# Methodological Approach to Addressing Joint Replacement Challenges in Osteopetrosis: A Clinical Review Perspective

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## Abstract

Osteopetrosis is considered a source of concern and a health problem because it is a rare disease that is difficult to detect and leads to many health risks. Osteopetrosis is a rare condition represented by a process disrupting normal bone formation and remodeling, which causes deformation of the teeth and skeleton, this deformity develops over time, causing an imbalance in the mineral balance. Also, osteopetrosis appears due to increased bone thickness and defective formation and disorganization, especially in areas of concentrated stress, such as the subtrochanteric areas, hip, knee, and femoral neck. The complication of osteopetrosis is degenerative osteoarthritis (OA) and directly affects hip or knee replacement operations in patients. The present review summarizes the most important previous and contemporary information and concepts and provides a detailed description of osteopetrosis, its causes, and risks that can be found in previous reviews and literature. In addition, the most important information and results reached in this literature regarding hip and knee joint replacement and its relationship to osteopetrosis. In our review, we emphasize the need to evaluate the results of recent studies related to osteopetrosis and its relationship to hip and knee joint replacements and how to detect and deal with this disease. In addition, it contributes to providing evidence-based information to help clinicians and researchers evaluate osteopetrosis and its impact on the hip and knee joints and increase their motivation to pay attention to this field.

**Keywords:** Osteoclasts, Osteopetrosis, Hip, Knee, Joint Replacement, Arthroplasty, Arthritis.

## 1. Introduction

Bone consists of a dynamic, self-renewing, continuous, and homeostasis tissue, the homeostasis of bone formation depends on the functional homeostasis between osteoclasts responsible for bone resorption, osteoblasts that are essential to forming the bone matrix, and osteocytes that contribute to the process in the transduction and reception mechanical stimuli (Coudert et al., 2015; Del Fattore et al., 2012). Therefore, the process of bone formation and resorption takes place in an accurate and balanced manner, and if any kind of perturbation occurs in this process in humans, it leads to bone diseases, including osteopetrosis. In general, osteopetrosis is considered a source of concern and a health problem because it is a rare disease that is difficult to detect and leads to many health risks (Wu et al., 2017; Strickland & Berry, 2005; Coudert et al., 2015; Vernejoul & Benichou, 2001), in addition to the fact that osteopetrosis is a rare condition represented by a process disrupting normal bone formation and remodeling, which causes deformation of the teeth and skeleton, and this deformity develops over time, causing an imbalance in the mineral balance (Wu et al., 2017). Where the osteoclasts function to dissolve bone minerals, and this process is necessary for mineral balance and bone remodeling (Charles & Aliprantis, 2014).

Many factors cause osteopetrosis, which is a rare inherited bone disorder that leads to increased bone density due to increased mineral density in it, which causes disability or deformation of various parts of the body's bones for individual's adults (Sharma et al., 2013; Cohen-Solal et al., 2023). In addition, osteopetrosis appears as a result of increased bone thickness and defective formation and disorganization, especially in areas of concentrated stress, such as the subtrochanteric areas, hip, and femoral neck (Manzi et al., 2012). Moreover, osteopetrosis is a rare disease and its incidence has been reported to range from 1:100 000 to 1:500 000 (Sharma et al., 2013; Lam et al., 2007).



Osteopetrosis does not affect a human's life expectancy, but it has many risks, including osteoarthritis (OA), fractures, and poor healing with non-union, as well as osteomyelitis (Siljander et al., 2021). According to these risks, osteopetrosis can represent major challenges and problems for clinicians, especially orthopedic surgeons, especially when performing joint replacement surgeries (Comulada et al., 2021). This is because osteopetrosis and a narrow medullary canal increase the risk of fractures during bone necrosis thus it is difficult to obtain the proper alignment for the specific osteotomy required in knee or hip replacement operations (Comulada et al., 2021; Wu et al., 2017). Furthermore, there are complications of osteopetrosis that appear after a long

period, namely degenerative OA (Mayer et al., 2012), which directly affects hip or knee replacement operations in patients. Hip arthritis is often associated with osteopetrosis, as 50% of cases of hip arthritis are the result of excessive stiffening of the subchondral bone (Coudert et al., 2015), and this inflammation can also affect other joints, such as the knee joint. In addition, the hip and knee joints are considered among the most important joints in the human body, they bear the weight of the body, control the force resulting from movements, and absorb shocks. Therefore, these joints are exposed to many risks that may require their replacement. However, hip or knee replacement surgeries in patients with osteopetrosis face more technical difficulties during surgery, as well as risks of complications after surgery (Siljander et al., 2021). This is because the hard, sclerotic bone in the femoral canal about the hip leads to the narrowing or obliteration of this canal. Thus, it is difficult for the thigh to accommodate the hip replacement process, and adding a femoral component leads to a prolongation of the surgical procedure time (Siljander et al., 2021; Strickland & Berry, 2005).

In the present review, we provide an overview of the most important previous and contemporary information and concepts and provide a detailed description of osteopetrosis, its causes and risks that can be found from previous reviews and literature. In addition, the most important information and results reached by previous literature regarding the topic of hip and knee joint replacement and its relationship to osteopetrosis. In particular, we directly emphasize the importance of studying and evaluating the results and the most important findings of studies regarding osteopetrosis and its relationship to the replacement of hip and knee joints and how to detect and deal with this disease. Finally, the aim of this review was also to provide a general idea of the most important information that researchers have found regarding osteopetrosis and its effect on the various bone joints the extent of their interest in this field, whether there is much literature that has dealt this topic, especially with the emergence of cases suffering from this disease.



## 2. Osteoclasts

Osteoclasts are considered giant, multinucleated cells in the human body, their function is to reabsorb and organize the bone matrix, which helps and ensures the continuous remodeling and development of the skeleton, as well as maintaining and developing the hematopoietic place in the bone marrow (Jacome-Galarza et al., 2019; Chen et al., 2019). Furthermore, the osteoclasts originated and are reproduced by the progenitors of fetal myeloid erythrocytes, these cells contain within them a group of complex organelles that work to transport proteins, solutes, and

macromolecules to their specific destinations in the body through intermediaries equipped for these function through their association with the membrane (Ng et al., 2019). Therefore, any defect or disorder in the function of bone cells, for example, a lack of activity of defective osteoclasts, leads to bone marrow failure and osteopetrosis. In contrast, in the case of increased activity of osteoclasts, this leads to osteoporosis and bone loss (Jacome-Galarza et al., 2019).

### 2.1 Osteoclast Function

The function of the osteoclast is represented in the process of bone decomposition through osteoclasts that perform the function of transport: motile and resorption (Jiang et al., 2021). The osteoclast begins to flatten and form lamellae, which are membranous protrusions that enable it to move during the motile stage (Alkhayal et al., 2023). In addition to that, osteoclasts are distinguished in their function in that their cytoskeleton at the point of disintegration, undergoes a reorganization process due to the adhesion of these cells to the marrow, and this process results in the creation of a sealing zone a result of membrane polarization (Jimi & Katagiri, 2022). The sealing zone has a plasma membrane containing Avb3 integrins, which are known as vitronectin receptors and their function is to strengthen and tighten the bone to connect with the underlying bone (Alkhayal et al., 2023). The resorptive zone is separated from the extracellular space by the sealing zone, which is the actin ring that surrounds the ruffles boundary (Alkhayal et al., 2023). Also, the bone matrix contains many proteins with a specific pattern of amino acids, an example of this are osteopontin and sialoprotein, which include the amino acid pattern (Arg-Gly-Asp (RGD)) and its function is to interact with the bone matrix receptor present in it (Huybrechts & Van Hul, 2022).



## 3. Osteopetrosis

Osteopetrosis is a name derived from the Greek language. The word “osteo” refers to the meaning of bone and the word “petrosis” refers to the meaning of stone. Therefore, this disease was often referred to in the colloquial language as “marble bone disease” (Bailey & Tapscott, 2023; Penna et al., 2019). Osteopetrosis was originally described in 1904 by radiologist Dr. Albers Schönberg in Germany, the radiological result that Dr. Albers relied on to detect and describe the disease showed an abnormal increase in bone density (Stark & Savarirayan, 2009; Sharma et al., 2013; Bailey & Tapscott, 2023). An increase in bone density due to a defect and disorder in osteoclast dysfunction leads to abnormal osteoporosis (Bailey & Tapscott, 2023). Osteopetrosis is a rare hereditary skeletal bone disorder in bone metabolism, it can be defined as a failure and disorder in osteoclast dysfunction, leading to increased bone mineral density (Comulada et al.,

2020; Xie et al., 2015; Wu et al., 2017). Moreover, some studies reported that osteopetrosis does not appear as a result of an increase in mineralization, but rather due to an increase in bone thickness and disorganization (Manolagas, 2000; Walker, 1973; Kovanlikaya et al., 1997) and the area of the skeleton most susceptible to osteopetrosis was the central area, such as the subtrochanteric areas and the femoral neck (Manzi et al., 2012). In addition, osteopetrosis appears as a result of a disorder that reduces the resorption of the skeleton, which leads to a defect in a group of bone tissue hardened by osteoclast-mediated skeletal. This disorder is also characterized by the obliteration of the medullary cavity osteosclerosis of the bones, and calcified cartilage (Bailey & Tapscott, 2023; Xie et al., 2015).

### 3.1 Causes of Osteopetrosis

There are two main causes of osteopetrosis (osteocondensing), which are failure of resorption by osteoclasts and increased bone formation. However, another cause of osteopetrosis is a defect in osteoclast function or differentiation (Coudert et al., 2015; Sobacchi et al., 2013; Stark, 2009). The genetic mutations that cause osteopetrosis in humans have been identified and are present in eight genes (*TCIRG1, CLCN7, OSTM1, PLEKHM1, SNX10, TNFSF11, TNFRSF11A, CAII*) (Coudert et al., 2015). Osteopetrosis is a rare hereditary disease that has shed light on important aspects of bone cell biology that were not well known (Coudert et al., 2015). Therefore, many studies have focused on identifying new mechanisms for osteoclast function and discovering new functions for skeletal cells, as they have proven that the skeleton has an effective and central role in bone physiology, this is because any bone disorder affects other organs of the body (Charles & Aliprantis, 2014; Guntur & Rosen, 2012; Oury, 2012; Lange et al., 2013; Blin-Wakkach et al., 2014). Therefore, it was necessary to focus studies on osteopetrosis to identify these disorders, especially since the genotype and phenotype of this disease are not always consistent and clear as mutations can change and produce different phenotypes (Coudert et al., 2015). In addition, the genetic mutations that have been explained and related to cases of osteopetrosis are 70%, while medical research and efforts continue to identify the remaining 30% of mutations responsible for new cases of osteopetrosis (Schulz & Kornak, 2015).



### 3.2 Types of Osteopetrosis

Osteopetrosis is divided into two types: autosomal dominant osteopetrosis called (ADO) and autosomal recessive osteopetrosis called (ARO). The first type is characterized by mild symptoms as described by Albers-Schonberg, and it is the most common form of osteopetrosis

that has been observed by many rheumatologists (Papagrigorakis et al., 2022; Waguespack et al., 2007). Moreover, autosomal dominant osteopetrosis is divided into three forms, including type I and type II, according to what was described by Bollerslev and Andersen (Bollerslev & Andersen, 1989) and Bollerslev and Mosekilde (Bollerslev & Mosekilde, 1993). All of these forms appear as a result of a defect in osteoclast function that causes decreased bone resorption with an increase in calcified cartilage and cortical bone (Papagrigorakis et al., 2022). As for autosomal recessive osteopetrosis is divided into three forms, including a benign autosomal dominant type and two types with a fatal autosomal recessive form (Coudert et al., 2015; Alkhayal et al., 2023).

## Symptoms of Osteopetrosis

The most important symptom of type 1 (ADO1) osteopetrosis was the thickening of the cranial vault, and symptoms of type 2 (ADO2) were sclerosis of the base of the skull, pelvis, and vertebrae (Papagrigorakis et al., 2022). In general, ADO does not affect human life expectancy, but it leads to an increased risk of OA, fractures, poor fracture healing, delayed fracture union, and osteomyelitis (Coudert et al., 2015). Although individuals with ADO2, known as Albers-Schönberg disease, have a normal lifespan, they suffer from many orthopedic problems such as frequent fractures, bowing of the long bones, and coxa vara (Landa et al., 2007; Coudert et al., 2015). In addition, the symptoms of ADO2 appear clearly in adulthood and include many complications that may lead to disability and death in some cases (Cohen-Solal et al., 2023). In contrast, the most important symptoms of recessive osteopetrosis (ARO), which affects newborns and children, are severe hematological complications, which often lead to death if not treated early (Cohen-Solal et al., 2023; Sharma et al., 2013; Sobacchi et al., 2013). In some rare cases, early childhood with ARO showed symptoms and signs of malignant osteoporosis (Lam et al., 2007; Roopashri et al., 2008). Also, this type of osteopetrosis causes excessive bone growth in the marrow, which leads to a lack of blood formation, causing hepatosplenomegaly, myelogenous anemia, neurological deficits, and optic nerve atrophy, which leads to blindness and deafness (Landa et al., 2007; Tolar et al., 2004). Finally, a study reported a general summary of the symptoms of osteopetrosis in three aspects: (1) It leads to reduced hematopoiesis, anemia, malnutrition, reduced bone marrow tissue, and a decreased level of immunity; (2) loss of cranial nerve function due to reduction in size of cranial nerve foramina; and (3) An excessive and abnormal increase in bone production, which causes fragility and the possibility of recurring fractures (CJ, 1971).

## 4. Replacement of Joint Hip and Knee

### 4.1 Total Hip Replacement

The hip is considered one of the largest joints in the human body that bears its weight. The hip consists of a ball known as the femoral head, which is located in the upper part of the thighbone, the thighbone known as the femur, which is located in a round socket known as the acetabulum, located in the pelvis, and a group of tissues band are called ligaments and their function is to connect the ball to the socket to keep the joint stable (Sivasankar et al., 2016; Gold et al., 2017). The hip joint is affected and may be damaged by osteopetrosis, which is accompanied by OA, rheumatoid arthritis, recurrent fractures (Thudium et al., 2020; Gold et al., 2017). All of these symptoms may lead to a hip fracture, and this can result in permanent disability for individuals who suffer from osteopetrosis (Gold et al., 2017). In addition, there are types of hip fractures, the most important of which are: femoral neck fracture, which is treated by replacing the head of the femur (hemiarthroplasty) with a high-strength metal device that is chosen according to medical standards so that it is compatible with the natural hip socket (Health Investigators, 2019; Gold et al., 2017). In addition, the total hip replacement (THR) technology is considered one of the latest technologies that serves people, especially those suffering from osteopetrosis. The process of replacing the total hip joint is called total hip arthroplasty (THA). it is generally known as the removal of cartilage and damaged bone and replacing them with suitable prosthetic metal components, also, it is the process of removing the damaged femoral head and its cartilage and replacing it with a metal device (stem) that is placed in the hollow center of the femur (Ghalme et al., 2016)



### 4.2 Total Knee Replacement

The knee is considered a hinge joint, allowing it to bend and extend the leg and perform some movements, and the knee joint is one of the most important and largest joints in the body (Gupton et al., 2018). The knee joint consists of two parts: the first is called the tibiofemoral joint, which is located between the thigh bone (femur) and the shin bone (tibia), and the second is called the patellofemoral joint, which is located between the kneecap (patella) and the end of the thigh bone (femur), the knee joint is also characterized as complex synovium due to the presence of the patellar and tibiofemoral joints (Chang, et al., 2023; Hyland et al., 2018). In addition to that, the importance of the knee joint is that all foot movements, such as jumping, walking, and running, depend on the safety of this joint (Gupton et al., 2018). Knee arthroplasty is known as a complete replacement and reconstruction of the knee joint (Hsu & Siwiec, 2018). Currently, total knee

arthroplasty (TKA) is a common and reliable procedure and an excellent treatment option for patients with osteopetrosis, which is accompanied by symptomatic osteoporosis spread in three parts of the knee, or OA also in any part of the knee. Conservative treatment did not work for them (Davies et al., 2019; Adie et al., 2019).

### 4.3 Osteopetrosis and Joint Replacement

One of the problems that people with osteopetrosis face is OA despite the increase in bone mass. Increasing bone density and excessive bone structure does not give it strength but results in structural fragility that makes the bones vulnerable to fracture (Wu et al., 2017). This causes another problem is the nonunions or difficulty around the joint, such as the hip and knee joints, and this problem is treated by total joint arthroplasty (Wu et al., 2017). In addition, osteopetrosis leads to OA, which can be treated by total joint replacement surgery. However, there are difficulties facing this procedure because, in most cases, fragile or hard bones do not have a spinal canal in their natural shape, which makes joint arthroplasty difficult and results in complications recursive (Strickland & Berry, 2005).

Patients with middle-aged ADO2 often suffer from hip OA, in which the articular cartilage between the acetabulum in the hip and the hard subchondral bone in the femoral head area is crushed (Girard et al., 2006). Therefore, patients with symptomatic hip OA of ADO2 after failure of treatment with analgesics require THA, although this surgical procedure faces a challenge due to bone fragility and obliteration of the medullary canal in the femur area (Bollerslev & Mosekilde, 1993; Cameron & Dewar, 1977). Several studies have indicated that patients with osteopetrosis are accompanied by the development of OA, which significantly affects the hip and knee joints (Xie et al., 2015; Cameron & Dewar, 1977; Kim & Han, 2024; Wu et al., 2017). In addition, osteopetrosis leads to thickening of the subchondral bone, thus causing excessive pressure on the articular cartilage and a change in the biomechanics of the joint (Kim & Han, 2024). Accordingly, patients with osteopetrosis as they grow older suffer from OA, and these cases can be treated with TKA (Kim & Han, 2024; Mayer et al., 2012).

Many studies have reported the challenges and risks associated with hip or knee replacement or arthroplasty for patients with osteopetrosis, including component sizing, compression fixation of components, preparation of the abnormal medullary canal, enlargement of the femoral canal, insufficient surfaces for cement interdigitation, broken drills and saws, and

drilling for multiple pins to secure jigs, in addition, the patient undergoing surgery suffered from osteomyelitis as a result of poor white cell function and decreased marrow vascularity (Bollerslev & Mosekilde,1993; Xie et al., 2015; Mayer et al., 2012; Siljander et al., 2021). However, knee and hip joint replacement or arthroplasty is a good option and a successful treatment for painful OA in patients suffering from osteopetrosis.

## 5. Conclusions

Our current review concluded that osteopetrosis is a rare disease that nevertheless poses risks to the body's joints, especially the hip and knee joints in the elderly. This is because osteopetrosis causes arthritis and osteoporosis that lead to joint problems. Studies of many of the cases highlighted have indicated that treatment of these problems is through THA and TKA, although there are some challenges and problems during and after surgery. Furthermore, there is a scarcity of studies that have addressed the subject of osteopetrosis and its harms, the most important information related to its effect on the joints, which types of osteopetrosis are the most effective, and what are the necessary therapeutic measures in various cases of joint arthritis. Therefore, the scope of research and study of this topic should be expanded and the most important aspects that must be considered and useful information and facts in the field of medicine and treatment as well as the research field should be considered. Finally, there is an urgent need to conduct more research and apply it to cases of hip and knee arthroplasty to evaluate and address the challenges and problems that arise in surgical operations.



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