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A Comprehensive Analysis of Alkaptonuria

Dr. Dhanraj Patidar*, Dr. Shailesh Jain,Mr. Ajay Kumar, Mr. Ritesh Raj,Mr. Prince Yadav

SAM College of Pharmacy, SAM Global University, Raisen, Madhya Pradesh, India.

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ABSTRACT

Our very oldest AKU patient is a mummy called Harwa from 1500BC.Alkaptonuria (AKU) is a rare disorder of autosomal recessive inheritance. It is caused by a mutation in a gene that results in the accumulation of homogentisic acid (HGA). Characteristically, the excess HGA means sufferers pass dark urine, which upon standing turns black. This is a feature present from birth. Over time patients develop other manifestations of AKU, due to deposition of HGA in collagenous tissues, namely ochronosis and ochronotic osteoarthropathy.Despite not lowering life expectancy, this illness has a major impact on quality of life.Despite understanding gaps, the natural history of this illness is becoming more clear. Along with the creation of a possibly disease-modifying treatment, clinical evaluation of the illness has also improved. Additionally, recent advancements in AKU research have provided fresh insights into the condition, and additional research on AKU arthropathy may impact treatment for osteoarthritis.

Keyword: Alkaptonuria, Alkaptonuria, mutation, Nitisinone, Tyrosine and phenylalanine.

I. INTRODUCTION

Tyrosine and phenylalanine are two protein building blocks (amino acids) that the body is unable to completely break down in alkaptonuria, often known as black urine illness, a relatively uncommon hereditary condition. It causes the body to accumulate a substance known as homogentisic acid. Over time, this can cause a variety of health issues and darken urine and bodily parts. Typically, a sequence of chemical processes breaks down amino acids. However, homogentisic acid, a byproduct of alkaptonuria, cannot be further broken down. This is due to a malfunction in the enzyme that typically breaks it down. Proteins called enzymes are responsible for chemical reactions. Dark-stained diapers are among the first indications of the illness as homogentisic acid turns urine black after a few hours of exposure to air. If this sign is missed or overlooked in a baby or child, the disorder may go unnoticed until adulthood, as there are usually no other noticeable symptoms until the person reaches their late 20s to early 30s.Alkaptonuria, also known as AKU or Black Bone Disease, is an extremely rare genetic condition, which can cause significant damage to the bones, cartilage and tissues of those affected. AKU normally only affects one in every 250,000 people worldwide.The body normally creates homogentisic acid (HGA) during food digestion, but AKU prevents patients' bodies from breaking it down. As a result, the body accumulates HGA, which eventually causes early-onset osteoarthritis and black, brittle bones and cartilage. The build-up of HGA in the body can also lead to other, sometimes more serious health complications.Because AKU is a recessive disorder which results from a mutation in each of a pair of chromosomes, a child of two persons who possess the defective gene has only a 25% chance of having AKU. It is a genetic condition caused by a lack of homogentisate 1,2 dioxygenase (HGD), an enzyme that breaks down HGA, an intermediary in the tyrosine degradation pathway, and is mostly generated by hepatocytes in the liver and kidney.

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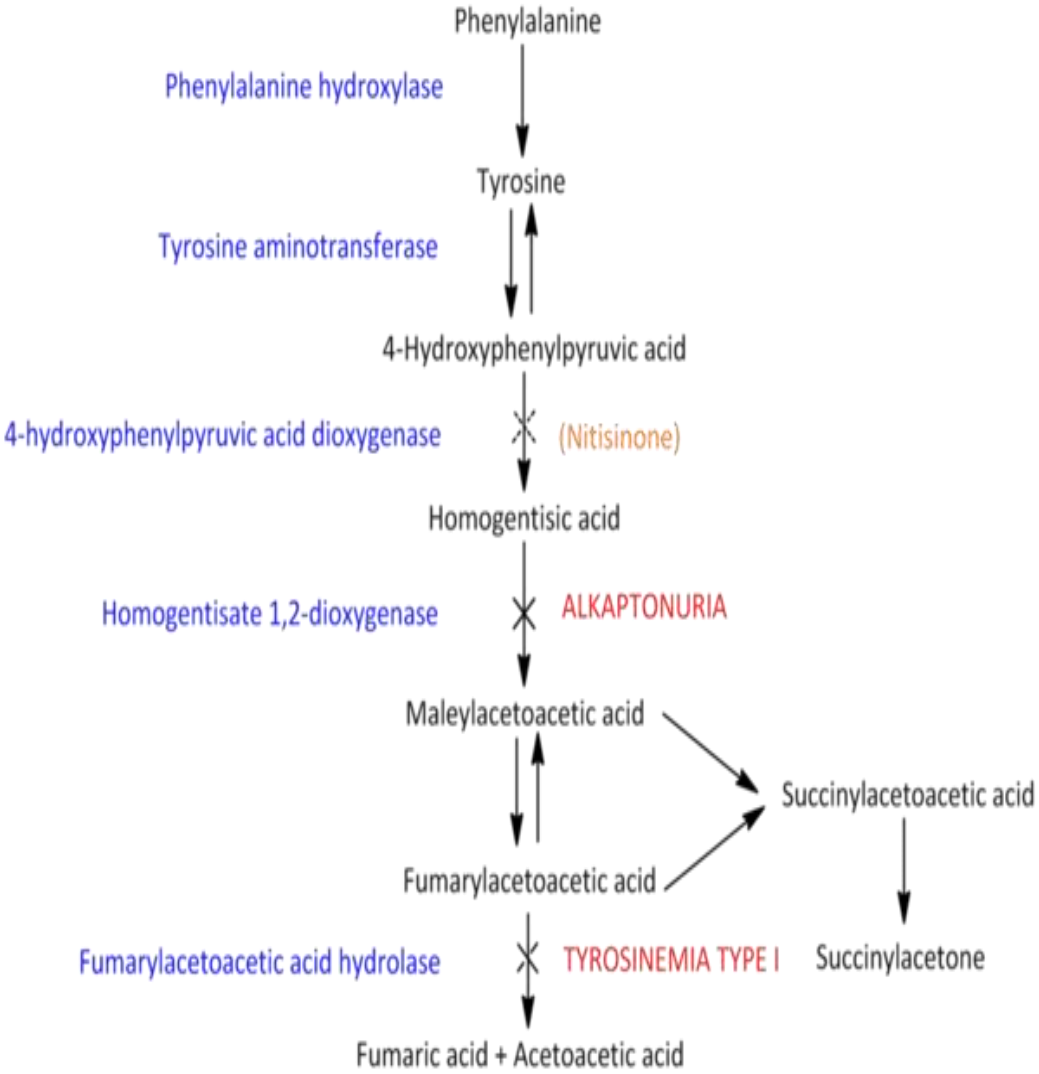

SIGNS AND SYMPTOMS IN ADULTS

Urine becoming black when exposed to air is the main sign of AKU. Dark brown to black is the range of this discolouration. This symptom is not present in all AKU patients, though. As homogentisic acid (HGA) accumulates over time, connective tissues like cartilage, tendons, and ligaments darken, a condition known as ochronosis. This causes pain, swelling, and stiffness in the joints, especially in weight-bearing joints like the knees and hips.Kidney stones, renal issues, and cardiac complications can also result from AKU.The intensity and course of symptoms can differ from person to person. In tissues all around the body, homogentisic acid gradually accumulates over many years.It may accumulate in nearly every part of the body, including the heart, tendons, bones, cartilage, nails, and ears. It creates a variety of disorders and darkens the tissues.

Black Urine

For the majority of AKU patients, dark or black urine is the first symptom. Urine contains large amounts of a substance known as homogentisic acid (HGA). The HGA in urine will oxidize and begin to become black if it is allowed to stand and is exposed to air. Urine from almost all patients will ultimately become black, however the amount of time it takes might vary from patient to patient.There is no physical risk associated with black urine. It is, nonetheless, a diagnostic tool. HGA in the urine can cause dark or crimson discoloration in the diaper of babies with AKU. To confirm an AKU diagnosis, doctors should

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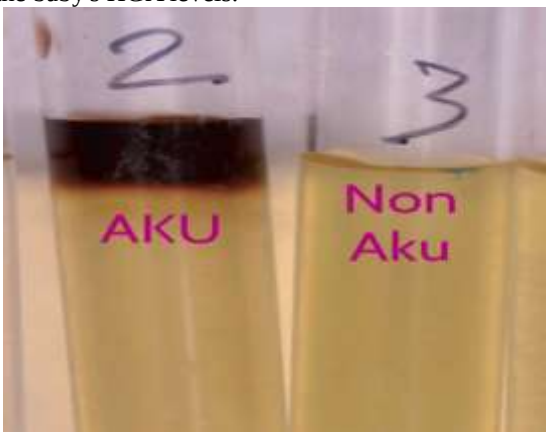
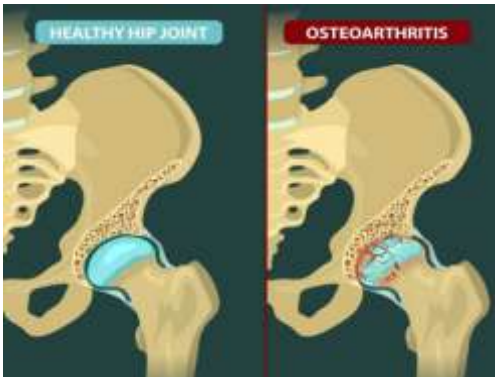
subsequently do a blood or urine test to measure the baby's HGA levels.



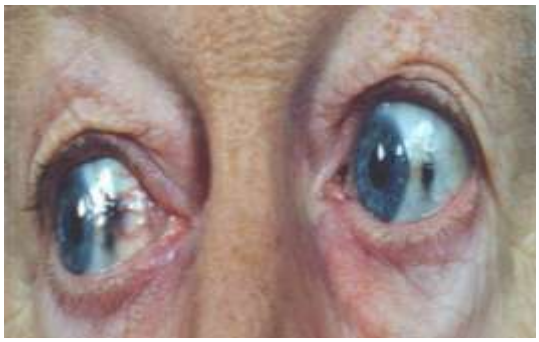
Osteoarthritis

Homogentisic acid (HGA) accumulation over time causes severe early-onset osteoarthritis. Over time, HGA damages the cartilage and bones, causing them to become brittle and black. Large weight-bearing joints including the knees, shoulders, hips, and spine are the most severely impacted, as joints lose their capacity to withstand activities that put them under stress.Each patient may have osteoarthritis at a very different time. Back and knee pain usually begin to bother patients in their 30s and 40s, respectively, while hip and shoulder pain usually appears by their 50s.Patients with AKU frequently need several joint replacements; many will have five to ten joint replacements during their lifespan.Because it keeps joints healthy, being active with little exercise can help reduce the progression of osteoarthritis. It is best to stay away from contact sports since they strain the joints. Swimming and hydrotherapy are beneficial to many patients, who report less stiffness and discomfort in their joints.



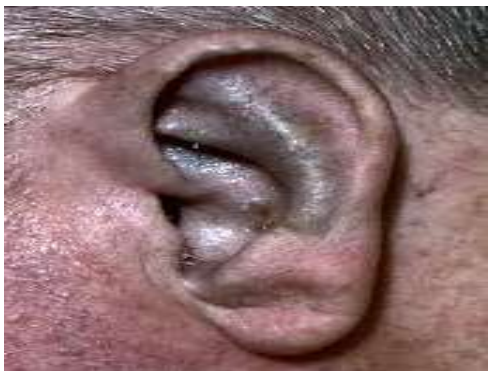
Black Spots in the Eyes

As they age, people with AKU begin to grow black patches in the whites of their eyes. The reason behind this is that a substance known as homogentisic acid (HGA) builds up in the eye over time until it starts to show.Despite the serious appearance, these black spots will not impair vision, cause eye discomfort, or result in any other issues. These patches will begin to enlarge as the patient ages.Almost all patients with AKU will ultimately develop the black patches, albeit they start to show at varying ages. The black patches typically start to show up in patients in their 40s.



Discolouration of Ears

The ears of the great majority of patients will ultimately start to become blue-black. This occurs as a result of homogentisic acid (HGA) binding to the ear cartilage. Similar to eye spots, this discoloration does not hurt or create any other issues.The buildup of HGA is also the reason why patients may get black ear wax.



Heart Complications

One of the most dangerous and potentially life-threatening effects of AKU occurs when HGA builds up in the arteries and inside of the heart. The HGA present in the blood sticks to the vessels and valves of the heart, causing them to harden. They then become blackened, brittle and narrowed,

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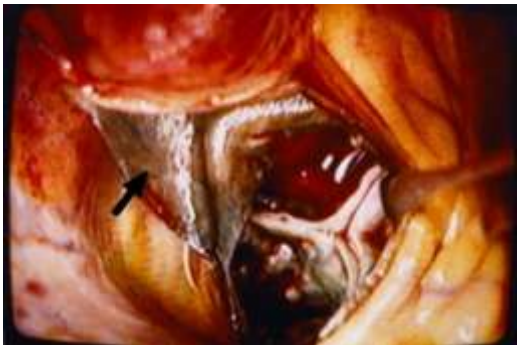
making it difficult to maintain the flow of blood around the body. This can cause increased pressure within the heart left ventricle and lead to heart failure.Patients over 40 should have regular checkups for any AKU-related cardiac issues. A CT/MRI scan of the chest can identify issues with the arteries, and an echocardiography (ECG) can identify issues with the heart valves.A heart valve replacement may be necessary for some AKU patients. The stiff and fragile tissue of the heart and aorta makes the procedure challenging, according to surgeons. Aortic valve surgery requires caution to prevent harmful tissue fragments from entering the bloodstream and raising the patient's risk of stroke.The identification of heart, blood pressure, and cholesterol issues in AKU patients has grown. These alkaptonuria-related cardiac symptoms might be lethal.AKU and cardiac issues may have been under-recognized in the past, according to some medical experts. Heart problems, however, are still thought to be a rare indication that often manifests later in life.



Other Symptoms

AKU, or alkaptonuria, is a multisystemic disorder that can impact several body parts. AKU symptoms differ from person to person. These will typically be observed to some extent, albeit they may not be applicable to every patient.

Stones

Although the majority of homogentisic acid (HGA) is removed from the body through urine, it can raise the risk of stones as it travels through the genitourinary tract, particularly in people who do not drink enough water. Male patients may get prostate stones, whereas female patients may experience kidney or bladder stones. One rather typical symptom of AKU is stones. Most of them spontaneously leave the body, however they might cause discomfort. Sometimes simple methods are required to remove bigger stones.

Skin

Where sweat glands are situated and exposed to the sun, the effects on the skin are most obvious. Sweat can leave brown stains on clothing, and skin can become speckled with blue-black. Some patients have more noticeable skin pigmentation than others. The ear lobe, nose bridge, cheeks, palms, and skin overlaying tendons are frequently the first places to notice it. Each person has a different age at which these impacts become apparent.

Parkinson's Disease

There may be a connection between AKU and Parkinson's disease. According to research, the prevalence of Parkinson's disease in AKU is almost 20 times higher than in the general population. In untreated AKU, exposure to homogentisic acid (HGA) can cause oxidative stress throughout life, which can lead to Parkinson's disease.

Other body systems

It may also have an impact on the teeth, endocrine organs (which produce hormones), and the central nervous system (brain and spinal cord). It may be necessary to remove cataracts, which are common in AKU.AKU symptoms differ from person to person. These will typically be observed to some extent, albeit they may not be applicable to every patient.

DIAGNOSIS

The diagnosis and evaluation of AKU can be established based on the severity scoring system. **The AKU Severity Score Index, or AKUSSI,** is a clinical grading system that measures severity objectively. Its foundation is a multidisciplinary, quantitatively validated examination.

System.

The clinical objectives include,

- Pigmentation of the eye and ear
- Prostate and salivary stone
- Osteopenia
- stroke
- Aortic valvular heart disease, heart failure, atrial fibrillation

Laboratory Diagnosis

1. The gold standard for diagnosing alkaptonuria is the urine test for HGA. Through the use of gas chromatography-mass spectrometry (GC-MS) measurement, the level of homogentisic

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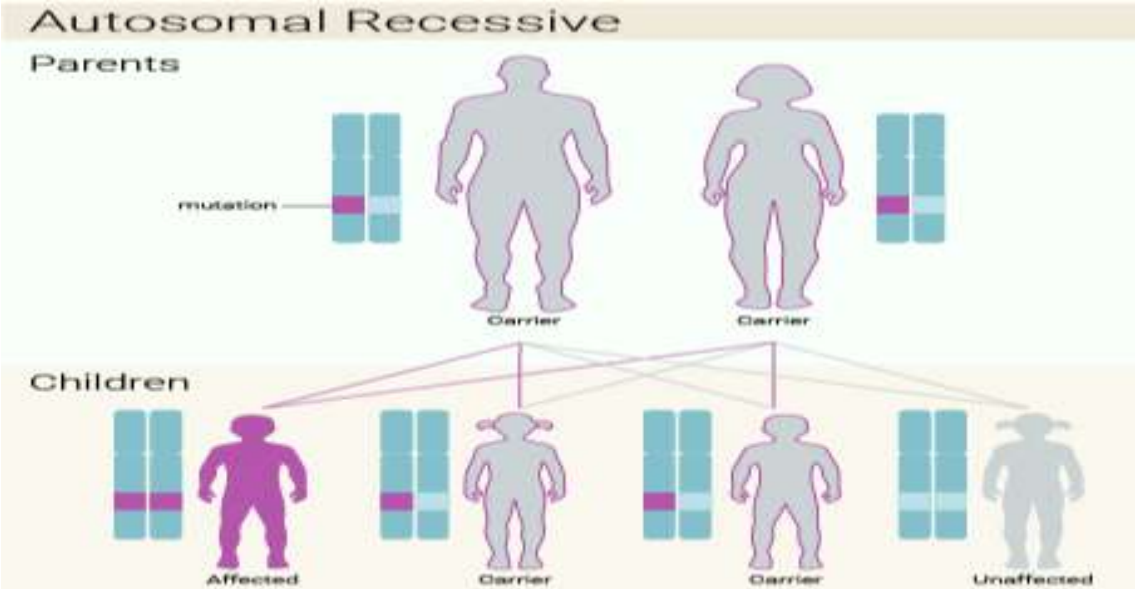
acid in the 24-hour urine. In individuals with AKU, the daily excretion of HGA typically ranges from 1 to 8 grams. Urine color changes in a non-specific way.

2. Family counseling can benefit from the identification of biallelic anomalies in HGD and other mutations by molecular genetic testing.
3. Various imaging modalities like CT scan or MRI help in assessing the severity of joint involvement.
4. 2D-Echocardiography can detect valvular abnormalities.
5. A CT angiogram can identify coronary artery calcification.

Alkaptonuria's Inheritance Pattern

There are twenty-three pairs of chromosomes in every cell in the body. These contain the genes your parents gave you. Since each parent contributes one copy of each pair of chromosomes, every cell has two copies of every gene (save for the sex chromosomes). The HGD gene is the one that causes alkaptonuria. This gives directions for producing homogentisate oxidase, an enzyme required to degrade homogentisic acid. To get alkaptonuria, you must inherit two copies of the defective HGD gene, one from each parent. Because of the low likelihood of this, the disorder is extremely uncommon. When a person has alkaptonuria, their parents often only have one copy of the defective gene, hence they will not exhibit any symptoms of the illness. Due to the autosomal recessive mode of inheritance, each cell's two copies of the gene display mutations.



HOW TO TREAT ALKAPTONURIA

Alkaptonuria is a chronic illness. To reduce the progression of alkaptonuria in adults, nitisinone is a medication. Painkillers and lifestyle adjustments may help you manage with the symptoms.

Nitisinone

The body produces less homogentisic acid when nitisinone is present. The National Alkaptonuria Centre, located at Royal Liverpool University Hospital, is the treatment facility for all alkaptonuria patients.The European Union has now formally granted nitisinone a license to treat AKU. The National AKU Center in the UK prescribes 2 mg per day to its patients. According to clinical studies, nitisinone can lower HGA levels by up to 95%. In 2013, We ran a series of international clinical trials called DevelopAKUre, that measured the effectiveness of nitisinone in treating AKU. In 2020 we found out that this trial was successful and showed that the drug markedly reduced HGA levels in the body.The body produces less homogentisic acid when nitisinone is present. The National Alkaptonuria Centre, located at Royal Liverpool University Hospital, is the treatment facility for all alkaptonuria patients.

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conducted a series of global clinical studies known as Develop AKU are starting in 2013 to assess how well nitisinone treated AKU. We learned that this experiment was successful in 2020 and that the medication significantly lowered the body's levels of HGA. AKU results from the body's inability to break down a chemical known as homogentisic acid (HGA) due to a missing enzyme. The way nitisinone works is by inhibiting the enzyme that produces HGA. As a result, HGA cannot accumulate in the body and cause damage. A patient will get a patient information booklet regarding nitisinone, which includes all the information they require, when they visit the National AKU Center. Leading AKU doctors at the NAC, Prof. L Ranganath and Dr. M Khedr, will talk one-on-one with patients about the medication and its adverse effects.

Diet & AKU: Nitisinone-Based Controlled Protein Diet

When using nitisinone for alkaptonuria in adults, a protein-restricted diet may help lower the chance of possible adverse effects. Your physician or nutritionist will evaluate this and provide you with advice. The reason for this is that using nitisinone raises blood tyrosine levels, which may have negative consequences. Restricting the amount of protein that patients consume can help keep their tyrosine levels within a reasonable range. Because it varies from person to person based on body weight and past protein intake, patients have proposed calling this a regulated protein diet instead of a reduced protein diet. Patients will get a meal journal to complete prior to the NAC, which will determine their typical daily protein consumption. After that, this will assist in determining their new protein consumption. We will figure out how much protein each person needs to maintain muscular health.

Exercise With Alkaptonuria

If you have pain and stiffness from alkaptonuria, you may think that working out may make your symptoms worse. However, regular exercise may help you build muscle and strengthen your joints. Exercise also helps you feel better by lowering stress, improving your posture, and helping you lose weight. However, avoid games that put additional strain on the joints, such as football, rugby, and boxing. Mild exercise, such as yoga and pilates, may help in the early stages; for more advanced alkaptonuria, swimming, walking, and cycling may be more suitable. Your general practitioner or a physiotherapist can help you design a suitable at-home exercise program. Adhering to this approach is essential since there is a possibility that the wrong type of exercise might cause joint damage.

Get some gentle exercise

Walking, swimming, gardening, and dancing are examples of simple, daily activities that can immediately reduce pain by preventing the brain from receiving pain signals. By extending tight and stiff muscles, ligaments, and joints, exercise also helps reduce pain. If exercising hurts and you are afraid of hurting yourself further, it is normal to be hesitant. However, it is unlikely that you will injure somebody if you steadily increase your level of activity. When you begin little exercise, you may experience discomfort because your muscles and joints are becoming more fit. Exercise has considerably more long-term advantages than disadvantages.

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Breathe right to ease pain

When you are in pain, it might be helpful to focus on your breathing. It is quite simple to start breathing quickly and shallowly when the pain is severe, which can make you feel lightheaded, nervous, or terrified. Breathe deeply and slowly instead.This will keep you calm, give you a sense of control, and stop any anxiousness or tense muscles from exacerbating your discomfort.

Talking therapies can help with pain

You may feel drained, nervous, sad, and irritable while you are in pain. This may worsen your agony and send you into a downward spiral. Treat yourself with kindness. Being obstinate, not timing your daily activities, and not understanding your limitations might make you your own worst enemy. Living with pain is not simple. To learn how to manage their emotions in connection to their pain, some people find it helpful to seek assistance from a psychologist or hypnotist. You can also find out more about talking therapies, also known as psychological therapies.

Distract yourself

Turn your focus to something else so that you are not thinking exclusively about the discomfort. Immerse yourself in an interesting or enjoyable activity. Even with limited movement, you may engage in a variety of hobbies, such as knitting, sewing, or photography.

Managing Pain with Alkaptonuria

Ask your doctor about medications and other pain management methods.

Emotional support With Alkaptonuria

At first, receiving an alkaptonuria diagnosis might be overwhelming and perplexing. When someone learns they have alkaptonuria, they may experience anxiety or depression, much like many others with chronic illnesses. However, you can speak with certain persons who can assist you. If you think you need help managing your disease, speak with your doctor.

Surgery

When joints are too damaged, joint replacement surgery is another way to relieve pain. Surgery may also be necessary for kidney, bladder, or prostate stones in certain AKU patients. Surgery may occasionally be required to replace broken joints or to replace hardened heart valves or arteries.

Your physician could suggest:

- replacement of the hip
- knee replacement
- Replacement of the aortic valve, etc.

HISTORY OF ALKAPTONURIA

The discovery of AKU

In 1902, Sir Archibald Garrod was the first to characterize AKU as an inherited condition. By using basic observations to comprehend basic facets of human biology, Sir Archibald was a real pioneer. He was a physician from the Edwardian era who focused on what is now known as metabolic medicine.

He discovered that AKU followed patterns after treating several patients and examining their family histories. Patients' siblings and sisters frequently had AKU as well, and offspring from consanguineous marriages were more likely to have it. He realized that there was some way to inherit AKU.

Sir Archibald recognized that AKU was the result of a chemical fault, which he called an "inborn error of metabolism" and which is today known to be the chemical homogentisic acid. Sir Archibald became acquaintances with Cambridge physicist William Bateson while he was delving into the secrets of AKU. Bateson came to the conclusion that AKU and its inherited metabolic mistake were truly Mendelian recessive traits, meaning they were a substance that was passable in a predictable manner and that led to illness.

This was revolutionary for the early 20th century when concepts like genetics and heredity were still developing. Less was known about how illnesses may run in families before the discovery of DNA, which was still fifty years away. The research of Garrod and Bateson demonstrated that a biochemical substance could decide a disease and that it could be inherited. This contributed to the development of the concept of a hereditary illness and makes AKU the first genetic disease in history.

At a Croonian speech in 1908, Sir Archibald Garrod went on to discuss AKU and three other hereditary illnesses: albinism, cystinuria, and pentosuria. He coined the phrase "inborn error of metabolism" here, which ultimately resulted in the founding of the Society for the Study of Inborn Errors of Metabolism (SSIEM)[5] in 1963 as a medical society.

In the meanwhile, William Bateson contributed to the development of modern genetics by using AKU as an example. Together with the well-known phrases "heterozygote," "homozygote,"

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and "allele," he is believed to have coined the term "genetics."He established the Journal of Genetics in 1910 to aid in the explanation of this novel scientific phenomena.

"The study of nature's experiments is of exceptional value; and many lessons which uncommon disorders may teach could hardly be learned in other methods," said Sir Archibald, summarizing the significance of his research into AKU and other rare diseases. Bateson, however, adopted the shorter phrase, "Treasure Your Exceptions!"

Harwa, the AKU Mummy

A 1500 BC mummy named Harwa is our earliest AKU patient. During his lifetime, he worked as a doorkeeper at the Temple of Amun, which at the time was the biggest temple in Egypt. He is presently on exhibit at the Field Museum of Natural History in Chicago and was the first mummy to be transported by air.

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