

Arthroplasty in Patients with Rare Conditions

Long-Term Outcomes of the Knee and Hip Arthroplasties in Patients with Alkaptonuria

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ABSTRACT

Alkaptonuria is a rare autosomal recessive metabolic disorder. It is characterized by the accumulation of homogentisic acid in the body due to a lack of enzymes that degrade it. Over time, it results in joint degeneration and eventually leads to ochronosis. Ochronosis refers to bluish-black discoloration of connective and other tissues within the body. In this study, we present 5 distinct cases diagnosed with alkaptonuria. They have undergone 8 total joint replacement surgeries (4 hips and 4 knees) within 8 years (2010–2018). All patients had an excellent outcome over several years. The follow-up period ranged from 2 to 10 years. Although none of the presented cases had intraoperative or postoperative adverse sequelae, we must take care when dealing with patients with ochronotic arthropathy. They carry a higher risk of complications than other patients with osteoarthritis disease. These complications include fractures due to fragile bone quality, muscle or tendon rupture, joint instability, and anesthesia-related complications. Total joint arthroplasty is a valid and safe option in the management of hip and knee ochronotic arthropathy.

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Introduction

Alkaptonuria (AKU) is a rare autosomal recessive metabolic disorder. The estimated incidence rate is 1 in 250,000–1,000,000 live births worldwide [1]. Genetically, AKU results from mutations in a 54,363-bp gene (mapped on chromosome 3q) that codes for homogentisate 1,2-dioxygenase (HGD). HGD is an enzyme that converts homogentisic acid (HGA) to maleylacetoacetic acid in the tyrosine degradation pathway [2]. Nonfunctional HGD enzyme results in the accumulation of HGA in the body despite normal renal clearance. Excess HGA undergoes oxidative conversion inside tissues into melanin-like polymers [1]. The accumulation of HGA and its metabolites in tissues results in ochronosis, a term used to describe the darkening of tissues [1].

Ochronotic arthropathy is a rare condition found in patients with AKU. The knee is the most frequently affected joint, followed by the hip joint [3]. Other sites of involvement include the shoulders, sacroiliac joints, and lumbar intervertebral discs. Other systemic features include renal stones/failure, salivary stones, osteopenia/fractures, and rupture of tendons/ligaments. In addition, respiratory compromise, gallbladder stones, hearing defects, and aortic valve disease are reported as complications [2].

There is no specific medical treatment for ochronosis. Hence, we manage symptoms as they appear or when they are getting worse.

Long-term ochronosis results in the development of ochronotic osteoarthritis. Unfortunately, it is often diagnosed inappropriately as early-onset osteoarthritis (OA) [1].

Published cases that underwent total joint replacement for ochronotic OA showed excellent outcomes. The results are comparable with those of patients with primary OA.

We present 5 cases of ochronosis who successfully underwent 8 total joint replacement surgeries. The surgeries are bilateral hip, unilateral knee, unilateral hip, unilateral hip and knee, and, finally,

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bilateral knee replacements. We performed the surgeries within 8 years (2010–2018) and followed up over several years, ranging from 2 to 10 years. We received written informed consent from each patient for publication of this information and the attached images.

All the upcoming cases are from Jordan. They were treated in Jordan University Hospital by a single expert arthroplasty orthopaedic surgeon. We received institutional review board approval for this article.

Of note, Jordan is the most prevalent country in the Middle East containing patients with AKU [4].

To the best of our knowledge, this article is the first case series emerging from Jordan that presents cases of AKU that were managed by arthroplasty with long-term follow-up.

We used the modified Harris Hip Score (HHS) to assess outcomes for patients who underwent total hip replacement. Patients who underwent total knee replacement were assessed by the Knee Injury and Osteoarthritis Outcome Score (KOOS).

Case histories

Case 1

A 60-year-old manual worker, a known case of AKU, sought medical attention because of chronic bilateral hip pain for 20 years. It was more severe on the right side. The pain led to restrictions on his activities of daily living. He was forced to use a cane as an assistive device for walking. He also complained of bilateral knee, shoulder, and back pain. He has 2 brothers and one sister with the same disease.

He had a painful limited range of motion on both hips and knees on physical examination.

The radiographs showed severe degenerative changes in both knees and hips, with the collapse of the right femoral head.

The patient underwent staged bilateral cemented total hip arthroplasty, 4 months apart. He was assessed for cardiac status before surgery. Echocardiography showed normal findings. We accomplished both surgeries using spinal anesthesia. Each surgery was performed using the direct lateral/transgluteal hip approach.

Black discoloration of the synovial tissue was noted during the surgery. The hip gained a stable and adequate range of motion intraoperatively. No intraoperative complications were encountered.

The postoperative course was uneventful after each surgery. We allowed him full weight-bearing on the second day after the surgery. He was discharged home after 4 days after each surgery.

His modified HHS improved from 29 preoperatively to 80 at a 10-year follow-up visit. He can now achieve right hip flexion of 75–80 degrees, abduction of 10–15 degrees, external rotation of 10–15 degrees, and adduction of 5–10 degrees.

The pelvis radiograph showed well-positioned acetabular and femoral components, without evidence of loosening.

Case 2

A 52-year-old housewife, a known case of AKU, presented with complaints of chronic bilateral knee pain for 10 years. The pain was severe that it affected her daily activities. It was more severe on the right side. Her 3 brothers also shared a history of AKU.

On physical examination, she had an antalgic gait. Tenderness over the joint line of both knees, diminished range of motion, and crepitation were also noted.

Both knee radiographs showed a narrowing of joint spaces, subchondral sclerosis, and irregularities of the joint surfaces.

Using the medial parapatellar approach, we performed right knee joint replacement surgery. We used a cemented, posterior-stabilized system with a tibial stem. We did not replace the patella. During surgery, a dark discoloration of all cartilaginous surfaces, bone, synovium, and menisci was noted as shown in [Figure 1a](#) and [b](#). We performed the surgery using spinal anesthesia and tourniquet control. No intraoperative complications were encountered.

After surgery, the patient was allowed weight-bearing as tolerated and range-of-motion exercises on the first postoperative day. She was discharged home 4 days after an unremarkable postoperative course.

At a 2-year follow-up visit, the patient was doing well. The KOOS escalated from 31.5 before surgery to 91.7 at 2 years

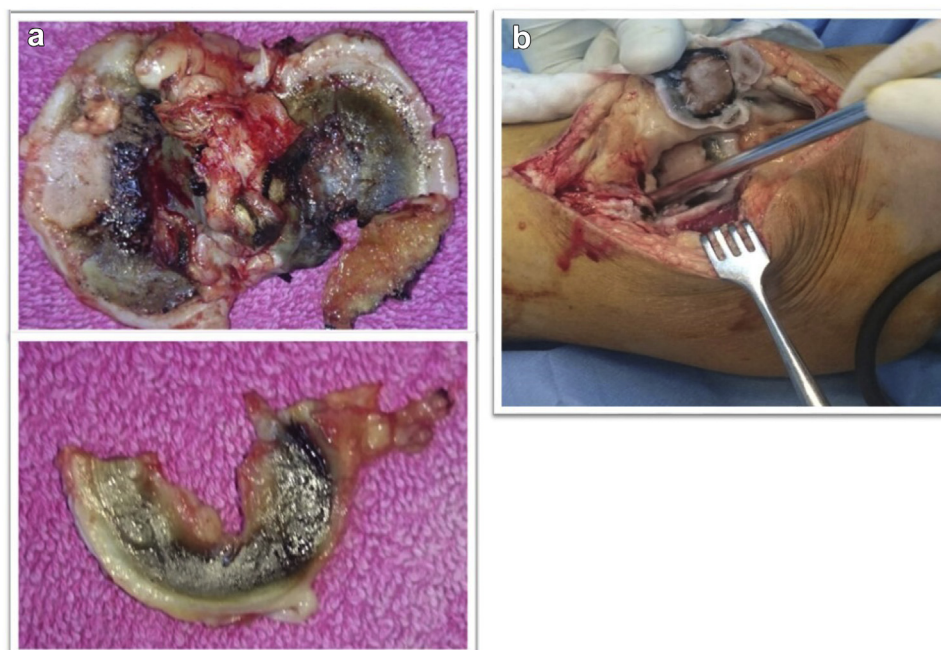


Figure 1. (a) Dark meniscus and tibial articular surface (an intraoperative photograph). (b) Dark synovial tissue and patellar articular surface (an intraoperative photograph).

postoperatively. The right knee is now stable on varus/valgus stress tests. She can achieve a full extension and flexion up to 110 degrees.

Radiographic imaging showed no evidence of osteolysis or component malposition.

Case 3

A 46-year-old female teacher, a known case of AKU, presented with right hip pain for 8 years. The pain was exhausting, for which she used oral narcotics. She also complained of bilateral knee, shoulder, and back pain. She walked using an assisted device.

A painful limited range of motion of the right hip was clear on examination.

The pelvic radiograph showed advanced degenerative changes on both hips, with more changes on the right side.

By a direct lateral/transgluteal hip approach, we performed cementless right total hip arthroplasty using spinal anesthesia. Intraoperatively, there was black discoloration of the bone and articular surfaces (Fig. 2). No intraoperative complications were encountered.

She had an uneventful postoperative course. She started regular rehabilitation on the next day after the operation. She was discharged after 1 week of hospitalization.

Recently, the patient could not return to the clinic. However, follow-up was completed via a phone call. The modified HSS improved from 34 before surgery to 89 3 years after surgery.

Case 4

A 50-year-old male patient presented with complaints of bilateral hip and knee pain of 10 years' duration. It was more severe on the right hip and knee. In addition, he reported bilateral shoulder and lower back pain. He has no family history of AKU. He was labeled inappropriately as a case of ankylosing spondylitis.

On examination, he had bilateral hip tenderness with significant limitation in the range of motion. We observed significant swelling and limited painful range of motion on both knees. He had black discoloration of both the ear pinnae and eye sclerae.

Plain radiographs showed diffuse arthritic changes in his hips, knees, and shoulders.



Figure 2. Black discoloration of the femur head with its overlying cartilage (an intraoperative photograph).

Using spinal anesthesia, he underwent right total hip arthroplasty and right total knee replacement 2 years apart. We performed hip replacement using the direct lateral/transgluteal approach. We used the hybrid system (cementless acetabular cup and cemented femoral stem). The knee replacement was performed using the medial parapatellar approach. We used a cemented, posterior-stabilized system with a tibial stem. We did not replace the patella. Intraoperatively, black discoloration of the tendons, capsule, and articular cartilage was noticed in both surgeries. No intraoperative complications were observed.

The diagnosis of AKU was made after initial surgery, as a high level of HGA was found in his urine.

We implemented routine postoperative analgesia and a rehabilitation protocol. He was allowed weight-bearing as tolerated the next day after each surgery. He had an uneventful postoperative course. The patient was discharged home after 4 days after hip surgery and 6 days after knee surgery.

At a 3-year follow-up visit, the modified HSS reached a value of 79 compared with 38 before hip replacement. The right hip range-of-motion examination revealed 75–80 degrees of flexion, 10–15 degrees of abduction, 5–10 degrees of external rotation, and 5–10 degrees of adduction. The right knee was stable on varus/valgus stress tests. The patient can achieve near full extension to 120 degrees flexion. The KOOS improved from 28 preoperatively to 90.5 at a 3-year follow-up visit.

Case 5

A 57-year-old female patient, a known case of AKU, presented with bilateral knee pain for 12 years. It was increasing progressively, which badly affected her activities of daily living. She also reported pain in both shoulders, hips, and lower back. Her past surgical history included gastric bypass surgery for morbid obesity and cholecystectomy. She has 2 brothers diagnosed with AKU.

On physical examination, she had limited and painful range of motion over the bilateral knees, hips, and shoulders. There was no evidence of effusion. Limited flexion of the lumbar spine was observed.

The radiographs showed advanced arthritic changes for all examined joints.

She underwent staged bilateral total knee arthroplasty over a 2-year interval. We performed a cardiology evaluation before the first surgery, and echocardiography showed normal findings. We performed both surgeries via the medial parapatellar approach using spinal anesthesia. A cemented posterior-stabilized system with a tibial stem was fixed in each knee. We did not replace the patella. Blackish discoloration of patellar, femoral, and tibial articular cartilages was found in each knee. We encountered no major intraoperative complications.

The patient had an uneventful postoperative course. She followed the regular postoperative management protocol. She was allowed weight-bearing as tolerated and knee range-of-motion exercises the next day after surgery. The length of hospitalization was 1 week for each surgery.

We followed up the patient for 5 years from the first knee surgery and 3 years from the second one. She reported no pain in her knees and regained a functional range of motion (0°–110°). The KOOS jumped from 30.4 before surgery to 89.9 at a 3-year follow-up visit.

Discussion

Ochronotic osteoarthropathy is a rare condition. It develops in patients with AKU because of the deposition of polymerized HGA pigment in the cartilage and synovial tissues [4]. Patients are usually asymptomatic, and arthropathy appears mostly after the fourth decade. It commonly affects males more than females.

Ochronotic arthropathy is often diagnosed during a total joint replacement, and it is difficult to suspect until dark synovium and cartilaginous surfaces are found intraoperatively. Other patients may complain of a tetrad of physical diagnostic features of AKU: dark urine, black scleral pigmentation, black/blue ear pigmentation, and clinical arthritis (with lower back pain). The first sign of AKU is often a change in the urine color.

Ochronotic patients usually have unusual arthritis, affecting the large weight-bearing joints and sparing the small joints of the hands and feet. We can divide skeletal involvement into spinal and extraspinal abnormalities. The knee is the most commonly affected peripheral joint and is found in up to 64% of cases. However, degeneration of the knee often occurs many years after the onset of spinal symptoms [5].

Currently, no available medical treatment options have shown to prevent the complications of AKU. A low tyrosine and phenylalanine diet, vitamin C or antioxidants, and nitisinone are a few of the suggested treatments [6]. Total joint replacement surgery is offered for severely affected hip and knee joints, where the destruction of the joint architecture and severe functional impairment is present.

Multiple studies have discussed the short-term and long-term outcomes of knee and hip joint replacement surgeries in known cases of ochronosis. The results have been excellent and are comparable with those of patients with primary OA [7,8].

Although there are well-known intraoperative complications during arthroplasties, such as patellar tendon rupture and bone fracture, in patients with ochronosis, all of the aforementioned operations were uneventful.

Many patients with AKU may have associated cardiac problems, making spinal anesthesia an appropriate choice. However, degenerative changes such as narrowed disk spaces and spinal fusions may impede the regional anesthesia techniques. In addition, the dura mater and arachnoid membrane could be damaged, having been made vulnerable by HGA [9]. Nonetheless, spinal anesthesia was successful in all the presented cases.

Although there are no specific guidelines for postoperative rehabilitation for a patient with AKU who underwent arthroplasty, following the guidelines for the usual patients may be helpful. All the presented cases showed excellent outcomes when routine postarthroplasty rehabilitation guidelines were applied.

Of note, a single expert arthroplasty surgeon performed all surgeries at an academic hospital using a prosthesis from Zimmer Biomet as the surgeon's preference (NexGen LPS-Flex Knee, Trilogy IT Acetabular Hip System, VerSys LD/Fx Cemented and Press-Fit Hip Prostheses, ZimmerBiomet, Warsaw, IN).

This study is unique as it is the first case series with 8 joint replacement surgeries emerging from Jordan and the Middle East region. It focuses on the Arab population with AKU who underwent knee/hip arthroplasty.

Few similar studies around the world have discussed arthroplasty as a solution to relieve the pain that results from severe ochronosis. Spencer et al. [10] studied the outcome for 11 joint replacements in 3 patients who had suffered from upper and lower limb ochronotic arthropathy. They reported excellent results at the 12-year follow-up. Only one case had a dislocation that was treated successfully by closed reduction.

Ilyas et al. [11], Hakim et al. [12], da Silva Martins Ferreira et al. [13], Araki et al. [14], and Demir [15] have reported cases of more than 2 joint replacement surgeries operated subsequently in the same patient who had multiple degenerative joints ochronosis. This can emphasize the role of arthroplasty in relieving pain and improving functional status in patients with AKU.

Rajkumar et al. [16] reported significant improvement in the modified HHS and the Knee Society Score in comparison with the preoperative values for 16 patients with AKU who underwent 27

joint replacements. Only one patient developed a deep infection, and another one was diagnosed with aseptic acetabular loosening 7 years later.

In this study, the mean of postoperative modified HHS was 82.6, which significantly improved over the preoperative mean value, which was 33.6. In parallel, the mean KOOS improved from 29.9 preoperatively to 90.7 postoperatively. Based on these results, this article could add to the existing literature about the usefulness of total joint arthroplasty in patients with AKU.

Limitations of this study include its descriptive and retrospective nature.

Current controversies and future considerations

There is no consensus in the literature about the fixation method of hip replacement in patients with AKU. Most of the published cases report the use of cementless total hip replacement. In this article, we used 3 cemented hip replacements (2 cemented and one hybrid), and we report excellent long-term outcomes for those patients.

During surgery, the bone quality was noticed to be soft with an osteoporotic quality. Therefore, a long-stem tibial component was chosen in the knee replacements of the discussed cases. However, there are no reported data about the regular use of long tibial stem in ochronotic knees. We need more studies to provide supporting evidence for the use of long stems.

In addition, Ozmanevra et al. [17] have concluded that arthroplasty is an excellent choice for patients with ochronotic arthropathy, but there is no obvious information in the literature about the prosthesis type. We should carry out more studies to explore the best age for arthroplasty in a patient with AKU and compare distinct prosthesis types and fixation methods.

Summary

AKU is a rare cause of degenerative joint disease. It goes beyond saying that we should think about it in the differential diagnosis of any degenerative joint disease, especially if multiple large joints are involved. We can consider joint replacement surgery as a valid and safe option with an excellent outcome in patients with significant degenerative ochronotic arthropathy. As for patients with OA, we can use routine intraoperative and postoperative measures in ochronotic joints.

Conflict of interests

The authors declare there are no conflicts of interest.

Key points

- 1 Alkaptonuria and ochronosis should always be considered in the differential diagnosis of patients with multiple joint degenerations.
- 2 Joint replacement surgery is valid and safe in ochronotic arthropathy.
- 3 Routine intraoperative and postoperative measures for patients with osteoarthritis can be used effectively in ochronotic joints despite the higher risk of complications.

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