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Assessment of Plasma Uric acid and Magnesium Levels in Sudanese Patients with Rheumatoid Arthritis in Khartoum State.

تقييم مستويات حمض اليوريك و المغنيسيوم في بلازما الدم لدى مرضى التهاب المفاصل الروماتويدي السودانيين في ولاية الخرطوم

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الآيــة

بسم الله الرحمن الرحيم

قال الله تعالى:

﴿ يَا أَيُّهَا الَّذِينَ آمَنُوا إِذَا قِيلَ لَكُمْ تَفَسَّحُوا فِي الْمَجَالِسِ فَافْسَحُوا يَفْسَحِ اللَّهُ لَكُمْ وَإِذَا قِيلَ انْشُزُوا فَانْشُزُوا يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ﴾

صدق الله العظيم

سورة المجادلة – الآية 11

Dedication

I dedicate this work to those who were causes of my existence and then my success after God Allah, for my parent, affection mother and my father the savior

To my brothers and sisters

To my dear husband

To my friends

To my teachers

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All and first thanks to the almighty ALLAH.

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Abstract

Background and aim of study: Rheumatoid arthritis is an autoimmune disorder, which causes chronic inflammation of the joints. Rheumatoid arthritis patients had higher risk of developing chronic kidney disease and chronic cardiovascular disease,

Objectives: The Aim of this study to evaluate the plasma levels of magnesium and uric acid in rheumatoid arthritis patients.

Materials and Methods: this was cross sectional-case control study conducted during the period from June to October 2019, the study carried on a total sample of 100 individual including 50 patients with rheumatoid arthritis already diagnosis as case and 50 healthy individual as control group. Plasma magnesium and uric acid were measured by using spectrophotometer biosystem-310 , xylidyl blue reagent for magnesium and enzymes for uric acid analyze and results were analyzed using statistical of package social science (SPSS) computer program.

Results: this study showed plasma magnesium and uric acid were significantly increase among rheumatoid arthritis patients(cases) versus healthy individual(control), mean ±SD values of plasma magnesium (mg/dL) was (2.95±0.91) versus (2.26±0.39) with P-value (0.000), plasma uric acid (mg/dL) was (4.82±1.36) versus (3.66±1.05) with P-value (0.000), all the differents were statistically significant. There were insignificant correlation between uric acids, magnesium and study variables (age and duration of disease), (r= 0.233, p-value= 0.101), (r= 0.014, p .value=0.925) respectively, and (r=0.080, P value= 0.582), (r= 0.076, P value= 0.600) respectively.

Conclusion: In rheumatoid arthritis patients plasma magnesium and uric acid are higher.

مستخلص الدراسة

التهاب المفاصل الروماتويدي هو اضطراب المناعة الذاتية ، والذي يسبب التهاب مزمن في المفاصل. كان التهاب المفاصل الروماتويدي أكثر عرضة للإصابة بأمراض الكلى المزمنة وأمراض القلب والأوعية الدموية المزمنة ، والهدف من هذه الدراسة لتقييم مستويات البلازما من المغنيسيوم وحمض اليوريك في مرضى التهاب المفاصل الروماتويدي.

المواد والطرق: تم إجراء دراسة مقطعية للسيطرة على الحالات خلال الفترة من يونيو إلى أكتوبر 2019 ، وقد أجريت الدراسة على عينة إجمالية من 100 فرد بما في ذلك 50 مريضا بالتهاب المفاصل الروماتويدي كحالة و 50 فردًا صحيًا كمجموعة تحكم. تم قياس المغنيسيوم وحمض اليوريك في البلازما باستخدام نظام قياس الطيف الحيوي biosystem-310 ، وتم تحليل النتائج وتحليلها باستخدام برنامج إحصائي لبرنامج الحزم في العلوم الاجتماعية (SPSS).

النتائج: أظهرت هذه الدراسة ارتفاع نسبة المغنيسيوم في البلازما وحمض اليوريك بشكل ملحوظ بين مرضى التهاب المفاصل الروماتويدي (الحالات) مقابل الفرد السليم (التحكم) ، يعني أن قيم ± SD لمغنيسيوم البلازما (mg/dL) كانت (2.95 ± 0.91) مقابل (2.26 ± 0.39)) مع قيمة (0.000 P) ، كان حمض اليوريك في البلازما (1.36 ± 4.82) (mg/dL) مقابل (3.66 ± 1.05) مع قيمة (0.000 -P) ، وكانت جميع الاختلافات ذات دلالة إحصائية.

الخلاصة: خلص الباحثون إلى أن المغنيسيوم وحمض اليوريك أعلى في مرضى التهاب المفاصل الروماتويدي.

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Abbreviations

RA	Rheumatoid arthritis
RF	Rheumatoid factor
FC	Fragment crystallizable region
IgG	Immunogloulin G
CVD	Cardiovasular disease
SUA	Serum uric acid
MHC	Major histocompatibility complex
IL-1	Interleukin 1
TNF	Tumor necrosis factor
IMR	Index of microcirculatory resistance
CRP	C reactive protein
ACPAS	Anti- Citrullinated protein antibodies
Anti CCP	Anti – cyclic Citrullinated peptide
HGPRT	Hypoxanthine- guanine phosphoribosyl transferase
PRPP	Phosphoribosyl pyrophosphate
PCT	Proximal convoluted tubule
PTH	Parathyroid hormone
MTP JOINTS	metatarsophalangeal joints

Chapter one

Introduction – Rationale – Objectives

1. Introduction – Rationale – Objectives

1.1 Introduction:

Rheumatoid arthritis (RA) is a common autoimmune disorder. It's mainly characterized by persistent joint inflammation that results in loss of joint function **(keskin *et al*., 2008).** RA is a systemic disease, associated with progressive joint destruction and deformity. Depending on the severity, there may also be extra-articular manifestation including blood vessels, skin and internal organ. If untreated appropriately, RA leads to a significant impairment of the quality of life **(Egerer *et al*., 2009).**The definite reason of RA is unknown. Moreover, there are some factors participating in the development of the disease, Infections are thought to be a causative agent of RA. There is an evidence relate Epstein –Barr virus and the incidence of RA. Rheumatoid factor (RF) is the autoantibody that was first found in rheumatoid arthritis against the fragment crystallizable region (FC) portion of immunoglobulin G are still a hallmark of diagnosis and severity of RA. And different RFS can recognize different parts of the IgG-**(Falkenurg, 2015).** Its clinical diagnosis made on the basis of medical history, symptoms, physical exam, radiographs (X-rays) and laboratory tests **(visser, 2005).**

Uric acid is achemical produced when the body breaks down foods that contain organic compounds called purines. High level of uric acid are associated with condition called Gout is form of arthritis that cause swelling of the joint especially in the feet and big toes **(WHO, 2017).** Rheumatiod arthritis (RH) is not thought to associate with high serum uric acid but is characterized by increased CVD morbidity and mortality**(Panoulas *et al*.,2007).**

Chronic inflammatory condition are likely to alter magnesium level and various biochemical parameters .Magnesium is the second most abundant intracellular bivalent cation, This cation plays an important role in central nervous system, The magnesium misbalance are involved in various pathological states such as attention deficit hyperactivity disorder ,ischemic brain injury, seizures and other, There are a lot of magnesium dependent enzyme, decrease of intracellular and extracellular magnesium concentration can increase the development of cardiovascular disease in diagnosed RA subjects**.(Vilas chavan *et al*., 2015).** Previous study done by **(Panoulas *et al* ., 2007)** showed that, there was significant increase in uric acid in

RA patients, another study done by **(Vilas *et a l*., 2015)**showed significant decreased in magnesium.

1.2. Rationale:-

RA affects between 0.5 and 1% of adults in the developed world between 5 and 50 per 100.000 people newly developing the condition each year **(Smolen *et al*., 2016)**. In 2010 it resulted in about 49.000 deaths globally **(Lozano *et al*6., 2012)** .Onset is uncommon under the age of 15 and from then on the incidence rises with age until the age of 80. Women are affected three to five times than men **(Shah and Ankur, 2012).**

Rheumatoid arthritis patient had increased mortality compared to the general population. This was observed in both sexes. Over 40% of deaths in all groups were due to cardiovascular diseases. RA patients were at increased risk of dying of urogenital, gastrointestinal, respiratory and cardiovascular diseases, infection, and cancers **(Sihvonen *et al* ., 2004)**.

Many study have shown that increased the plasma levels of uric acid and decrease in plasma magnesium association with cardiovascular disease. According to the knowledge, in the Sudan, there is no publish studies showed the disturbance in plasma uric acid and magnesium in rheumatoid arthritis patient, therefore this study high light to measure plasma levels of uric acid and magnesium in RA patients and help in early detection of cardiovascular disease and renal disease.

1.3. Objective:

1.3.1. General Objective

To assess plasma uric acid and magnesium among rheumatoid arthritis patient.

1.3.2. Specific Objectives

1-To measure and compare mean concentration of uric acid , magnesium in study groups

2-To correlate between serum uric acid , magnesium and study variables (age and duration of disease) .

Chapter two

Literature review

2. Literature review

2.1 Rheumatoid arthritis:

Is a long –term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both side of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lung, and inflammation around the heart. Fever and low energy may also be present**.** While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factor. The underlying mechanism involves the body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage **(Handout on Health: Rheumatoid** Arthritis**, 2014)**. Often, symptoms come on gradually over weeks to month **(Majithia and Geraci , 2007).**

2.1.1 Signs and symptoms of rheumatoid arthritis:

The majority of patients complain of pain and stiffness of the small joints of the hands and feet. The wrist, elbows, shoulders, knee and ankles are also affected. In most cases many joints are involved, but 10% present with a monoarthritis of the knee or shoulder or with carpal tunnel syndrome. The patient feels tired and unwell and the pain and stiffness are significantly worse in the morning and may improve with gentle activity. The joints are usually warm and tender with some joint swelling there is limitation of movement and muscle wasting. Deformities develop as the disease progresses **(Kumar and Clark, 2013).** It also affects other organs in more than 15-25% of cases; associated problems include cardiovascular disease, osteoporosis interstitial lung disease, infection, cancer, feeling tired, depression, mental difficulties, and trouble working **(Cutolo *et al.*, 2014)**. Constitutional symptoms including fatigue, low grade fever, malaise, morning stiffness, loss of appetite and loss of weight seen in people with active RA**(Assassi and Shervin, 2016).**

2.1.2 Rheumatoid arthritis complication:

2.1.2.1 Septic arthritis:

This is a serious complication with significant morbidity and mortality. Affected joints are inflamed and hot with accompanying fever and neutrophil leukocytosis in the blood. However this signs are absent, and any effusion, particularly of sudden onset, should be aspirated. Staphylococcus aurous is the most common organism. Blood cultures are often positive. Treatment is with systemic antibiotic and drainage.

2.1.2.2 Amyloidosis:

RA is the most common cause of secondary AA Amyloidosis. AL Amyloidosis causes a polyarthritis that resemble RA in distribution and is also often associated with carpal tunnel syndrome and subcutaneous nodules **(Kumar and Clark, 2013).**

2.1.3 Joint involvement in rheumatoid arthritis:

2.1.3.1 Hands and wrists:

The impact of RA on the hand is severe. In early disease the fingers are swollen, painful and stiff. Inflamed flexor tendon sheaths increase functional impairment and may cause carpal tunnel syndrome. Swelling and dorsal subluxation of the ulnar styloid leads to wrist pain and may cause rupture of the finger leading in turn to a sudden onset of finger drop.

2.1.3.2 Shoulder:

RA commonly affects the shoulders. Initially the symptoms mimic rotator cuff tendonitis with a painful arc syndrome and pain in the upper arms at night. As the joint become more, stiffening occurs.

2.1.3.3 Elbows:

Synovitis of the elbows causes swelling and a painful fixed flexion deformity. In late disease flexion may be lost and sever difficulties with feeding result especially combined with shoulder, hand and wrist deformities.

2.1.3.4 Feet:

One of the earliest manifestations of RA is painful swelling of the MTP joints The foot becomes broader and a hammer-toe deformity develops. Ulcers or callouses may develop under the metatarsal heads and the dorsum of the toes. Mid- and hind foot RA causes a flat medical arch and loss of flexibility of the foot. The ankle often

assumes a valgus position. Appropriate broad, deep, cushioned shoes are essential, and walking is often painful and limited.

2.1.3.5 Hips:

The hips are rarely affected in early RA and are less commonly affected than the knees at all stage of disease. Pain and stiffness are accompanied by radiological loss of joint space and juxta-articular osteoporosis. The latter may permit medical migration of the acetabulum (protrusion acetabulae). Later, secondary OA develops. Hip replacement is usually necessary.

2.1.3.6 Cervical spine:

Painful stiffness of the neck in RA is due to rheumatoid Synovitis affecting the synovial joints of the upper cervical spine leads to bone destruction, damages the ligaments and causes upper cervical instability. Subluxation and local synovial swelling may damage the spinal cord, producing pyramidal and sensory signs **(Kumar and Clark, 2013).**

2.1.4 Non-articular manifestations:

2.1.4.1 Kidneys:

Renal Amyloidosis can occur as aconsequence of untreated chronic inflammation.

2.1.4.2 Eyes:

The eye can be directly affected in the form of episcleritis or scleritis, which when severe can progress to scleromalacia, when severe, dryness of the cornea can lead to keratitis and loss of vision as being painful.

2.1.4.3 Liver:

Liver problems in people with rheumatoid arthritis may be due to the underlying disease process or as a result of the medication (**Selmi *et al* ., 2011)**.

2.1.4.4 Neurological:

Peripheral neuropathy and mononeuritis multiplex may occur. The most common problem is carpal tunnel syndrome caused by compression of the median nerve by swelling around the wrist. Rheumatoid disease of the spine can lead to myelopathy **(Wasserman *et al*., 2011)**.

2.1.4.5 Bones:

Local osteoporosis occurs in RA around inflamed joints. It is postulated to be partially caused by inflammatory cytokines. More general osteoporosis is probably

contributed to by immobility, systemic cytokine effects, local cytokine release in bone marrow and corticosteroid.

2.1.4.6 Cancer:

The risk of non-melanoma skin cancer is increased in people with rheumatoid arthritis compared to the general population, an association possibly due to the use of immunosuppressant agents for treating RA**(Assassi and Shervin, 2016).**

2.1.5 Risk factors of rheumatoid arthritis:

RA is a systemic autoimmune disease. Some genetic and environmental factors affect the risk for RA.

2.1.5.1 Genetic:

A family history of RA increases the risk around three to five times. RA is strongly associated with genes of the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DR4 is the major genetic factor implicated –the relative importance varies acroos ethnic groups **(Doherty *et al* ., 2010).**

2.1.5.2 Environmental:

Smoking is an established risk factor for RA in Caucasian population , increasing the risk three times compared to non-smokers , particularly in men , heavy smokers , and those who are rheumatoid factor positive **(Sugiyama *et al* ., 2010).**

No infectious agent has been consistently linked with RA and there is no evidence of disease clustering to indicate its infectious cause (**Doherty *et al*., 2013).**

The many negative findings suggest that either the trigger varies, or that it might, in fact, be a chance event inherent with the immune response **(Edwards *et al* ., 1999).**

2.1.6 Pathophysiology of rheumatoid arthritis:

RA primarily starts as a state persistent cellular activation leading to autoimmunity and immune complexes in joints and other organ .The initial site of disease is the synovial membrane .Three phases of progression of RA are an initiation phase (due to non-specific inflammation) ,an amplification phase(due to T cell activation),and chronic inflammatory phase, with tissue injury resulting from the cytokines, IL-1,TNF-alpha and IL-6 **(Shah and Ankur., 2012).**

2.1.7 Diagnosis of rheumatoid arthritis:

The diagnosis relies on the clinical features .The initial investigations include: X ray of the hands and feet are generally performed when many joints affected. In RA there may be no changes in the early stages of the disease or the X-ray may show

osteopenia near the joint, soft tissue swelling, and a smaller than normal joint space. As the disease advance, there may be bony erosions and subluxation. Other medical imaging techniques such as magnetic resonance imaging (IMR) and ultrasound are also used **(Schueller-Weidekamm and Claudia, 2010)** Anti-CCP is positive earlier in the disease , and in early inflammatory arthritis indicate the likelihood of progressing to RA . Rheumatoid factor is present in approximately 70% of cases, is a non –specific antibody and seen in about 10% of healthy people, in many other chronic autoimmune diseases. ESR and CRP are raised in proportion to the activity of the inflammatory process. Aspiration of the joint if an effusion is present .The aspirate looks cloudy owing to white cells **(Kumar and Clark, 2013).**

2.1.8 Prevention and Treatment of rheumatoid arthritis:

There is no known prevention for the condition other than the reduction of risk factors.

Treatments can improve symptoms and slow the progress of the disease. Disease - modifying treatment such as hydroxychloroquine and methotrexate, has the best results when it is started early and aggressively **(Saag *et al*., 2008).** The goals of treatment are to minimize symptoms such as pain and swelling, to prevent bone deformity, and to maintain day-to-day functioning **(Wasserman, 2011)**. RA should generally be treated with at least one specific anti-rheumatic medication **(Singh *et al* ., 2016).**

Regular exercise is recommended as both safe and useful to maintain muscles strength and overall physical function (Hurkmans E et al., 2009). Physical activity is beneficial for people with rheumatoid arthritis who experience fatigue**(Cramp *et al* ., 2013).** but there is evidence to suggest that exercise may make little to no difference on physical function in the long term (**Williams *et al* ., 2018)** Occupational therapy has a positive role to play in improving functional ability in people with rheumatoid arthritis .

2.2 Uric acid:

2.2.1 Biochemistry and Physiology of Uric Acid:

Uric acid is the major product of the catabolism of the purine nucleosides,adenosine and guanosine .The daily synthesis rate of uric acid is approximately 400 mg; dietary sources contribute another 300mg.Over production of uric acid may result from increased synthesis of purine precursors .Approximately 75% of the uric acid

excreted in the urine ; most of the remainder is secreted in to the GI tract , where it is degraded to allantoin and other compounds by bacterial enzymes.

Renal handling of uric acid is complex and involves four sequential steps glomerular filtration , reabsorption of about 98% to 100% in the proximal convoluted tubule, secretion in to the lumen of the distal portion of the proximal tubule; and, further reabsorption in the distal tubule. The net urinary excretion of uric acid is 6% to 12% of the amount filtered .The physiological properties of uric acid are important in consideration of uric acid concentration in the circulation, tissues and kidneys. The first p*k* of uric acid is 5.57; above a PH of 5.57, uric acid exists chiefly as urate ion, which is more soluble than uric acid.

2.2.2 Disease correlations:

Three major disease states are associated with elevated plasma uric acid concentration: gout, increased catabolism of nucleic acids, and renal disease.

Gout is a disease found in men and usually is first diagnosed between 30 and 50 years of age .Patient have pain and inflammation of the joints caused by precipitation of sodium urate. In 25-30% this patients, hyperuricemia is a result of production of uric acid , although hyperuricemia may be exacerbated by a purine rich diet, drugs, or alcohol. Plasma uric acid concentration in these patient is greater than 6.0 mg/dl. Patient with gout are susceptible to the development of renal calculi, In severe cases, deposits of urates called tophi form in tissue , causing deformities .Another common cause of elevated plasma uric acid concentration is increased metabolism of cell nuclei, as occurs in patients on chemotherapy for such proliferative disease as leukemia, lymphoma, multiple myeloma, and polycythemia **(Bishop *et al* ., 2010).**

2.2.3 Hyperuricemia:

Hyperuricemia, is defined by serum or plasma uric acid concentration greater than 7.0 mg/dl in men or greater than 6.0 mg\dl in women. The causes of hyperuricemia are; increased formation due to increased purine synthesis, inherited metabolic disorder, increased nucleic acid turnover ,alcohol and tissue hypoxia .Other causes of hyperuricemia are decreased excretion due to chronic renal failure, increased renal reabsorption, reduced secretion and organic acid. Hyperuricemia also is attributed to primary defects of enzymes in the pathways of purine metabolism. The lesch-Nyhan syndrome is characterized by complete deficiency of hypoxanthine-

guanine phosphoribosyl transferase (HGPRT), This sex-linked genetic disorder is manifested clinically by mental retardation, abnormal muscle movement, and behavioral problems. Biochemically, it is characterized by hyperuricemia, hyperuricaciduria, and markedly decreased levels of HGPRT in erythrocytes, fibroblasts, and other cells. Intracellular levels of phosphoriosylpyrophosphate (PRPP) and rates of purine synthesis are increased (**Carl *et al* ., 2008).**

2.2.4 Hypouricemia:

Defined as serum concentration less than 2.0 mg/dl (0.12 mmol/l), is less common than hyperuricemia . It may be secondary to severe hepatocellular disease with reduced purine synthesis ; defective renal tubular reabsorption of uric acid . Defective reabsorption may be congenital or acquired .Over treatment of hyperuricemia with allopurinol or uricosuric drugs and cancer chemotherapy with azathioprine also have caused hypouricemia (**Carl *et al* ., 2008).**

2.2.5 Uric acid and Rheumatoid arthritis:

Rheumatoid arthritis is not thought to associate with high serum uric acid but is characterized by increased hypertension and cardiovascular disease morbidity and mortality.**(Panoulas *et al*., 2007)**. High levels of uric acid inhibit the production of rheumatoid factor and could therefore have immunosuppressive properties, persistent hyperuricemia may protect against or decrease the expression of rheumatoid inflammation **(Vasileios *et al*., 2008)**.

2.3 Magnesium:

Magnesium (**mg**) is the fourth most abundant cation in the body and second most abundant intracellular ion, the role of (Mg) in the body is widespread. It is an essential cofactor of more than 300 enzymes, including those important in glycolysis, transcellular ion transport, neuromuscular transmission, synthesis of carbohydrate, proteins, lipids, and nucleic acids, and release of an response to certain hormones **(Bishop *et al*., 2010).** It also has important role in cell cycle, mitochondrial integrity, modulating ion transport (**Romano, 2011**) The binding of magnesium with important intracellular anionic-ligand especially ATP and the competition with calcium for binding site on protein membranes are the most important role of magnesium that help to perform those function **(Swaminathan, 2003).**It is also important for normal neurological and muscular function, and cardiac excitability.

2.3.1Body content and distribution of magnesium:

Adult human body contains approximately 1mol (25g) Mg. Of total magnesium content in human body, less than 1% is found in serum and red blood cell **(Kielstein *et al* .,2013)**.About 63% of the magnesium is found between bone, 27% in intracellular compartment of muscles, 90% of which is bound and with only 10% being free. In the serum, 32% of magnesium is bound to albumin, whereas 55% is free **(Vormann *et al* ., 2003).** It stays in equilibrium with ionized magnesium of extra cellular fluid and antagonizes calcium during muscle contraction **(Baaij *et al*., 2012).**The availability of magnesium in one decreases with age and therefore might not be completely available when there is magnesium deficiency **(Maguire and Cowan, 2002),** Serum magnesium is present in three different states; free, complexes to anions and bound to protein, Approximately 33% are protein bound mostly to albumin and phosphate **(Elin, 1987)** However ionized magnesium is the one which is most involved in biological activity, The reference value for magnesium concentration in blood plasma range from 0.65 to 1.05 mmol/l for adults **(Saris *et al*., 2000)** and for ionized magnesium reference value ranges from 0.53 to 0.67 mmol/l in normal healthy people **(Altura *et al*., 1991).**

2.3.2 Magnesium intake:

Magnesium concentration depends on the magnesium intake from food and drinking water, Whole seeds, unmilled grains, green leafy vegetables (rich in magnesium containing chlorophyll) legumes and nuts are the most important source of dietary magnesium , Meat, fish, fruits are also good sources of magnesium. Drinking water especially hard water is also one of the sources of ,magnesium which might account for almost 10% of daily magnesium intake, the absorption of magnesium is influenced y various dietary factors either promoting or inhibiting the absorption, Absorption of magnesium can be inhibited by phytate, fibre, alcohol or excess of calcium and phosphate. Processing and refining of food leads to loss of magnesium content in food, The effects of vitamin Din magnesium absorption is still unclear, some studies have shown that vitamin D and its active metabolites increases intestinal magnesium absorption in normal human beings and also in patients with chronic renal failure **(Shils *et al*., 2006),** The normal serum magnesium

concentration or(Mg) ranges between 0.75 and 0.95 mmol/l **(Weisinger and Bellorin-Font, 1998).**

2.3.3 Magnesium homeostasis and regulation:

Magnesium homeostasis is maintained by intestine, the bone and the kidney, In brief magnesium is absorbed through gut, stored in bones through kidney if excess, Intestinal absorption of magnesium was inversely related to magnesium intake in a healthy volunteer which ranged from 65% at low intake and 11% at high intake **(Fine et al., 1991).** Two pathways that is paracellular and trancellular pathways are involved in the absorption of Mg^{+2} **,** paracellular pathway which is a passive mechanism absorbs Mg^{+2} through small spaces between epithelial, The transcellular pathway involves movement of Mg^{+2} to the blood through the interior of epithelial cell, Around 30 to 40% of normal dietary intake of magnesium is absorbed through intestine, Jejunum and ileum are the important sites where magnesium absorption takes place, After 1 hour of ingestion the absorption begins and continues for 2 to 8 hours, After 12 hours the ingested material reaches large bowel in human where little or no absorption takes place **(de Baaij *et al.*, 2012)**. regulation of body Mg^{+2} is controlled largely by the kidney, which can reabsorb Mg^{+2} in deficiency states or readily excrete excess Mg^{+2} in overload states, Of the non protein-bound Mg^{+2} that gets filtered by the glomerulus, 25%-30% is reabsorbed by the proximal convoluted tubule (PCT) , un like Na in which 60%-75% is absorbed in the PCT, Hennls loop is the major renal regulatory site, where 50%-60% of filtered Mg is reabsorbed in the ascending limb, In addition, 2%-5% is reabsorbed in the distal convoluted tubules, The renal threshold for Mg^{+2} is approximately 0.60- 0.85 mmol/L (1.64-2.07 mg/dL), Because this is close to normal serum concentration, slight excesses of Mg^{+2} in serum are rapidly excreted by the kidneys, Normally, only about 6% of filtered Mg^{+2} is excreted in the urine per day, Mg^{+2} regulation appears to be related to that of Ca^{+2} and Na parathyroid hormone(PTH) increases the renal reabsorption of Mg^{+2} and enhances the absorption of Mg^{+2} in the intestine, However, changes in ionized Ca^{+2} have a far greater effect on PTH in the kidney, increasing the renal excretion of Mg^{+2} **(Bishop *et al.*, 2010)**.

2.3.4 Hypomagnesia:

The level of magnesium in our body might not always be the same., Hypomagnesia indicates depletion of body magnesium. It is defined as Hypomagnesia when the

serum magnesium is less than 1.8mg/dl (0.74mmol/l). Most of the cases of Hypomagnesia are asymptomatic., Symptomatic cases are seen only one serum magnesium falls below 1.2mg/dl **(Assadi., 2010),** Magnesium deficiency or hypomagnesia can occur due to various reasons and mechanisms, some of the reasons for magnesium deficiency are redistribution of magnesium, reduction in dietary intake and intestinal absorption, renal loss, endocrine causes, diabetes mellitus, alcohol, drugs **(Swaminathan., 2003).**

2.3.5 Hypermagnsia:

Hypermagnesia, the excess of magnesium in body may be the result of high intake of magnesium salt or magnesium containing drugs which is mostly seen in people with renal failure or reduced renal function. Occurrence of hypermagnesia is very rare but it may result in various neuromuscular, cardiovascular manifestation and hypocalcaemia. Higher level of magnesium also leads to cardio toxicity **(Swaminathan**, **2003)**. Hypermagnesia has been associated with several endocrine disorders, Thyroxin and growth hormone cause a decrease in tubular reabsorption of Mg^{+2} **.(Bishop *et al*., 2010),** Chronic kidney disease or end stage kidney disease is the only strong clinical predictor for hypermagnesia and net positive magnesium balance. Dialysis patients have higher magnesium level**(Spiegel, 2011).**

2.3.6 Magnesium and Rheumatoid arthritis:

Rheumatoid arthritis causes magnesium deficiency due to chronic inflammation and autoimmune injury, decreased supply (lesser appetite) and reduced absorption caused by disturbances in the digestive system functions. Minerals disturbances may lead to sever and even life-threatening metabolic abnormalities such as coronary heart disease, lung function, liver disease, kidney failure, and disorders of endocrine system **(Vasileios F et al., 2008).**

Chapter three

Materials and method

3. Materials and Methods

3.1. Materials:

3.1.1. Study approach:

A quantitative method was used to measure the levels of plasma uric acid and magnesium in rheumatoid arthritis patients during the period from June to October 2019.

3.1.2 Study design:

This was cross sectional, case control hospital base study.

3.1.3 Study area:

The study was conducted in Al Rayyan and Baraa hospital, in Khartoum state.

3.1.4 Study population and sample size:

The study included 50 patient with rheumatoid arthritis and 50 apparently healthy subjects as control

3.1.5 Inclusion Criteria:

Patients with rheumatoid arthritis and healthy individual as control were included.

3.1.6 Exclusion Criteria:

This study excluded hypertension, smoking, renal, liver, heart diseases, alcoholism, bone diseases, SLE or any other major illness were excluded from the study. Subjects who were on medication which can affect plasma magnesium and uric acid levels were also excluded from this study.

3.1.7 Ethical Considerations:

Verbal Consent was taken regarding acceptance to participate in the study and reassurance of confidentiality. Before the specimen was collected, the donors knew that this specimen was collected for research purpose.

3.1.8 Data Collection:

Data were collected using a structural questionnaire, which was designed to collect all valuable information concerning each case examined.

3.1.9 Sample collection and processing:

About 2.5 ml of venous blood were collected by safe aseptic procedures.

Samples were collected by using dry, plastic syringes, tourniquet was used to make the veins more prominent, then they were centrifuged at 4000 rpm to obtain the plasma samples, and stored in -20 until the analyzed.

3.2 Methods:

3.2.1 Estimation of plasma uric acid:

3.2.1.1 Principle of uric acid method:

Uric acid in the sample originate by means of the coupled reactions described below, acoloured complex that can be measured by spectrophotometer.

Uric acid +O $\xrightarrow{\text{Uricase}}$ Alantoin +CO_2 + H_2O_2

$2H_2O_2$ +4-Aminoantipyrine +DCFS $\xrightarrow{\text{Peroxidase}}$ Quinoneimine +$4H_2O$

3.2.1.2 Procedure of uric acid: **Appendix(x)**

3.2.2 Estimation of plasma magnesium:

3.2.2.1 Principle of magnesium method:

Magnesium in the sample reacts with xylidyl blue in alkaline medium forming a coloured complex that can be measured by spectrophotometer. EGTA is included in the reagent to remove calcium interference.

3.2.2.2 Procedure of magnesium method: Appendix (xi)

3.3 Quality control:

The precision and accuracy of all methods used in this study were checked by commercially prepared control (control serum normal level **1** and control serum abnormal level **11**) sample before application for the measurement of test and control samples.

3.4 Statistical analysis:

Data were analyzed to obtain means standard deviation and correlation of the sampling using statistical package for social science (SPSS) version 25 computer programs using independent t test and person correlation were applied for correlation between variables, result was expressed as Mean± SD and significant difference was expressed as P value ≤ **0.05).**

Chapter four

Results

4. Results

The result of biochemical determinant plasma of uric acid and magnesium in rheumatoid arthritis patients (cases) and control were given in tables and figures:

Table (4-1): Represent the mean of levels of plasma uric acid and magnesium in both stuɑy groups. The Mean ± SD values of plasma uric acid (mg/dL) to be (4.82 ± 36) versus (3.66 ±.05) with P value 0.000, plasma magnesium to be (2.95 ± 0.91) versus (2.26 ± 0.39) There were significant increased in uric acid and magnesium in rheumatoid arthritis patients compared to control group.

Table (4-2): Show the comparison between the means levels of plasma uric acid (mg/dL) and magnesium (mg/dL) according to gender. The Mean ± SD of plasma uric acid in male (4.93 ± 1.34) versus female (4.73 ± 1.40) with P value 0.623, plasma magnesium in male (2.86±0.92) versus female (4.73 ± 1.40) with P value 0.623 and there were insignificant difference between the mean of magnesium and uric acid according to gender.

Figure (4-1): show correlation between magnesium level and age of rheumatoid arthritis patient. The scatter showed insignificant correlation between magnesium level and age of rheumatoid arthritis patients (r = 0.014, P- value = 0.925).

Figure (4-2): show correlation between uric acid level and age of rheumatoid arthritis patient. The scatter showed insignificant correlation between uric acid level and age of rheumatoid arthritis patients (r=0.233, P = 0.101).

Figure (4-3): show correlation between magnesium (mg/dl) level and duration of rheumatoid arthritis patients. The scatter showed insignificant correlation between magnesium level and duration of rheumatoid arthritis patients (r = 0.076, P = 0.600).

Figure (4-4): show correlation between uric acid (mg/dl) and duration of rheumatoid arthritis patients. The scatter showed no correlation between uric acid level and duration of rheumatoid arthritis patients (r = 0.080, P= 0.600).

Figure (4-5): show correlation between magnesium (mg/dl) level and uric acid(mg/dl) level. The scatter showed no correlation between magnesium and uric acid levels(r= 0.167, P= 0.245).

Table (4-1) Comparison of uric acid and magnesium levels in rheumatoid arthritis patients group and control group:

Parameters	Case (Mean ± SD)	Control (Mean ± SD)	P-value
Uric acid (mg/dI)	4.82 ± 1.36	3.66 ± 1.05	0.000
Magnesium (mg/dI)	2.95 ± 0.91	2.26 ± 0.39	0.000

Results given in mean ± SD.

P-value ≤ 0.05 consider significant.

Table (4-2) Comparison of uric acid and magnesium according to gender.

Parameters	Male (Mean ± SD)	Female (Mean ± SD)	P-value
Uric acid (mg/dI)	4.93 ± 1.34	4.73 ± 1.40	0.623
Magnesium (mg/dI)	2.86 ± 0.92	3.02 ± 0.90	0.565

Results given in Mean ±SD.

P- value ≤ 0.05 consider significant.

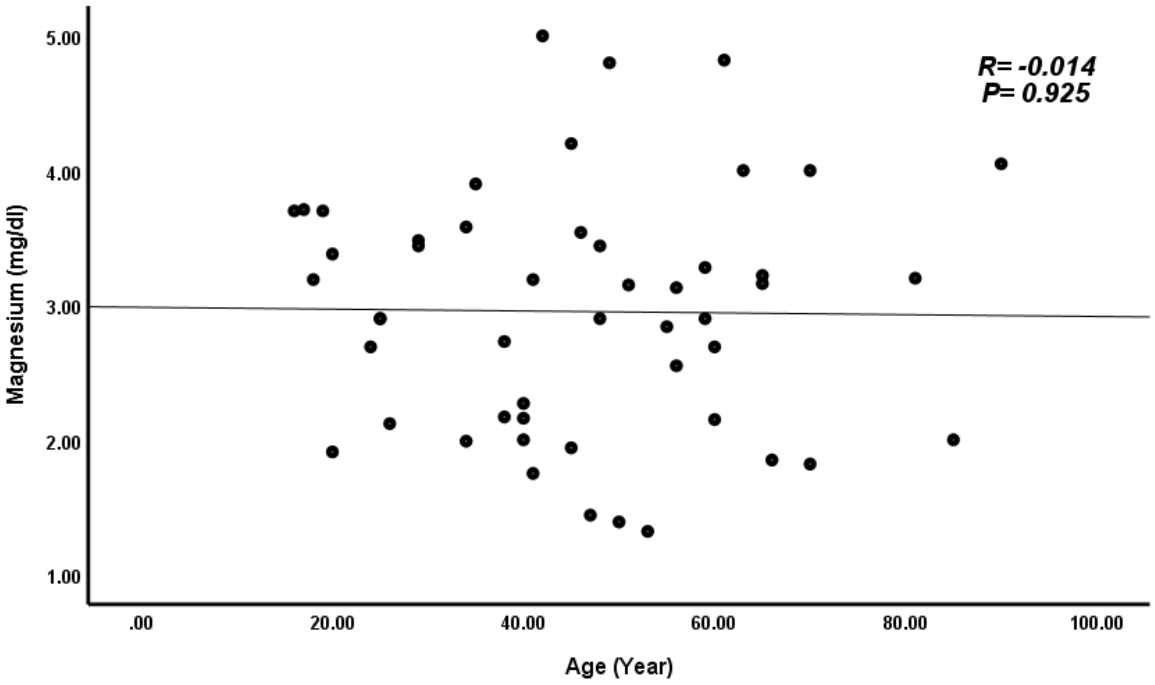

Figure (4.1) Correlation between magnesium level and age of rheumatoid arthritis patients (r= 0.014, P=0.925).

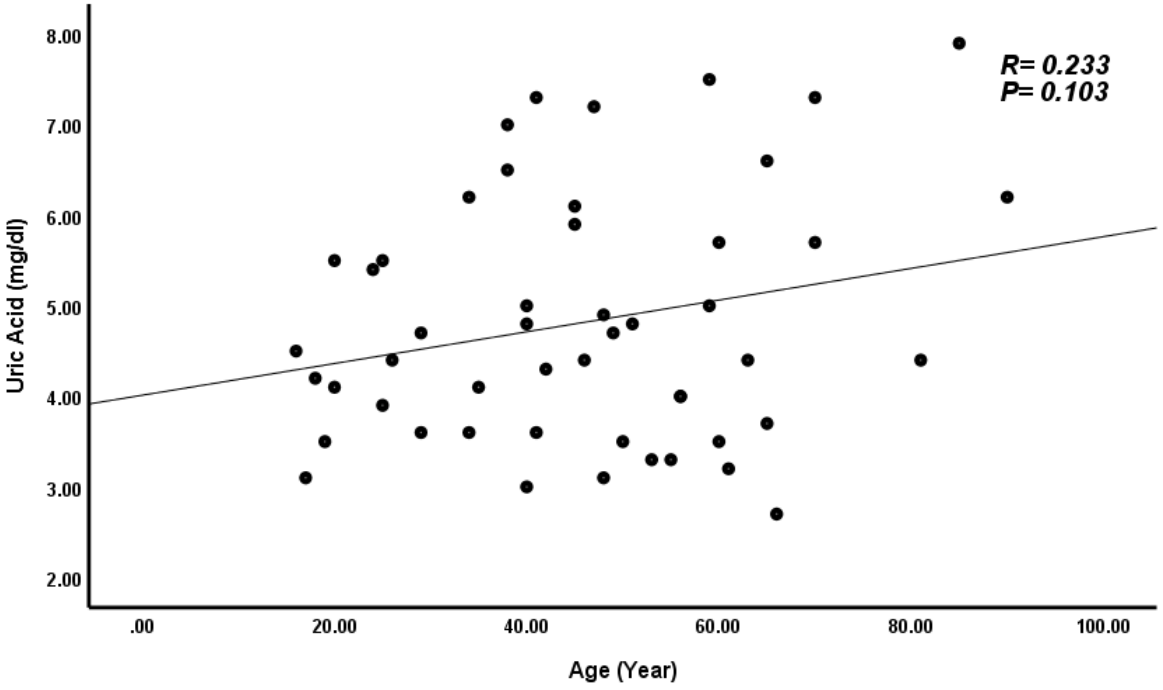

Figure (4.2) correlation between uric acid level and age of rheumatoid arthritis patients (r= 0.233, P= 0.103).

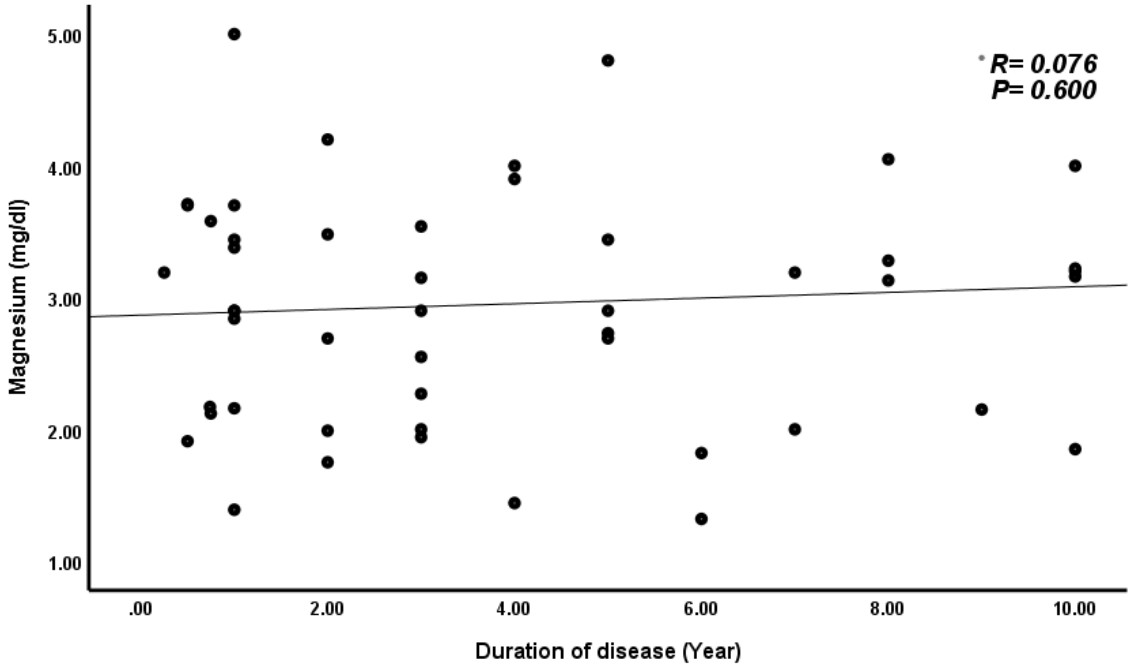

Figure (4.3) correlation between magnesium level and duration of rheumatoid arthritis patients (r= 0.076, P= 0.600).

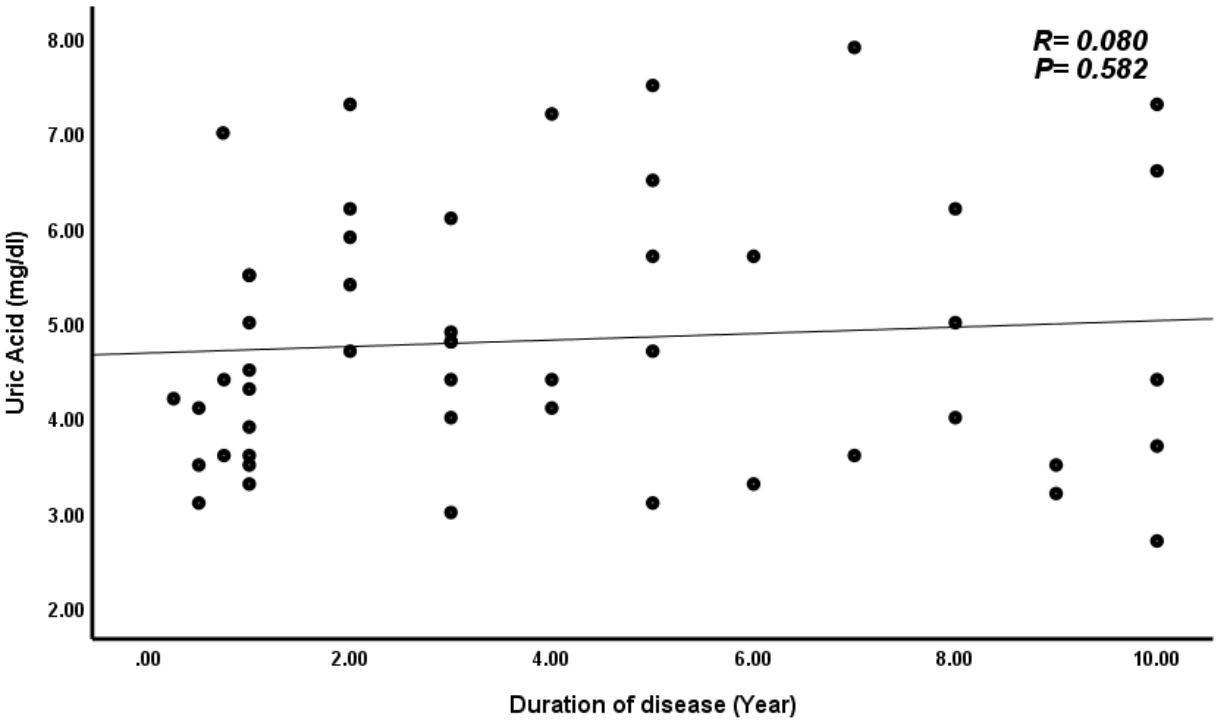

Figure (4. 4) correlation between uric acid level and duration of rheumatoid arthritis patients (r= 0.080, P= 0.582).

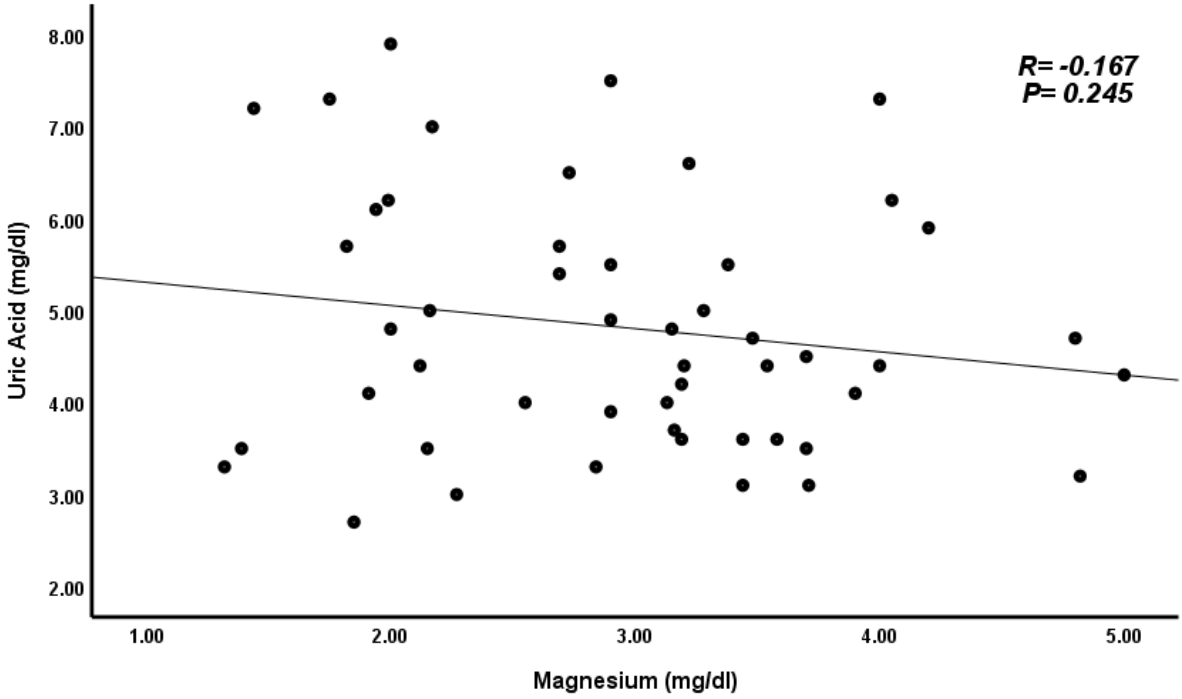

Figure (4.5) correlation between magnesium and uric acid levels of rheumatoid arthritis patients (r=- 0.167, P= 0.245).

Chapter five

Discussion, Conclusion and Recommendations

5. Discussion, Conclusion and Recommendations

5.1 Discussion

Rheumatoid arthritis is the most common inflammatory arthritis, is the major cause of disability and an risk for cardiovascular disease **(Gary S, 2003).** patients with rheumatoid arthritis have an excess burden of cardiovascular disease and a variety of pulmonary disorder **(Vokko P *et al.*, 2006).**

This study conducted to estimate plasma magnesium and uric acid levels in rheumatoid arthritis patients. Preliminary investigated and findings obtained from specially designed questionnaire revealed that plasma level of uric acid was significantly increased (P- value= 0.000).This result agreed with another result of study carried by **(Vilas U *et al.*, 2015)**, which demonstrate that elevated plasma uric acid level is associated with an increased risk of cardiovascular disease in rheumatoid arthritis patients. This result also agreed with another result of study carried by **(Vasileios F *et al.*, 2008).** Which demonstrate that plasma uric acid levels were significantly higher in rheumatoid arthritis patients compared to control. The use of rheumatoid arthritis drugs and dose of aspirin which is commonly given for primary and secondary cardiovascular disease prevention in elderly(RA) patients can lead to significant increase of serum uric acid **(Vasileios F *etal*.,2008)**.

The level of plasma magnesium was significantly increased (P- value= 0.000) in the Sudanese rheumatoid arthritis patients versus control subjects, this result disagreed with another result of study carried by **(Vilas U *et al.*, 2015),** which demonstrate that decreased plasma magnesium level may be more potent risk factors for CVD in newly diagnosed RA subjects. Rheumatoid arthritis causes magnesium deficiency due to chronic inflammation and autoimmune injury, decreased supply (lesser appetite) and reduced absorption caused by disturbances in the digestive system functions.

Also the findings of this study showed, there were insignificant weak positive correlation between age of rheumatoid arthritis patients and magnesium, uric acid (r= 0.014, P= 0.925), (r= 0.233, P= 0.101) respectively. This result disagreed with another result of study carried by **(Suad *et al.*, 2017)**. Which demonstrate that serum uric acid maintained a significant correlation with age. Also there were insignificant correlation between magnesium, uric acid and duration of disease(r= 0.076, P= 0.600), (r= 0.080,

P= 0.582).And there was insignificant correlation between plasma magnesium level and uric acid level.

5.2 Conclusions:

According to the results of this study it is concluded that:

Serum magnesium and uric acid are increased in rheumatoid arthritis patients. There are no correlation between; magnesium, uric acid and study variables (age and duration of disease).

5.3 Recommendations:

From the finding of this study it is recommended that:

1- Rheumatoid arthritis patients should be monitoring of magnesium and uric acid to prevent cardiovascular diseases.

2- Farther research is needed with large sample size to study other related parameters.

3-Rheumatoid arthritis patients with elevated uric acid may require screening for renal dysfunction and appropriate management.

References

References:

- **Assassi and Shervin. (2016).** Rheumatoid arthritis ,TNF inhibitors, and non-melanoma skin cancer *B.M.J*.352:472.
- **Altura, B.T.**, **Altura, B.T**.(**1991).** Measurement of ionized magnesium in whole blood, plasma and serum with a new ion-selective electrode in healthy and diseased human subjects. Manges Trace elem;10(2-4):90-98.
- **Assadi, F.(2010).** Hypomagnesia: an evidence based approach to clinical cases. Iranian *Journal* of Kidney disease ; 4(1): 13-19.
- **Bishop, Michael, L.I.I., Fody, Edward, P.I.I.I.I., Schoeff, Larry, E.(2010).** DNLM:1Chemistry, Clinical methods. Clinical chemistry Testes, QY 90c5776 616. 07,56-dc 22.
- **Cramp, F., Hewlett, S., Almedia, C., Kirwan, J.R., Choy, E.H. , Chalder ,T., et al.(2013).** Pharmacological interventions for fatigue in rheumatoid arthritis.The cochrance database of systematic reviews(8):322.
- **Cutolo, M., Kitas, G.D., van Riel, P.L. (2014).** Burden of disease in treated rheumatoid arthritis patients: going beyond the joint". Seminars in Arthritis and Rheumatisim; 43 (4): 479-88.
- **Doherty, M., Lanyon, P., Ralston, S.H.(2010).** Musculosketal Disorders-Davidson's Principal of Internal Medicine(20th ed).Elsevier: 1100-1106**.**
- **De Baaij, J.H.F., Henderop, J.G.J., Bindels, R.J.M. (2012).** Regulation of magnesium balance: Lessons learned from human genetic disease. *Clinical kidney J* ;5(1):15-24.
- **Edwards ,J.K., Camridge, G., Abrahams, V.M. (1999).** Do self-perpetuating B lymphocytes drive human autoimmune disease. Immunology.97 (2):188-96.
- **Egerer, K., Feist, E and Bur, M ., Ester, G.R. (2009).** The Serological diagnosis of RA; antibodies to citrullinated antigens, Dtsch. Arztebl ;106 (10) :159-63.
- **Elin, R.J.(1987).** Assessment of magnesium status. Clinical Chemistry;33(11):1965 70.
- **Fine, K.D., Santa Ana, C.A., Porter, J.L., Fortran, J.S. (1991).** Intestinal absorption of magnesium from food and supplements. The *Journal* of Clinical Investigation; 88 (2): 396-402.

- **Falkenburg, W., Van Schaardenburg, D., Ooijevaar-de Heer, P., Wolbink, G., Rispens, T. (2015).** Annals of the Rheumatoid Diseases ;74 (Suppl 2): 425-425.
- **Gary, S ., Firestein.(2003).** Nature; 423 (6937): 356-361
- **Handout on Health: Rheumatoid Arthritis .(2014).** National Institute of Arthritis and Musculoskeletal and skin diseases.
- **Keskin, G., Inal, A., Keskin, D., Pekel, A., Baysal, O., Dizuer and Sengul, A.(2008).** Diagnostic utility of anticyclic citrullinated peptide and anti – modified citrullinated vimentin antibodies in rheumatoid arthritis. Protein pept . let .15: 314-7.
- **Kielstein, J. I.**, **Davi, S. (2013).** Magnesium: The earth cure of AKI Nephrol Digital Transplant; 28: 785-710.
- **Lazano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K and Aoyans, V. (2012)"** Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010" Lancet;36(12):617.
- **Majithia, V., Geraci, S.A. (2007)."** Rheumatoid arthritis diagnosis and management". The American *Journal* of Medicine; 120 (11): 936-9.
- **Maguire, M.E., Cowan, J.A.(2002**). Magnesium chemistry and biochemistry. Biometals2002;15:203-210.
- **Mclnnes, I.B. (2016)."** Rheumatoid arthritis "(PDF). Lancet; 388(10055):2023-2038
- **Parveen Kumar and Michael Clark. (2013).** Clinical medicine, 7th edition: 525**.**
- **Panoulas, V. F., Milionis, H .J., Douglas, K.M.J., Nightingale, P., Kita, M.D., Klocke, R., Elisaf, M S., Kitas, G.D.(2007).** Rheumatology ;46 (9):1466-1470.
- **Romano, A.M.P. (2011).** Cellular magnesium Homeostasis. Archive of Biochemistry and Biophysics; 512(1):1-23.
- **Shah and Ankur. (2012).** Harrisons Principles of**.** Internal Medicine (18th ed)United States : McGraw Hill:2738.
- **Schueller-Weidekamm, Claudia. (2010).** Modern ultrasound methods yield stronger arthritis work up .Diagnostic Imaging:32**.**

- **Saris, N.E., Mervaala, E., Karppanen, H., Khawaja, J.A., Lewenstam, A. (2000).** Magnesium**.** An update on physiological, clinical and analytical aspects. Clinchim Acta Apr; 294(1-2):1-26.
- **Sihvonen, S., Korpela, M., Laippala, P., Mustonen, J., Pasternack, A. (2004).** Scandinaian *journal* of rheumatology ;33 (4), 221-227.
- **Selmi, C., De Santis, M., Gershwin ,M.E. (2011).** Liver involvement in subject with rheumatic disease .Arthritis Research and therapy;13(3):226.
- **Shils, N.E., Shike, M., Ross, A.C., Caballero, B., Cousins, R.J. (2006).**Modern Nutrition in Health and Disease. 10th edition. Lippincot Williams and Wilkins: 223-247.
- **Sugiyama, D., Nishimura, K., Tamaki, K., Tsuji, G., Nakazawa, T., Morinobu, A., Kumagai, S. (2010).** Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Annals of the Rheumatic Diseases;69(1): 70-81.
- **Shah and Ankur. (2012).** Harrisons Principles of internal medicine(18th ed).Unite: McGraw Hill: 2738.
- **Saag, K.G., Teng, G.G., Patkar, N.M., Anuntiyo, J., Finney, C., Curtis, J.R., Paulus, H.E., Mudano, A.,Pisu,M., Elkins-Melton, M., Outman, R., Allison, J.J., Suarez Almazur , M., Bridges, S.L., Chatham, W.W., Hocherg, M., Maclean, C., Mikuls, T., Moreland, L.W. (2008).** American college of Rheumatology recommendations and biologic disease modifying antirheumatic drugs in rheumatoid arthritis .Arthritis and rheumatisim 59(6):762-84
- **Singh, J.K., Saag, K.G., Bridges, S.L., A.K.I.E.A, Bannuru, Sullivan, M.C., Vaysbrot, E., Mc. Naughton, C., Osani, M., Shmerling, R.H., Curtis, J.R., Furst, D.E., Parks, D., Kavanaugh, A., Odell, J., King, C., Leong, A., Matteson, E.L., Schousboe, J.T., Drevlow, B., Ginsberg, .S, Grober, J., St Clair, E.W., Tindal , E., Miller, A.S., McAlindon,T. (2016).** Arthritis and Rheumatology.68(1): 1-26.
- **Spiegel, D.M.(2011).** Magnesium in chronic kidney disease: unanswered questions. Blood purify; 31(1-3):172-16.
- **Swaminathan, R.(2003).** Magnesium metabolism and it is disorder. Clinical Biochemistry; 24(2): 47-66.

- **Smolen, J.S., Aletaha, D, Mclnnes I.B.(2016).**" Rheumatoid arthritis"(PDF).Lancet; 388(10055):2023-2038.
- **Vormann, J. (2003).** Magnesium : nutrition and metabolism ;24: 27-37.
- **Visser, H. (2005).** Early diagnosis of rheumatoid arthritis . Best pract Res Clin Rheumatol ; 19 (1): 55-72
- **Vasileios, F., Panoulas, Karen, M.J., Douglas, Haralampos, J., Mmilionis, A., Stavropoulos- Kalinglou, Peter. (2007).** Rheumatology; 46 (9):1477-1482 .
- **Vasileios, F., Panoulas, H., Karen, MG., Douglas, Haralampos, J., Milionis, Peter, Niqhtinqale, Marina, D., Kita, Rainer. (2008).** *Journal* of Human hypertension ;22(3):177-182.
- **Vokko, P., Michael, T., Nurmohamed, Jo**s **W.R Twisk, Ben, A.C., Dijkmans, Alexandre, E., Voskuyl. (2006).** Arthritis research and therapy; 8 (5):151.
- **Vilas, U., Chavan, D.V.S.S Ramavataram, Payal, A., Patel, Mihir, P., Rupani. (2015).** *Journal* of clinical and diagnostic research; *J*CDR 9 (4):BC01.
- **World Health Organization (WHO)**. **(2017).** https://www . healthline . com.
- **Wasserman, B.R., Moskovich, R., Razi, A.E. (2011**). Rheumatoid arthritis of the cervical spine-clinical considerations(PDF). Bulletin of the NYU Hospital for joint Diseases. 69(2): 136-48.
- **Williams, M.A., Srikesavan,C., Hein, P.J., Bruce, J., Brosseau, L., Hoxey-Thomas, N and Lamb, S.E. (2018).** Exercise for rheumatoid arthritis of the hand. The cochrane database of systematic Reviews.7:3832.
- **Wasserman, A.M. (2011).** Diagnosis and management of rheumatoid arthritis. American Family physician.84(11) : 1245-52.
- **Weisinger, J.R.**, **Bellorin-Font, E. (1998).** Magnesium and phosphorus. The lancet; 352(9125):391-396.
- **Weisinger, J.R.**, **Bellorin-Font, E. (1998).** Magnesium and phosphorus. The lancet;352(9125):391-396.

Appendices

Appendix-1

Questionnaire

Sudan University of Science and Technology

College of Graduate Studies

Assessment of plasma uric acid and magnesium levels in Sudanese patients with rheumatoid arthritis in Khartoum state

General Information:

.Pt. No: ……..

. Age: …….

. Sex: …….

. Duration of disease: ……

Gender:

. Male: …….

. Female: ……

History:

Yes …. No…….

Results:

Serum Uric acid: ……

Serum magnesium……..