used in the treatment regime starting in 1998 and have been improving over the years to create 9 different drugs. A biologic drug is produced from living organisms, or includes the components of living organisms. They may also include genes, proteins or cells. Biologics may also be called anti-TNF drugs, which target the tumour necrosis factor. Unfortunately, biologics can be expensive, but less expensive versions of biologic drugs have been created, called biosimilars. Biosimilars are not the same as generic medications because it is almost impossible to replicate the same drug.[22] Sometimes biosimilar is referred to as “reference product” because it has to meet FDA standards. Some examples of the biosimilar and biologic drugs include:

Biosimilar	Biologic
Inflectra	Remicade
Erelzi	Enbrel
Amjevita	Humira
Renflexis	Remicade
Cyltezo	Humira

Hyrimoz Humira

[22]

Three of the eight biologic drugs that are prescribed most often include adalimumab, etanercept, infliximab. These three drugs block the action of tumor necrosis factor, TNF, secreted by various immune cells that can potentially stimulate immune response and inflammation.[23]

Holistic or alternative treatments for rheumatoid arthritis work well for people that do not want to depend on medication to help alleviate the symptoms. Some people also want healthy and natural therapy due to their lifestyle and beliefs. Some types of alternative treatments include: essential oils, cryotherapy, acupuncture, floating, herbal tea, physical therapy, chiropractic, massage, heat or LED light therapy, and meditation. Since all of these treatments are alternative medicine, they are not preferred by everyone and they also do not have the same results/outcomes for everyone. Some people may get relief from some of these treatments while others do not have any relief. It depends on the person and at what stage the disease has progressed to. Depending on the type of treatment, it may not be recommended if someone is having an RA flare up because the treatment could make it worse. Usually it is not recommended to go to a chiropractor, but that decision is up to the person and if he/she gets pain relief from the treatment. As stated, there is no cure for rheumatoid arthritis. All of these methods mentioned for the treatment of rheumatoid arthritis are to alleviate symptoms and to slow or stop the progression of this disease.[24]

Depending on the severity of the pain and damage of the joint, surgery may be the only option. Joint replacements are the most common for the knees and hips. These are major joints that affect everyday life and movement.[1]

Treatments can be a combination of everything mentioned above. Treatment may vary for each individual and this disease will affect each individual differently. Many people may become debilitated and unable to work, which can be a burden on the individual and the family. All types of insurance coverages are different, with some covering all the treatment, covering part of the treatment, or none of the treatment.[25] On average, someone diagnosed with rheumatoid arthritis will spend about $20,000 a year for treatment.[14]

In 1932, the International Committee on Rheumatism was created. It was later named the American Rheumatism Association and the American College of Rheumatology.[11] Since then, trials for new drugs have been conducted. The newest trials have been shown to be successful with biologic drugs. Recently, in 2018, Phase 3 was conducted with some positive results. This drug reduced symptoms and improved daily physical needs for those where other treatments were not successful. Phase 3 was a twenty-four week trial that was a double blinded and placebo study. There were over five hundred participants that had to meet requirements to participate in the study. Patients had to be at least eighteen years of age with active severe rheumatoid arthritis and with a minimum of six tender and swollen joints. They must have stopped taking TNF inhibitors due to no improvement, no response, or severe side effects.

The drug in Phase 3 is called baricitinib and it is categorized under the Janus-kinase inhibitors. Janus-kinase inhibitors work by interfering with intracellular enzymes that signal action is necessary for various inflammatory substances in the body to be effective. The 527 patients were divided up into three different categories: four milligrams of baricitinib, two milligrams of baricitinib, and placebo over a twenty-four week time frame. At the twelve week endpoint, the high group showed a twenty percent decrease in number of joints affected, the low group showed a forty nine percent decrease in number of joints affected, and in the placebo group, twenty percent saw the same effect.

At twenty four weeks, adverse events occurred in the form of a mild upper respiratory infections. The percentage of mild upper respiratory infections was higher with those on the high dose than the low dose and even lower with those on the placebo. At week twelve, it was also shown that two percent of people on the high dose developed the herpes zoster virus, or shingles, versus those on the low dose and placebo that had less than one percent. Baricitinib also raised the high and low density lipoprotein levels and the implications are unknown of this result. This drug is known to work in clinical trials when other drugs have not worked for others.[23]

In conclusion, rheumatoid arthritis can affect anyone at any age. The population needs to be educated about this disease and how it can affect a person. Since the symptoms are similar to other diseases, getting examined by a doctor may be helpful. Rheumatoid arthritis is hard to diagnose, but through all the tests discussed, an accurate diagnosis will help with the treatment of

this disease. RA can affect people differently, but it starts with the same effect on everyone. This disease is not curable, but it can be regulated and the progression can be slowed or stopped if treatment is involved. There are several different types of treatments and treatment plans that can accommodate many lifestyles.

Image 1

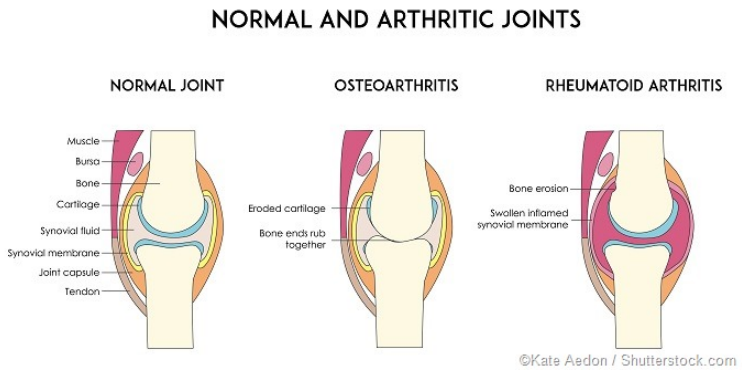


Image 2

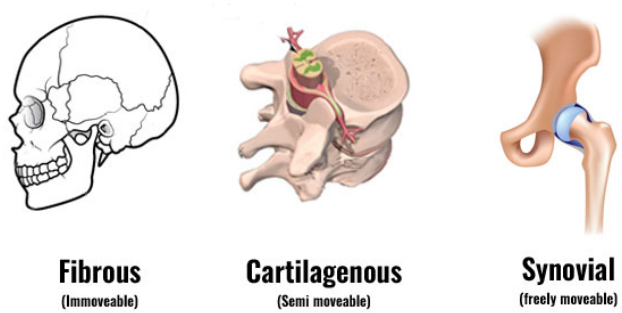


Image 3

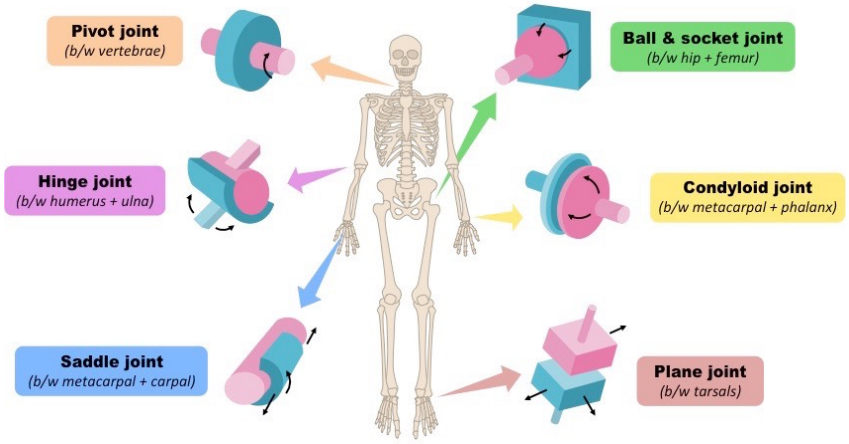


Image 4 *"The Three Graces"*

Image 5- unable to be pictured *"The Temptation of St. Anthony"*

Image 6

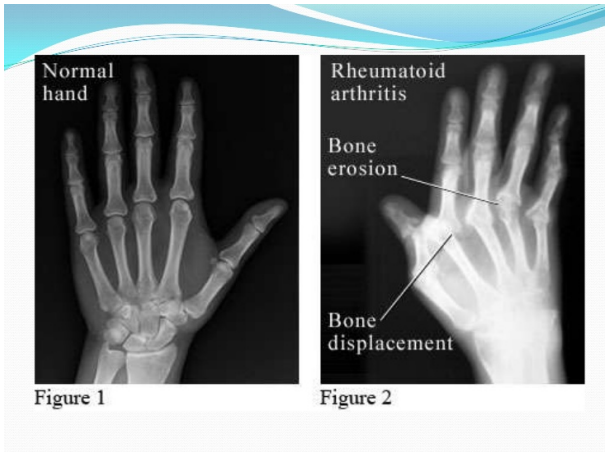
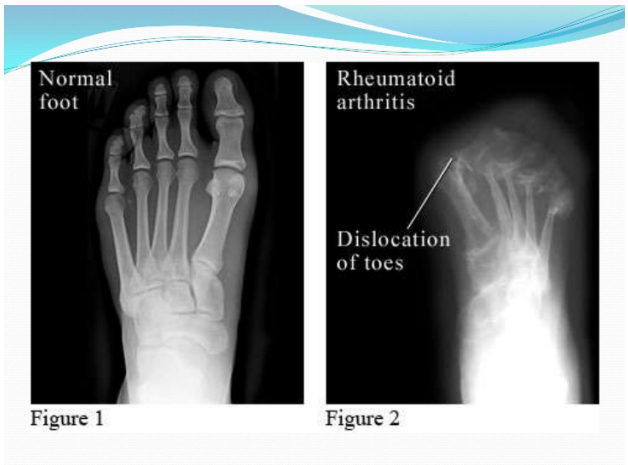


Image 7



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