بسم الله الرحمن الرحيم

Republic of the Sudan
Ministry of Higher Education and scientific Research
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LEVEL OF URIC ACID AMONG PATIENTS WITH DIABETES MELLITUS TYPE TWO IN SHENDI LOCALITY IN RIVER NILE STATE IN SUDAN

By

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A thesis submitted in partial fulfillment for the requirements of Master Degree in Laboratory Sciences (*Clinical Chemistry)*

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الآيـــــة

بسم الله الرحمن الرحيم

قال تعالى :

﴿ قُلْ يَا عِبَادِيَ الَّذِينَ أَسْرَفُوا عَلَى أَنفُسِهِمْ لَا تَقْنَطُوا مِن رَّحْمَةِ اللَّهِ إِنَّ اللَّهَ يَغْفِرُ الذُّنُوبَ جَمِيعاً إِنَّهُ هُوَ الْغَفُورُ الرَّحِيمُ ﴾

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DECLARATION OF AUTHORSHIP

A – Student Declaration:

This research is my original work and has not been presented for a degree in any other University.

Signature: _____ Date: _____

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B – Supervisor Declaration:

This research has been submitted for review with our approval as a university supervisor.

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Dedication

To my parents …

Who encouraged me at all stages of life

To my husband …

To my brother and sisters …

For their unlimited support …

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I would like to express my sincere gratitude and thankfulness to my supervisor

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Abbreviations

DM	Diabetes Mellitus
GI	Gastrointestinal
hOAT1	Human Organic Anion Transporter
SUA	Serum Uric Acid
UA	Uric Acid
UAT	Urate Transporter
URAT	Urate/Anion Exchanger
WHO	World Health Organization
SPSS	Statistical Package for Social Sciences
TGL	Triglycerides
HDL	High Density Lipoproteins
LDL	Low Density Lipoproteins
USRUA	Urine/serum ratio Uric acid

ABSTRACT

Diabetes affects more than (120) million people world-wide and it is estimated that it will affect (220) million by the year (2020) and it is almost double in (2030). Diabetes mellitus is a syndrome of chronic hyperglycemia due to relative insulin deficiency, resistance or both. Uric acid acts as a natural antioxidant. Uric acid cannot scavenge all radicals, with superoxide as an example. Uric acid is an antioxidant only in the hydrophilic environment, which is probably a major limitation of the antioxidant function of uric acid. Thus the role of uric acid in the pathogenesis and the development of the diabetic complications is controversial. Several studies shown that hyperuricemia is one of the risk factors of metabolic syndrome and it clearly has a strong correlation between various components of diabetic dyslipidemia including increased LDL, TGL and reduced HD

The main objective of this study to examine the association between serum uric acid and prevalent diabetes in a representative sample of diabetic adults in Shendi Locality, River Nile state, Sudan, (2018)

This is case control study conducted in Shendi University in period between March and June 2018 to evaluated uric acid level in diabetes mellitus. (25ml) had been taken to be measured for serum uric acid from all study groups. Data collected, cleaned and analyzed using SPSS version (25.0).

This case control study covered 50 cases who diagnosed with diabetes type 2 and 50 healthy controls. Only 19% of the study participants were above 60 years in age among cases and all of them were from inside Shendi city. The majority of study groups were females (35%) in cases versus (40%) in controls), and only few proportion of them had no formal education (14% in cases and 4% in controls). More than half of the study participants were housewives (53%). Concerning the duration of the diabetes, the study found that nearly half of the study participants (44%) had been diabetes for (5 - 10 years) while third of them (34%) had duration

for less than five years. The common presentation among study groups, no study participants had complained from joint pain, renal disease, renal stone or vesical stone. Only 2% of the study participants (among cases group) had loin pain while 16% (among cases also) were hypertensive. This study found that the mean level of serum uric acid was 4.8 ± 1.2 mg/dl in all study participants. The serum uric acid level higher among DM cases (5.2 ± 1.4 mg/dl) compared with controls (4.4 ± 0.7 mg/dl). The difference in uric acid level was highly significant (p = 0.0003). The study didn't show any significant effect of age, gender on this difference. Generally, the study participants with DM (cases group) had (7%) of them with high level of uric acid compared with international references ranges.

The serum uric acid level measurements can be used as a powerful tool in identifying the diabetic condition and help an individual to make the necessary lifestyle adjustments so that the progression of the diseases can be stopped or may be infinitely delayed. A longitudinal prospective study is suggested to examine whether differences in the serum uric acid levels is adjusted to other possible confounding factors.

ملخص البحث

يؤثر مرض السكري على أكثر من (120) مليون شخص في جميع أنحاء العالم، ويقدر أنه سيؤثر على (220) مليون نسمة بحلول عام (2020م)، ويكاد يتضاعف في عام (2030م)، مرض السكري هو متلازمة ارتفاع السكر في الدم المزمن بسبب نقص الأنسولين النسبي أو مقاومته أو كليهما. أما حامض اليوريك هو مضاد للأكسدة الطبيعية. وبالتالي فإن دور حام اليوريك في التسبب في المرض ومضاعفات مرض السكري أمر مثير للنقاش .أظهرت العديد من الدراسات أن فرط حمض يوريك الدم هو أحد عوامل اختطار متلازمة التمثيل الغذائي ومن الواضح أنه يرتبط ارتباطًا وثيقًا مع فرط الدهون بما في ذلك زيادة الدهون الخفيفة الكثافة والعالية الكثافة وثلاثي الجليسريد.

دراسة العلاقة بين حمض اليوريك بالبلازما بين المصابين بالسكري من البالغين في منطقة شندي ، ولاية نهر النيل، السودان 2018م.

دراسة حالات مع حالات تحكم (حالات غير مصابة) أجريت في جامعة شندي في الفترة بين مارس ويونيو 2018م لتقييم مستوى حمض اليوريك مع داء السكري .تم أخذ 25 مل لقياس حمض اليوريك في الدم من جميع مجموعات الدراسة. البيانات التي تم جمعها وإعدادها وتحليلها باستخدام SPSS الإصدار 25.0.

شملت الدراسة (50) حالة مصابة بمرض السكري من النوع الثاني و(50) من الحالات غير المصابة. فقط (19٪) من المشاركين في الدراسة كانوا فوق سن (60) سنة من بين الحالات وجميعهم كانوا من داخل مدينة شندي. كانت أغلبية مجموعات الدراسة من الإناث (35% في الحالات مقابل 40% في الضوابط)، ولم يكن هناك سوى نسبة ضئيلة منها لم يتلقوا أن نوع من التعليم الرسمي (14% في الحالات و4% في الضوابط)، أكثر من نصف المشاركين في الدراسة كانوا ربات بيوت (53%)، وفيما يتعلق بمدة مرض السكري، وجدت الدراسة أن ما يقرب من نصف المشاركين في الدراسة (44%) كانوا مصابين بداء السكري لمدة (5 – 10 سنوات) في حين أن الثلث منهم (34%) لديهم المرض منذ مدة أقل من خمس سنوات الأعراض الشائعة بين مجموعات الدراسة، لم يشتك أي من المشاركين في الدراسة من آلام المفاصل، أو أمراض الكلى، أو الحصاوي الكلوية أو الحصاوي بالمثانة (2%) فقط من المشاركين في الدراسة(بين مجموعة الحالات) لديهم ألم في احد الجوانب بالبطن بينما (16%) من بين الحالات أيضا كانوا يعانون من ارتفاع ضغط الدم. وجدت هذه الدراسة أن متوسط مستوى حمض اليوريك في المصل كان 1.2 ± 4.8 ملغم / ديسيلتر عند جميع المشاركين في الدراسة. مستوى حمض اليوريك في المصل أعلى بين الحالات (1.4 ± 5.2 ملغ / دل .) كان الفرق في مستوى حمض اليوريك ذو دلالة إحصائية ± 0.7

4.4 ملغ / ديسيلتر مقارنة مع غير المرضى .(p = 0.0003) لم تظهر الدراسة أي تأثير مهم من العمر والجنس على هذا الفرق في مستوى حمض اليوريك.

يمكن استخدام قياسات مستوى حمض اليوريك في المصل كوسيلة مقبولة لتحديد حالة مرضى السكري ومساعدة المريض على إجراء المعالجات والتغييرات الضرورية على نمط الحياة بحيث يمكن إيقاف تطور المرض .يقترح عمل دراسة استطلاعية على مدى زمني طويل لدراسة ما إذا كانت الاختلافات في مستويات حمض اليوريك في المصل يمكن أن تتأثر بعوامل أخرى محتملة.

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1. Introduction

Diabetes affects more than 120 million people world-wide and it is estimated that it will affect 220 million by the year 2020 and it is almost double in 2030 [(1)]. Diabetes mellitus is a syndrome of chronic hyperglycemia due to relative insulin deficiency, resistance or both [(1-2)].

Hyperuricemia associated with glucose intolerance due to various mechanism, however, the most important is the association between insulin and renal resistance to absorption of urates. Patients with diabetes mellitus are at greater risk of developing cardiovascular diseases because of lipid changes [1-2]. It has been well observed that controlling diabetes and lipid levels provide great benefit to diabetic patients [(2)].

Uric acid acts as a natural antioxidant. Serum uric acid cannot scavenge all radicals, with superoxide as an example. Uric acid is an antioxidant only in the hydrophilic environment, which is probably a major limitation of the antioxidant function of uric acid [[3]].

Thus the role of UA in the pathogenesis and the development of the diabetic complications is controversial. Several studies showed that hyperuricemia is one of the risk factors of metabolic syndrome and it clearly has a strong correlation between various components of diabetic dyslipidemia including increased LDL, TGL and reduced HDL [[3-4]].

Recently, studies that have been performed in different populations, i.e., European, American, African and Chinese, have indicated that elevated serum UA levels are a strong, independent risk factor for type 2 diabetes mellitus, and this finding has been confirmed in recently published systematic reviews and meta-analyses. As indicated by the findings of these studies, higher concentrations of uric acid

increase the risk of developing diabetes regardless of the presence of other risk factors [4].

Potential pathogenic factors that link UA to the development of type 2 diabetes include the following: endothelial dysfunction, impaired nitric oxide synthesis, oxidative stress, and subclinical inflammation.[3-4] These factors are expected to lead to insulin resistance and subsequent carbohydrate metabolism abnormalities. The primary causes of increased UA serum levels remain unclear but may include diet-related factors, such as excessive intakes of fructose and products containing purines [4].

The value of elevated levels of UA in serum as a risk factor for diabetes development is still under scrutiny. [5] Recent data suggest that clearance of UA is being reduced with increase in insulin resistance and UA as a marker of prediabetes period. However, conflicting data related to UA in serum of patients with Type 2 diabetes prompted researchers to study the urine/serum ratio of UA levels (USRUA) in these patients and healthy controls [5].

Furthermore, studies showed that there was a trend of correlation of USRUA value with the blood glucose levels in diabetic patients, which was more prominent in diabetic men than in women. With aging, levels of uric acid increased in serum of diabetic patients, and this effect was also more profound in male than in female diabetics [6].

A new study suggests that serum uric acid (SUA) is an independent predictor of mortality in patients with type 2 diabetes. The association remains significant regardless of sex, renal function, or diuretic use. Prospective studies are needed to determine whether reduction in uric acid will reduce the risk diabetes mellitus [7].

However, only limited data are available on the way uric acid relates to adverse outcomes in type 2 diabetes patients. Part of the problem has been clarifying the relationship between uric acid and glucose. When glucose is high, uric acid tends

to go down, so it's harder to determine the effect of uric-acid levels in people with diabetes than in non-diabetics [6-7].

So, finally, Serum uric acid, an end product of purine metabolism, has been shown to be associated with an increased risk of hypertension, cardiovascular disease, and chronic kidney disease in previous epidemiological studies. Also, elevated levels of uric acid are a risk factor for peripheral arterial disease, insulin resistance, and components of the metabolic syndrome [7].

However, the putative association between serum uric acid levels and diabetes mellitus is not clear. Some studies reported that there is a positive association between high serum uric acid levels and diabetes, whereas other studies reported no association, or an inverse relationship [7].

In this context, the main purpose of our study was to examine the association between serum uric acid and prevalent diabetes in a representative sample of diabetic adults.

1.2 Justification

Many Studies demonstrated a positive relationship between serum glucose and serum uric acid concentrations up to about 8.0 mmol/l; at higher levels of glucose, serum uric acid decreased. It probably reflected the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyper-glycaemia and glycosuria [16].

Within the local context, the elevated values of uncorrelated serum uric acid, precludes them to be useful for consideration as consistent predictive indicator (s) for a various uric acid related health problem among diabetic patients.

According to the best knowledge of the researcher, there is no available of published research work that assess in this context, the main purpose of our study was to examine the association between serum uric acid and prevalent diabetes in a representative sample of diabetic adults in Sudan within the previous few years.

Moreover, this study may help to offer valuable rationalized information for variety of beneficiaries such as the diabetic patients themselves and their families by availing the updated information about the possible levels of uric acid among diabetic patients.

Similarly, for laboratory specialists, pathologists, endocrinologists and relevant medical staff; in order to be more critical in investigation to be more precise in overall management outcome for the diabetic patients in Sudan.

1.3 Objectives

1.3.1General objective:

To evaluate uric acid levels in diabetes mellitus individuals.

1.3.2 Specific Objectives:

1. To estimate the differences on uric acid according to the age.
2. To estimate the variation according to the frequency of the treatment.
3. To estimate the variation according to gender.
4. To estimate the measure of uric acid to compared it with reference interval.

Chapter Two

Literature Review

2. Literature Review

2.1 Diabetes Mellitus

Diabetes mellitus consists of an array of dysfunctions characterized by hyperglycemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. [8] Poorly controlled diabetes is associated with an array of microvascular, macrovascular, and neuropathic complications [8-9].

Microvascular complications of diabetes include retinal, renal, and possibly neuropathic disease. Macrovascular complications include coronary artery and peripheral vascular disease [9]. Diabetic neuropathy affects autonomic and peripheral nerves. Unlike patients with type 1 diabetes mellitus, patients with type 2 are not absolutely dependent on insulin for life. This distinction was the basis for the older terms for types 1 and 2, insulin dependent and non–insulin dependent diabetes [10].

However, many patients with type 2 diabetes are ultimately treated with insulin. Because they retain the ability to secrete some endogenous insulin, they are considered to require insulin but not to depend on insulin. Nevertheless, given the potential for confusion due to classification based on treatment rather than etiology, the older terms have been abandoned [10 -11].

Another older term for type 2 diabetes mellitus was adult-onset diabetes. Currently, because of the epidemic of obesity and inactivity in children, type 2 diabetes mellitus is occurring at younger and younger ages [11] . Although type 2 diabetes mellitus typically affects individuals older than 40 years, it has been diagnosed in children as young as 2 years of age who have a family history of diabetes. In many communities, type 2 diabetes now outnumbers type 1 among children with newly diagnosed diabetes [11].

Diabetes mellitus is a chronic disease that requires long-term medical attention to limit the development of its devastating complications and to manage them when they do occur. It is a disproportionately expensive disease. [12] The direct and indirect costs of diagnosed diabetes were estimated to be $245 billion; people with diagnosed diabetes had average medical expenditures 2.3 times those of people without diabetes [12].

Diabetes prevalence ranged from 2.6% in rural Sudan to 20.0% in urban Egypt. Diabetes prevalence was significantly higher in urban areas than in rural areas. Undiagnosed diabetes is common in Northern Africa with a prevalence ranging from 18% to 75%. The prevalence of chronic diabetes complications ranged from 8.1% to 41.5% for retinopathy, 21% to 22% for albuminuria, 6.7% to 46.3% for nephropathy and 21.9% to 60% for neuropathy [13].

2.2 Uric Acid

The final breakdown product of purine catabolism in humans is uric acid. The liver and intestinal mucosa produce most of the uric acid. [14] The kidneys eliminate two thirds of the uric acid, with the GI tract excreting the other one third. Uric has a pKa of 5.75 and 10.3 and thus is a weak acid. The ionized forms of uric acid, urates, are present in synovial fluid and in plasma; approximately 98% exists as monosodium urate, with a pH of 7.4 [14] .

In hospitalized patients, the most common causes of uric acid elevation are azotemia, metabolic acidosis, gout, diuretic use, and myelolymphoproliferative diseases [14-15].

Approximately 80% of patients with elevated serum triglyceride levels also have increased serum uric acid levels. Various ethnic groups, such as Pima Indians, Blackfoot Indians, New Zealand Maoris, and Filipinos, have increased serum uric acid levels. About 5% of hospitalized patients have decreased serum uric acid

levels, with a postoperative state, diabetes mellitus, drugs, and SIADH being the most common causes [16].

One end product of nucleoprotein metabolism is uric acid, which is excreted in the urine. Hyperuricemia (plasma urate concentration >6.8 mg/dL) can result from decreased elimination or uric acid, increased formation of uric acid, or a combination of these processes. In general, hyperuricemia is present in 2-13.2% of ambulatory adults and is even more common in hospitalized patients [17].

Urate levels correlate with the risk developing gouty arthritis or urolithiasis. Chronically elevated urine uric acid levels predispose some individuals to develop urolithiasis, gouty arthritis, and renal dysfunction. Because pure uric acid urinary stones typically are radiolucent, they may not be detected with plain abdominal radiography but can be detected with non contrast CT scanning. Uric acid levels are affected by age, sex, and renal function [18].

2.3 Pathophysiology

Uric acid in the blood is saturated at 6.4-6.8 mg/dL at ambient conditions, with the upper limit of solubility placed at 7 mg/dL. Urate is freely filtered at the glomerulus, reabsorbed, secreted, and then again reabsorbed in the proximal tubule. The recent cloning of certain urate transporters will facilitate the understanding of specific mechanism by which urate is handled in the kidney and small intestines [19].

A urate/anion exchanger (URAT1) has been identified in the brush-border membrane of the kidneys and is inhibited by an angiotensin II receptor blocker, losartan. [19] A human organic anion transporter (hOAT1) has been found to be inhibited by both uricosuric drugs and antiuricosuric drugs, [4] while another urate transporter (UAT) has been found to facilitate urate efflux out of the cells [20]. These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate. Underexcretion accounts for most causes of

hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and, finally, post-secretary reabsorption. Consequently, altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption [20].

Overproduction accounts for only a minority of patients presenting with hyperuricemia. The causes for hyperuricemia in overproducers may be either exogenous (diet rich in purines) or endogenous (increased purine nucleotide breakdown). A small percentage of overproducers have enzymatic defects that account for their hyperuricemia [20].

2.4 Influencing factors

Factors that partly account for an increased prevalence of gout and hyperuricemia in African and Asian countries include alcohol consumption, obesity, and hypertension; however, prevalence is also influenced by genetic factors. One mechanism by which alcohol is associated with hyperuricemia is that it increases adenine nucleotide breakdown and increases lactate levels in the blood [21].

With regard to plasma uric acid levels, purines also contribute to an increase in plasma uric acid in beer drinkers. Further, dehydration and alcoholic ketoacidosis lead to increases in serum uric acid levels. By accelerating adenine nucleotide breakdown and possibly weakly inhibiting xanthine dehydrogenase activity, ethanol also raises plasma concentrations and urinary excretion of hypoxanthine and xanthine [22].

Experimental evidence in rats has shown that hyperuricemia can increase systemic blood pressure, renal dysfunction, progressive renal scarring, proteinuria, and vascular disease. Evidence supports the idea that hyperuricemia may be a key mechanism for activation of the renin-angiotensin and cyclooxygenase-2 (COX-2) systems in progressive renal disease [21-22].

Whether uric acid acts as an independent risk factor for heart disease is controversial. However, data have elucidated important information on the complex relationships between hyperuricemia, gout, and co-morbid conditions, particularly the association of serum urate levels with cardiovascular morbidity and mortality [22].

2.4.1 Indications

Indications are as follows

- To monitor gout treatment
- To monitor chemotherapeutic treatment of neoplasms to avoid renal urate deposition and possible renal failure[23].

2.4.2 Reference Range

- Men: 3.6 – 7.7 mg/dL.
- Women: 2.5-6.8 mg/dL. [24].

Serum urate concentrations in most children range from 3-4 mg/dL. During male puberty, levels begin to rise. Female levels remain low until menopause. Adult men have mean serum urate values of 6.8 mg/dL, and premenopausal women have mean serum urate values of 6 mg/dL [24]. Values for women increase after menopause and approximate those of men. Throughout adulthood, concentrations rise steadily and can vary with height, blood pressure, body weight, renal function, and alcohol intake [24].

2.4.3 Interpretation of serum uric acid level

Elevated uric acid levels can be seen in the following [25]:

- Gout.
- Renal failure.

- Destruction of massive amounts of nucleoproteins (leukemia, anemia, chemotherapy, toxemia of pregnancy, psoriasis, sickle cell anemia, hemolytic anemia, polycythemia, resulting pneumonia).
- Drugs (especially diuretics, barbiturates).
- Lactic acidosis.
- Hypothyroidism.
- Chronic kidney disease.
- Parathyroid diseases.
- Low-dose salicylates.
- Metabolic acidosis.
- Diet (high-protein weight-reducing diet, alcohol, liver, and sweetbread).
- Chronic lead poisoning.
- Down syndrome.
- Polycystic kidney disease.
- Sarcoidosis.
- Lesch-Nyhan syndrome.
- von Gierke disease.
- Chronic berylliosis [2].

Decreased uric acid levels can be seen in the following:

- Drugs such as uricosuric drugs (salicylates, probenecid, allopurinol), estrogen, phenothiazines, indomethacin, corticotrophin.
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatremia.
- Wilson disease.
- Fanconi syndrome.
- Acromegaly.

- Celiac disease.
- Xanthinuria [25].

2.4.4 Collection and Panels

Tiger top or Red-Top tube.

2.4.5 Limitations

Limitations of uric acid testing are as follows:

- Methodological interference and in cases of vitamin C, levodopa, and alpha-methyldopa.
- Early purine-rich diet (eg, liver, kidney, sweetbread).
- Severe exercise increases uric acid level.
- Rapid degradation of uric acid, which occurs at room temperature in the plasma of patients with tumor lysis syndrome treated with rasburicase (Blood should be collected in prechilled tubes containing heparin, and it should be immediately immersed in an ice-water bath and centrifuged in a precooled centrifuge. The separated plasma should then be maintained in an ice-water bath and analyzed within 4 hours of collection.) [26].

2.5 Uric acid levels in diabetes mellitus

Identifying risk factors for the development of type 2 diabetes is essential for its early screening and prevention. Serum uric acid (SUA) level has been suggested to be associated with risk of type 2 diabetes. Biologically, uric acid (UA) plays an important role in worsening of insulin resistance in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake [27] .

However, hyperinsulinemia as a consequence of insulin resistance causes an increase in SUA concentration by both reducing renal UA secretion and accumulating substrates for UA production. Therefore, it remains controversial

whether SUA is independently associated with the development of type 2 diabetes. The aim of our meta-analysis was to summarize the association between SUA level and risk of type 2 diabetes derived from previously published cohort studies and to examine the effect of study characteristics on this association [28].

Raised serum uric acid has been associated with a lot of diseases like hypertension, cardiovascular diseases, chronic kidney disease, peripheral vascular diseases and metabolic disorders. But the association of serum uric acid levels to that of diabetes mellitus has not been successfully understood [28].

Elevated serum uric acid (SUA) levels (i.e. hyperuricaemia) have been associated with metabolic syndrome (MetS) and cardiovascular disease (CVD) morbidity and mortality. Elevated SUA levels predict the onset of type 2 diabetes (T2DM). SUA levels are increased during the early stages of impaired glucose metabolism. Furthermore, in diabetic patients, hyperuricaemia has been linked to both micro- and macrovascular complications [28].

2.6 Relevant studies

Recently, a variety of publications closely examining this association showed discordant results. Thus, the relationship between SUA and DM still remains controversial [28] .

In a study conducted in Sudan by Assmalli and Hamza, in which they investigated the serum levels of Uric acid and other markers in Sudanese residents in UAE Diagnosed with Diabetes Mellitus Type 2. They found that of 100 participants 50 with type 2 diabetes as test control and 50 from healthy volunteer as control group, age and gender of test group was matched with the control group, Male account as 96% (n=50) in the test group and 98 %(n=50) from control group, while females account 4% (n=50) from test group and 2% (n=50) from control group. Significant difference between the mean of Urate levels in test group and control group (295$\pm$123) versus (358$\pm$61) p=0.000 [29].

A study by Chakrapani et al from Pakistan, addressed the correlation of serum uric acid levels in diabetes mellitus and its significance in pre-surgical evaluation. The results show a rise in the serum uric acid levels in the pre-diabetic and not so much in the non-diabetics and the confirmed diabetics. They concluded that the serum uric acid level measurements can be used as a powerful tool in identifying the pre-diabetic condition and help an individual to make the necessary lifestyle adjustments so that the progression of the diseases can be stopped or may be infinitely delayed [30] .

A systematic review conducted by Yi-Li et al from China for elevation of serum uric acid and incidence of type 2 diabetes. In this study, a total of 970 articles were retrieved from the searches. Sixteen publications of cohort studies containing 61,714 participants were included. The pooled RR was 1.131 (95% CI: 1.084–1.179) with significant heterogeneity among studies (I2 = 51.9%, P = 0.018). Adjusted RR to evaluate the stability of the relationship between SUA and T2DM in the sensitivity analysis was similar (RR = 1.140, 95% CI: 1.087–1.197), with statistically significant heterogeneity (I2 = 54.5%, P = 0.015). Stratified analysis and meta-regression showed that the positive relationship remained irrespective of age, sex, region, and adjustment for confounding factors including body mass index, fasting blood glucose, systolic blood pressure, diastolic blood pressure, alcohol consumption, smoking, blood cholesterol, waist circumference, fatty liver, and drugs affecting SUA. The paper concluded that although SUA is independently associated with development of T2DM, insulin resistance increased as the baseline SUA concentration increased; thus, the correlation between SUA and T2DM requires further evaluation and the baseline insulin resistance status should also be considered [31].

Satoru Kodama et al from Japan assessed the association between serum uric acid and development of type 2 diabetes. This study found 11 cohort studies (42.834

participants) that reported 3,305 incident cases of type 2 diabetes during follow-up periods ranging from 2.0 to 13.5 years. The pooled RR of a 1 mg/dl increase in SUA was 1.17 (95% CI 1.09–1.25). Study results were consistently significant (i.e., >1) across characteristics of participants and study design. Publication bias was both visually and statistically suggested (P = 0.03 for Egger's test, 0.06). Adjustment for publication bias attenuated the pooled RR per mg/dl increase in SUA (RR 1.11 [95% CI 1.03–1.20]), but the association remained statistically significant (P = 0.009). They concluded that SUA level is positively associated with the development of type 2 diabetes regardless of various study characteristics. Further research should attempt to determine whether it is effective to utilize SUA level as a predictor of type 2 diabetes for its primary prevention [32] .

A study by Abbas Dehghan from **Netherlands** investigated the high Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes. The study found that the age- and sex-adjusted hazard ratios (HRs) (95% CIs) for diabetes were 1.30 (0.96–1.76) for the second, 1.63 (1.21–2.19) for the third, and 2.83 (2.13–3.76) for the fourth quartile of serum uric acid, in comparison with the first quartile. After adjustment for BMI, waist circumference, systolic and diastolic blood pressure, and HDL cholesterol, the HRs decreased to 1.08 (0.78–1.49), 1.12 (0.81–1.53), and 1.68 (1.22–2.30), respectively. The results of this population-based study suggest that serum uric acid is a strong and independent risk factor for diabetes. Serum uric acid is positively associated with serum glucose in healthy subjects. However, this association is not consistent between healthy and diabetic individuals, as a low serum level of uric acid is reported in the hyperglycemic state. Since most individuals experience a phase of impaired glucose tolerance before progression to diabetes, it is not clear whether raised serum uric acid predicts the risk of type 2 diabetes. The paper investigated the association between serum uric acid and risk

of diabetes in the Rotterdam Study, a large population-based, prospective cohort study among subjects aged 55 years and older [33] .

In Canada, a prospective study conducted by Vidula Bhole et al investigated the Serum Uric Acid Levels and the Risk of Type 2 Diabetes. The researchers identified 641 incident cases of diabetes in the original cohort and 497 cases in the offspring cohort. The incidence rates of diabetes per 1000 person-years for serum uric acid levels <5.0, 5.0-5.9, 6.0-6.9, 7.0-7.9 and ≥8.0 mg/dL were 3.3, 6.1, 8.7, 11.5, and 15.9 in the original cohort, and 2.9, 5.0, 6.6, 8.7, 10.9 in the offspring cohort, respectively (P-values for trends <0.001). Multivariable RRs per mg/dL increase in serum uric acid levels were 1.20 (95% CI, 1.11 to 1.28) for the original cohort and 1.15 (95% CI, 1.06 to 1.23) for the offspring cohort. These prospective data from two generations of the Framingham Heart Study provide evidence that individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes independent of other known risk factors. These data expand on cross-sectional associations between hyperuricemia and the metabolic syndrome, and extend the link to the future risk of type 2 diabetes [34] .

Other study from **Bosnia** by Causevic et al investigated the relevance of uric Acid in progression of type 2 diabetes mellitus. This study showed significantly elevated USRUA levels in patients with Type 2 diabetes, a negative USRUA correlation with the blood glucose levels in diabetic patients, and an effect of sex and age on the uric acid levels. Since literature data suggest a strong genetic effect on UA levels, it would be pertinent to perform further, possibly genetic studies, in order to clarify gender and ethnic differences in UA concentrations [35] .

In American study, addressed the association between Serum Uric Acid Levels and Diabetes Mellitus by Pavani Bandaru et al. They examined the association between serum uric acid levels and diabetes mellitus in participants from the third National Health and Nutrition Examination Survey (52.5% women). Serum uric

acid levels were categorized into quartiles. Diabetes mellitus was defined as fasting glucose ≥126mg/dL, non fasting glucose ≥200mg/dL, or use of oral hypoglycemic medication or insulin. In multivariable logistic regression models, They found that higher serum uric acid levels were inversely associated with diabetes mellitus after adjusting for age, sex, race/ethnicity, education, smoking, alcohol intake, body mass index, hypertension, and serum cholesterol. Compared to quartile 1 of serum uric acid, the odds ratio (95% confidence interval) of diabetes mellitus was 0.48 (0.35–0.66). The results were consistent in subgroup analysis by gender and hypertension status. Higher serum uric acid levels were inversely associated with diabetes mellitus in a representative sample of US adults[36].

Chapter Three

Materials and Methods

3. Materials and Methods

3.1 Study design

This is descriptive cross -sectional study conducted in Shendi locality in period between March and August 2018 to evaluated uric acid level in diabetes mellitus.

Study place

Conducted in Shendi.

Study period

In period between March and August 2018.

3.2 Study population

This study involved Shendi locality. Study group was selected randomly of 100 subjects from people 50 of diabetes and 50 as control.

Chapter Four

Results

4. Results

Table (1): The distribution of the study participants according to their study groups (n = 100, 50 Cases + 50 Controls)

Study groups	Frequency	Percent
Cases (Diagnosed with diabetes	50	50.0
Control (Healthy)	50	50.0
Total	100	100.0

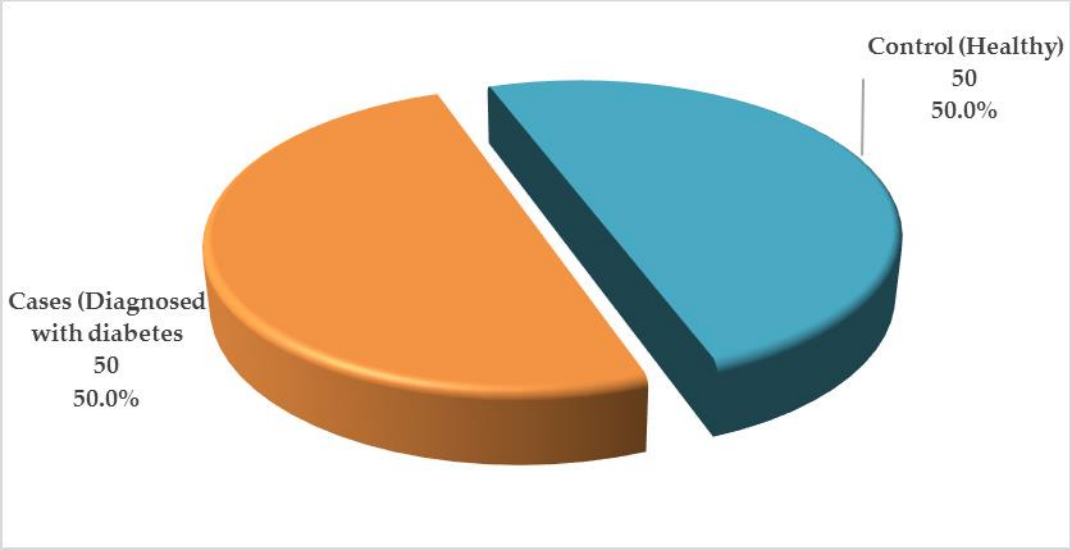

Figure (1): The distribution of the study participants according to their study groups (n = 100, 50 Cases + 50 Controls)

Table (2) The distribution of the study participants according to their age (n = 100, 50 Cases + 50 Controls)

Age - years	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
<40	3	3.0	13	13.0	16	16.0
40 – 50	10	10.0	17	17.0	27	27.0
51 – 60	18	18.0	8	8.0	26	26.0
61 – 70	8	8.0	6	6.0	14	14.0
71 – 80	7	7.0	6	6.0	13	13.0
81 – 90	4	4.0	0	0.0	4	4.0
Total	50	50.0	50	50.0	100	100.0

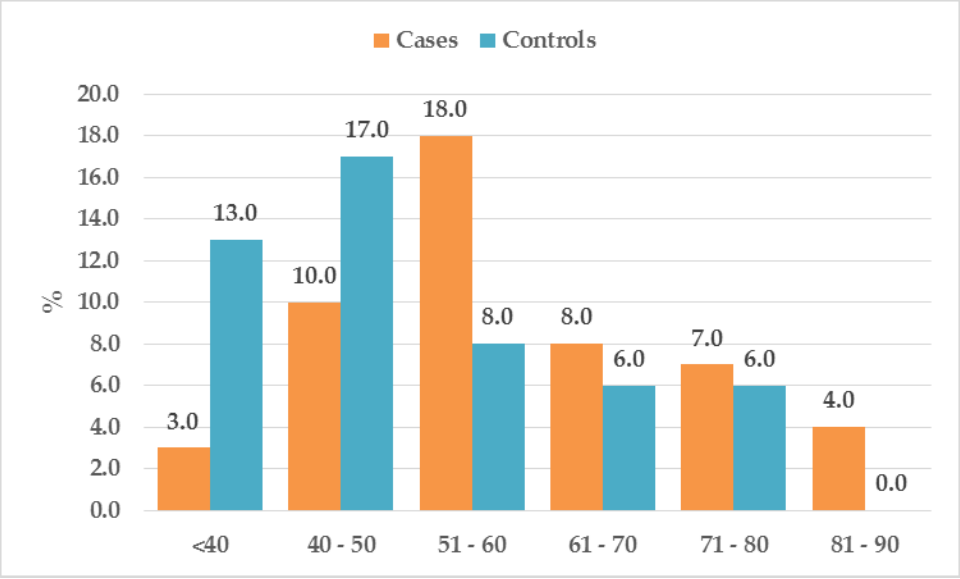

Figure (2) The distribution of the study participants according to their age (n = 100, 50 Cases + 50 Controls).

Table (3) The distribution of the study participants according to their residence (n = 100, 50 Cases + 50 Controls)

Residence	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Outside Shendi	0	0.0	0	0.0	0	0.0
Inside Shendi	50	50.0	50	50.0	100	100.0
Total	50	50.0	50	50.0	100	100.0

Table (4) The distribution of the study participants according to their gender (n = 100, 50 Cases + 50 Controls)

Gender	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Male	15	15.0	10	10.0	25	25.0
Female	35	35.0	40	40.0	75	75.0
Total	50	50.0	50	50.0	100	100.0

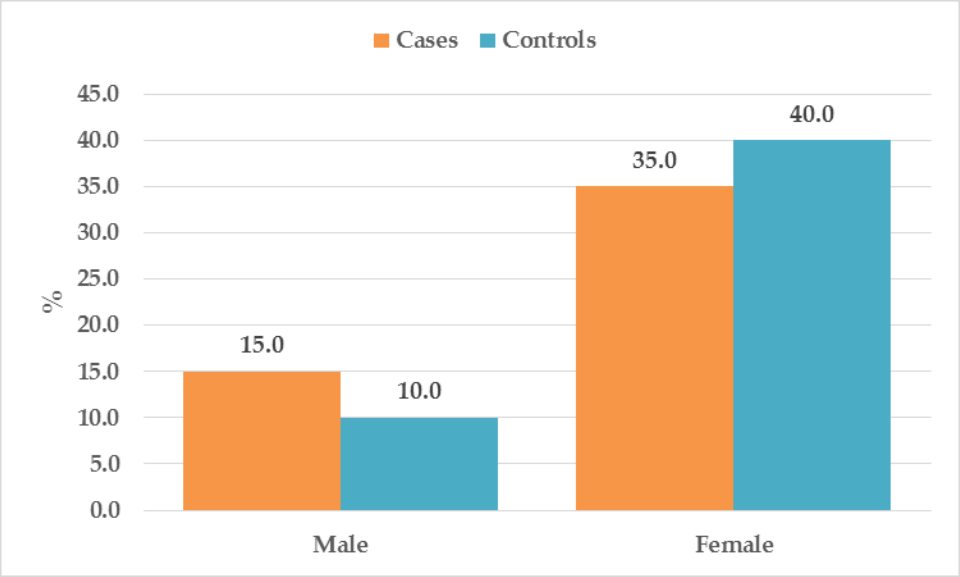

Figure (3) The distribution of the study participants according to their gender (n = 100, 50 Cases + 50 Controls)

Table (5) The distribution of the study participants according to their education (n = 100, 50 Cases + 50 Controls)

Education	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Illiterate	14	14.0	4	4.0	18	18.0
Primary	11	11.0	10	10.0	21	21.0
Secondary	13	13.0	10	10.0	23	23.0
University	12	12.0	26	26.0	38	38.0
Total	50	50.0	50	50.0	100	100.0

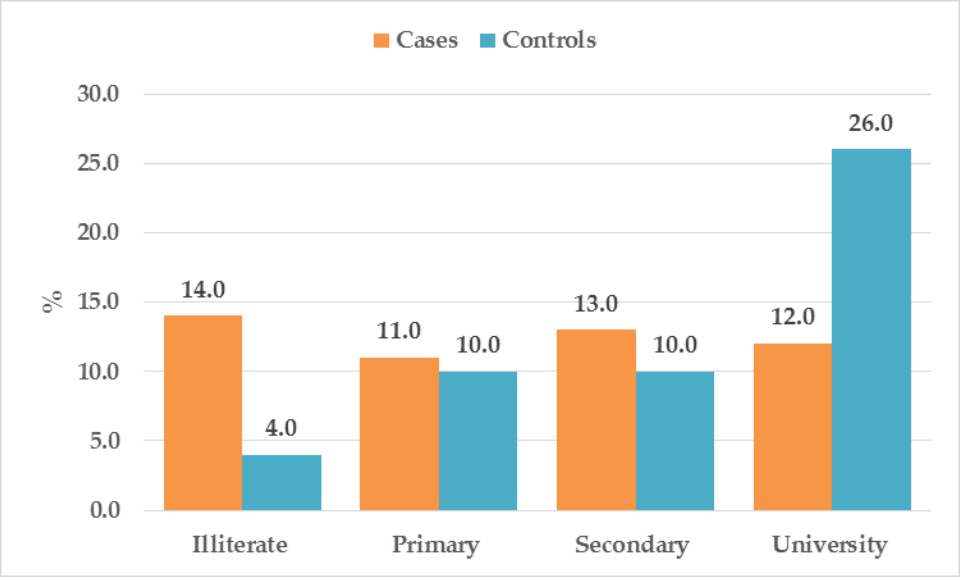

Figure (4) The distribution of the study participants according to their education (n = 100, 50 Cases + 50 Controls)

Table (6) The distribution of the study participants according to their Occupation (n = 100, 50 Cases + 50 Controls)

Occupation	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Housewife	26	26.0	27	27.0	53	53.0
Officer	16	16.0	18	18.0	34	34.0
Worker	5	5.0	4	4.0	9	9.0
Retired	2	2.0	0	0.0	2	2.0
Driver	0	0.0	1	1.0	1	1.0
Free lancer	1	1.0	0	0.0	1	1.0
Total	50	50.0	50	50.0	100	100.0

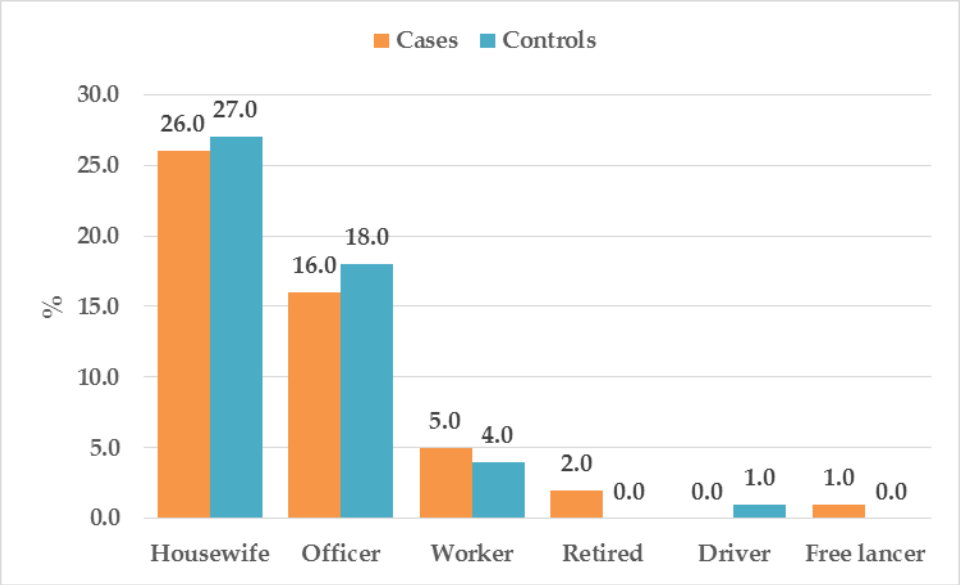

Figure (5) The distribution of the study participants according to their Occupation (n = 100, 50 Cases + 50 Controls)

Table (7) The distribution of the study participants according to their Diabetes duration - years (n = 50 cases)

Diabetes duration - years	Frequency	Percent
<5	17	34.0
5 - 10	22	44.0
>10	11	22.0
Total	**50**	**100.0**

Table (8) The distribution of the study participants according to Diabetes duration – years with the mean uric acid level (n=50cases)

Diabetes duration - years	Mean uric acid level
<5	4.8
5 - 10	5.4
>10	5.3

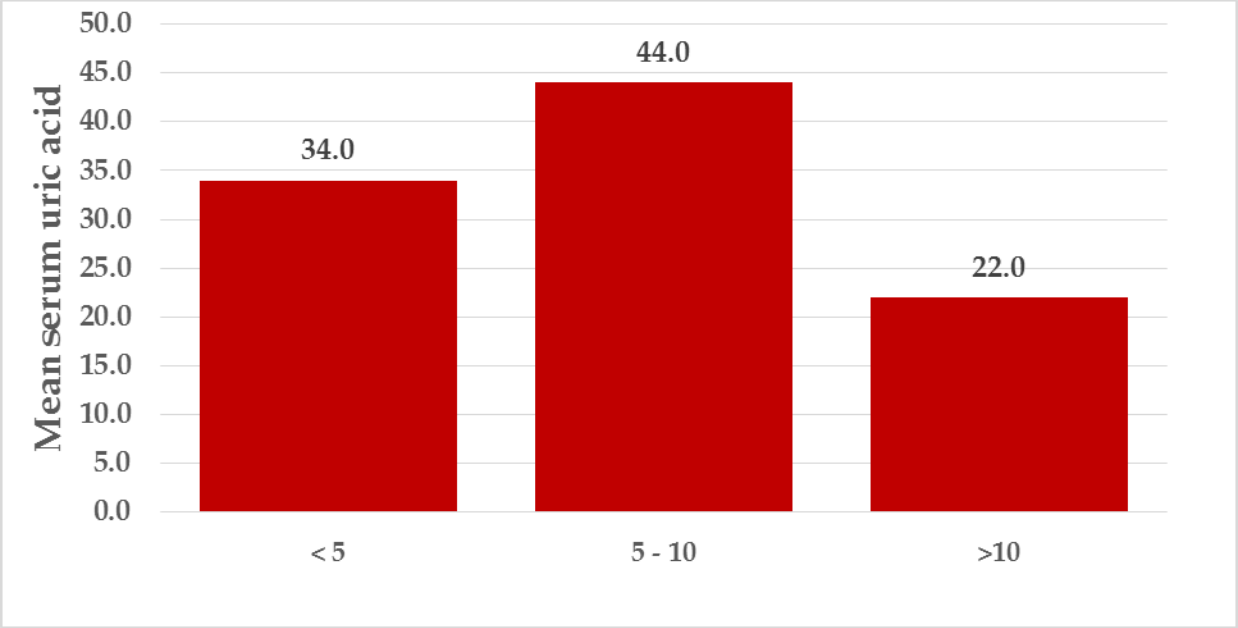

Figure (6) The distribution of the study participants according to their Diabetes duration - years (n = 50 cases)

Table (9) The distribution of the study participants according to the presence of joint pain (n = 100, 50 Cases + 50 Controls)

Joint pain	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Yes	0	0.0	0	0.0	0	0.0
No	50	50.0	50	50.0	100	100.0
Total	50	50.0	50	50.0	100	100.0

Table (10) The distribution of the study participants according to the presence of loin pain (n = 100, 50 Cases + 50 Controls)

Loin pain	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Yes	2	2.0	0	0.0	2	2.0
No	48	48.0	50	50.0	98	98.0
Total	50	50.0	50	50.0	100	100.0

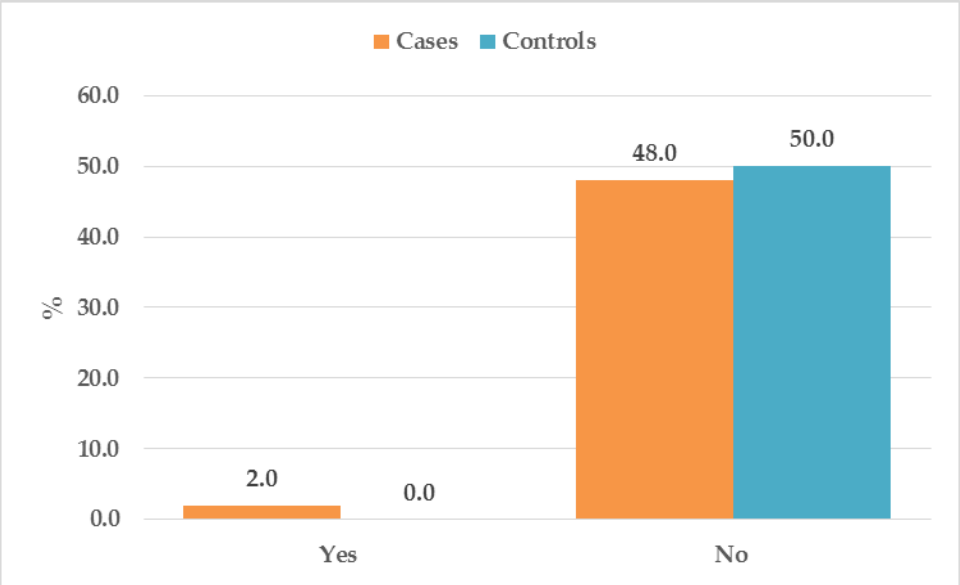

Figure (7) The distribution of the study participants according to the presence of loin pain (n = 100, 50 Cases + 50 Controls)

Table (11) The distribution of the study participants according to the presence of renal disease (n = 100, 50 Cases + 50 Controls)

Renal disease	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Yes	0	0.0	0	0.0	0	0.0
No	50	50.0	50	50.0	100	100.0
Total	50	50.0	50	50.0	100	100.0

Table (12) The distribution of the study participants according to the presence of hypertension (n = 100, 50 Cases + 50 Controls)

Hypertension	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Yes	16	16.0	0	0.0	16	16.0
No	34	34.0	50	50.0	84	84.0
Total	50	50.0	50	50.0	100	100.0

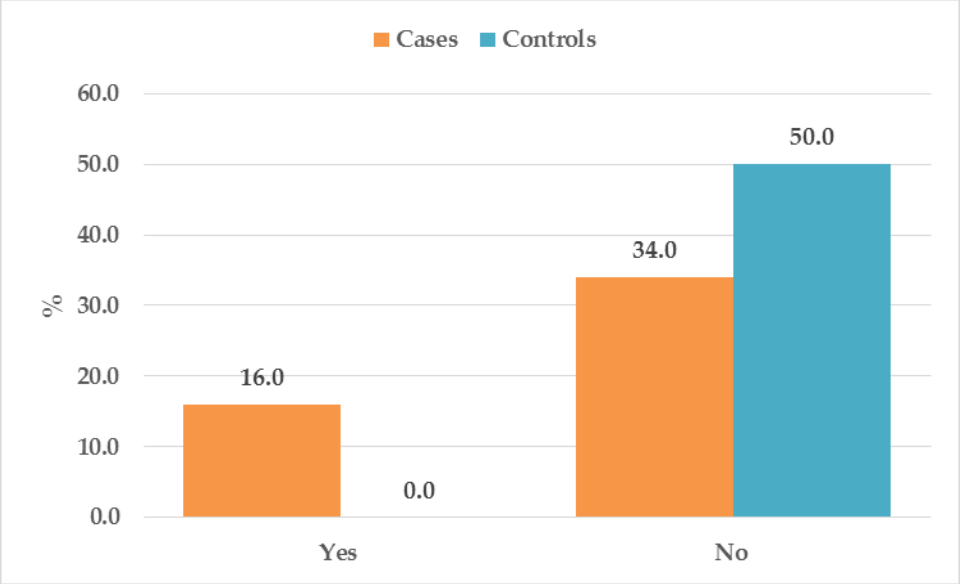

Figure (8) The distribution of the study participants according to the presence of hypertension (n = 100, 50 Cases + 50 Controls)

Table (13) The distribution of the study participants according to the presence of renal stone (n = 100, 50 Cases + 50 Controls)

Renal stone	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Yes	0	0.0	0	0.0	0	0.0
No	50	50.0	50	50.0	100	100.0
Total	50	50.0	50	50.0	100	100.0

Table (14) The distribution of the study participants according to the presence of vesical stone (n = 100, 50 Cases + 50 Controls).

Vesical stone	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
Yes	0	0.0	0	0.0	0	0.0
No	50	50.0	50	50.0	100	100.0
Total	50	50.0	50	50.0	100	100.0

Table (15) The summary statistics for serum uric acid (Mg/dl) among the study participants (n = 100, 50 Cases + 50 Controls)

	Observations	Mean	Std. deviation	Minimum	Maximum
Serum uric acid in Mg/dl	100	4.8	1.2	3.3	8.6

Table (16) The summary statistics for serum uric acid (Mg/dl) among the study groups (n = 100, 50 Cases + 50 Controls)

Study group	Observations	Mean	Std. deviation	Minimum	Maximum
Cases	50	5.2	1.4	3.3	8.6
Controls	50	4.4	0.7	3.3	6.1

Table (17) The difference between the study group in the level of uric acid (n = 100, 50 Cases + 50 Controls)

Study group	Mean serum uric acid	Difference	P vale
Cases	5.2	0.8	0.0003
Controls	4.4		

* Note that P value is corresponding to t - statistics test to assess the difference between two independent means. P value < 0.05 is significant.

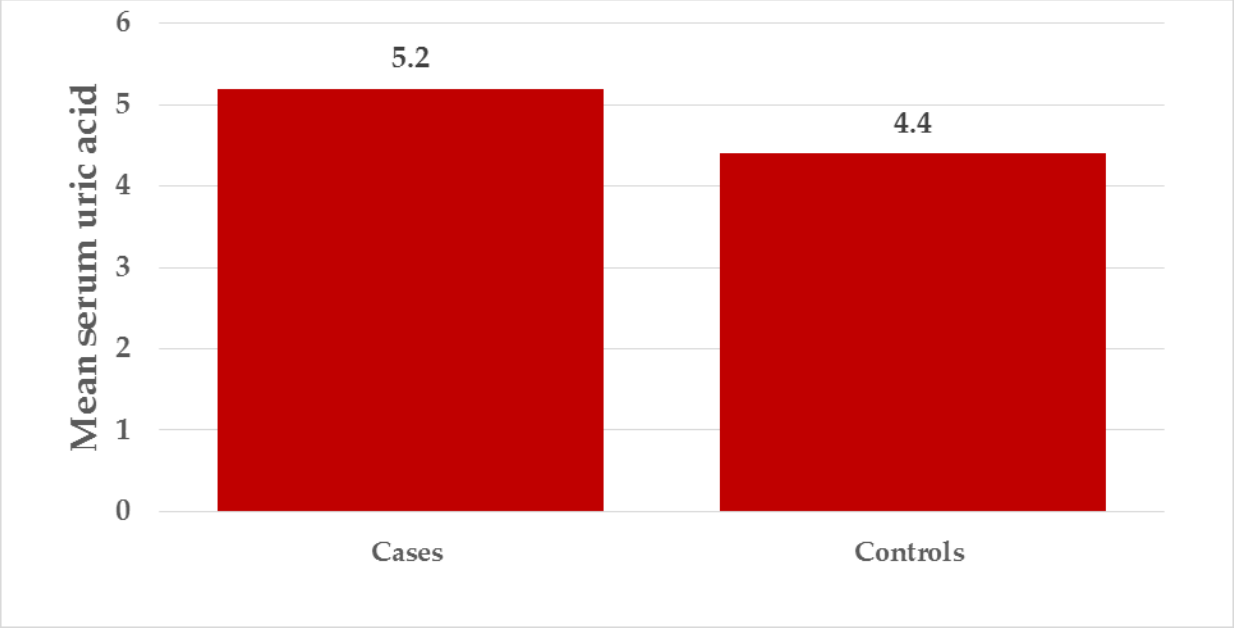

Figure (9) The difference between the study group in the level of serum uric acid (n = 100, 50 Cases + 50 Controls)

Table (18) The difference between the two study groups in the serum uric acid according to age groups (n = 100, 50 Cases + 50 Controls)

Age - years	Study groups		Overall mean
	Cases	Controls	
<40	4.2	4.5	4.4
40 - 50	5.0	4.4	4.6
51 - 60	5.2	4.2	4.9
61 - 70	6.1	4.5	5.4
71 - 80	4.7	4.2	4.5
81 - 90	5.6	0.0	5.6
Overall mean	**5.2**	**4.4**	**4.8**

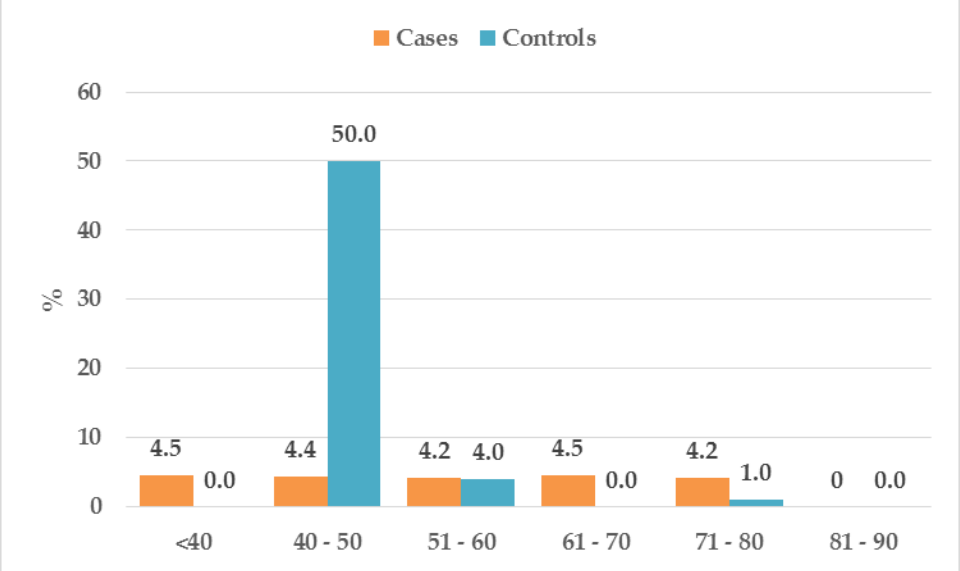

Figure (10) The difference between the two study groups in the serum uric acid according to age groups (n = 100, 50 Cases + 50 Controls)

Table (19) The difference between the two study groups in the serum uric acid according to gender (n = 100, 50 Cases + 50 Controls)

Gender	Study groups		Overall mean
	Cases	Controls	
Male	5.4	4.9	5.2
Female	5.1	4.3	4.7
Overall mean	5.2	4.4	4.8

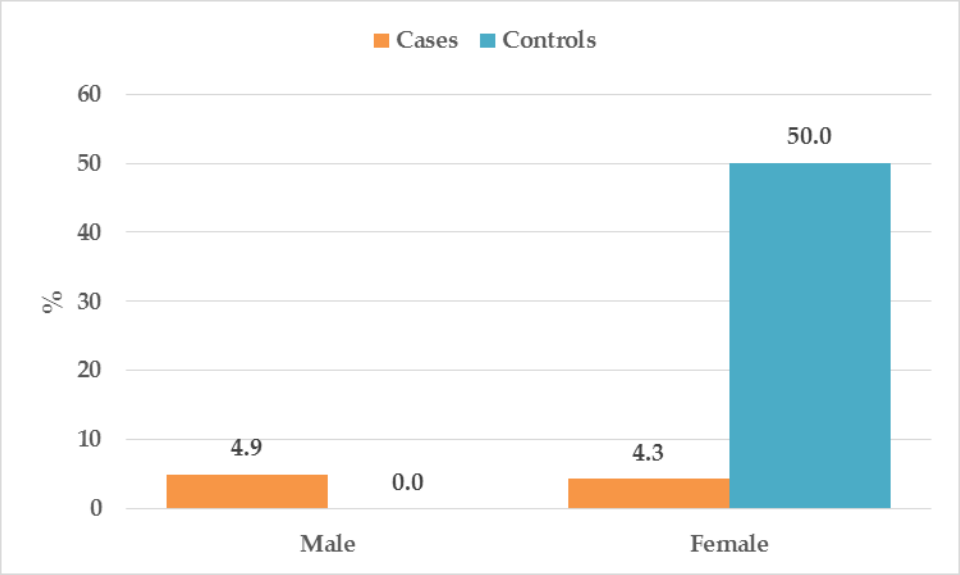

Figure (11) The difference between the two study groups in the serum uric acid according to gender (n = 100, 50 Cases + 50 Controls)

Table (20) The distribution of the study participants according to the serum uric acid compared to normal reference values (n = 100, 50 Cases + 50 Controls)

Serum uric acid	Study groups				Total	
	Cases		Controls			
	Freq.	%	Freq.	%	Freq.	%
High	7	7.0	0	0.0	7	7.0
Normal	43	43.0	49	49.0	92	92.0
Low	0	0.0	1	1.0	1	1.0
Total	50	50.0	50	50.0	100	100.0

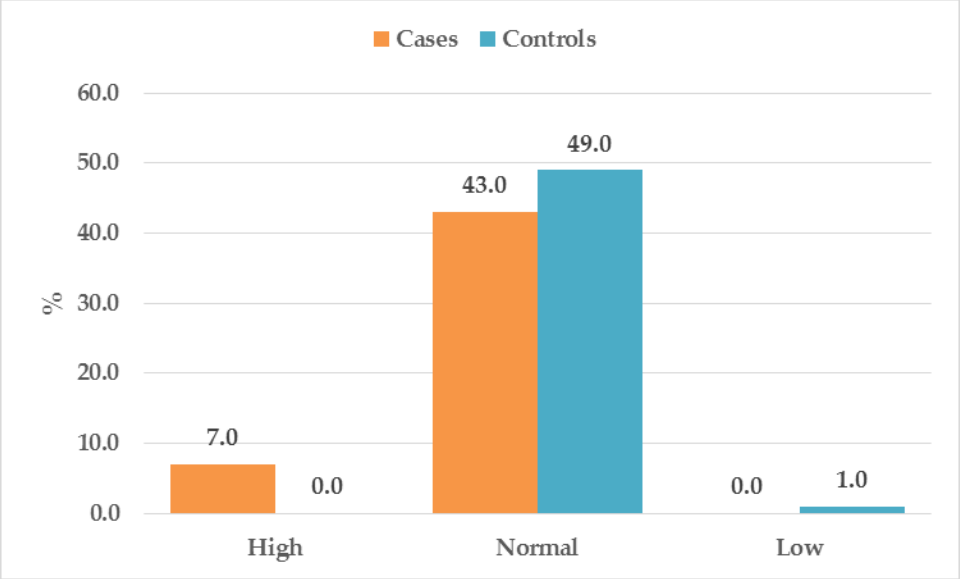

Figure (12) The distribution of the study participants according to the serum uric acid compared to normal reference values (n = 100, 50 Cases + 50 Controls)

Chapter Five

Discussion

Conclusion

Recommendations

5.1 Discussion

This study aimed to assess the serum uric acid levels in diabetes mellitus individuals attending in Shendi hospital, River Nile State, Sudan, from March to August 2018. However, the supposed association between serum uric acid levels and diabetes mellitus is not clear. Some studies reported that there is a positive association between high serum uric acid levels and diabetes, whereas other studies reported no association, or an inverse relationship. In this case control study, which covered (50) cases who diagnosed with diabetes type two and (50) healthy controls. Only 19% of the study participants were above 60 years in age among cases and all of them were from inside Shendi city.

The majority of study groups were females (35% in cases versus 40% in controls), and only few proportion of them had no formal education (14% in cases and 4% in controls). More than half of the study participants were housewives (53%). This results were almost similar to other study by Assmalli et al [29], who investigated the serum levels of Uric acid and other markers in Sudanese residents in UAE Diagnosed with Diabetes Mellitus Type 2 Male account as 96 %(n=50) in the test group and 98 % (n=50) from control group, while females account 4% (n=50) from test group and 2% (n=50) from control group [29].

This study result was a little bit different for similar study conducted in Netherlands, that claimed serum uric acid is positively associated with serum glucose in healthy subjects. However, this association is not consistent between healthy and diabetic individuals, as a low serum level of uric acid is reported in the hyperglycemic state [33].

Concerning the duration of the diabetes, the study found that nearly half of the study participants (44%) had been diabetics for (5 – 10) years while third of them

(34%) had duration for less than five years. Other studies in Sub Saharan Africa reported similar mean duration of DM was 9.2 ± 4.9 years [12].

Regarding the common presentation among study groups, no study participants had complained from joint pain, renal disease, renal stone or vesical stone. Only 2% of the study participants (among cases group) had loin pain while 16% (among cases also) were hypertensive. Other study agreed with these findings. They found that A significant positive correlation was seen between serum UA and systolic (r = 0.312, P = .02) and diastolic blood pressure (r = 0.297, P = .03). Results of this study suggest that serum uric acid had a strong association with levels of systolic and diastolic blood pressure in type 2 diabetic patients [30].

This study found that the mean level of serum uric acid was 4.8 ± 1.2 mg/dl in all study participants. The serum uric acid level higher among DM cases (5.2 ± 1.4 mg/dl) compared with controls (4.4 ± 0.7 mg/dl). The difference in serum uric acid level was highly significant (p = 0.0003). Similarly, in Chinese study they found that serum uric acid was independently associated with development of T2DM, insulin resistance increased as the baseline SUA concentration increased [31].

In Japan, they agreed that SUA level is positively associated with the development of type 2 diabetes regardless of various study characteristics [32].

Generally in this study the participants with DM (cases group) had 7% of them with high level of uric acid compared with international references ranges. Other study from Bosnia by Causevic et al showed significantly elevated USRUA levels in patients with Type 2 diabetes, a negative USRUA correlation with the blood glucose levels in diabetic patients, and an effect of sex and age on the uric acid levels.

In other American study conducted by Pavani et al, they realized similar findings. The results were consistent in subgroup analysis by gender and hypertension

status. Higher serum uric acid levels were inversely associated with diabetes mellitus in a representative sample of US adults [36].

It is expected that our study can contribute to the prevention of high serum uric acid and its complications or provide new insights into a treatment that would slow the progression of DM.

The study had some limitations. The relatively limited number of study participant (100 only) may affect negatively the probability of founding significant relationships between different factors and characteristics with the overall incidence of high serum uric acid Sudanese and for that may be the researchers observed that the evidence on this topic is currently limited and weak. Future research should be based on this type of design, but with larger sample sizes.

5.2 Conclusion

This study aimed to assess the uric acid levels in diabetes mellitus individuals in Shendi hospital, River Nile state, Sudan, 2018.

This study found that the mean level of serum uric acid was 4.8 ± 1.2 mg/dl in all study participants.

The serum uric acid level higher among DM cases (5.2 ± 1.4 mg/dl) compared with controls (4.4 ± 0.7 mg/dl). The difference in uric acid level was highly significant ($p = 0.0003$)

5.3 Recommendation

1. The correlation between serum uric acid and T2DM requires further evaluation and the baseline insulin resistance status should also be considered.
2. Further research should attempt to determine whether it is effective to utilize serum uric acid level as a predictor of type 2 diabetes for its primary prevention.
3. More attention to the serum uric acid level and treatment of hyper-uricemia could halt the progress of diabetic complications.

Chapter Six

References

Appendixes

References

1. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010;33(Suppl 1):S62-S69.
2. Olokoba AB, Obateru OA, Olokoba LB. Diabetes Mellitus: A Review of Current Trends. Oman Medical Journal. 2012;27(4):269-273.
3. De Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. Diabetology & Metabolic Syndrome. 2012;4:12.
4. Barr WG. Uric Acid. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 165. Available from: https://www.ncbi.nlm.nih.gov/books/NBK273/
5. So A, Thorens B. Uric acid transport and disease. J Clin Invest. 2010Jun;120(6):1791-9.
6. El Ridi R, Tallima H. Physiological functions and pathogenic potential of uric acid: A review. Journal of Advanced Research. 2017;8(5):487-493.
7. Katsiki N, Papanas N, Fonseca VA, Maltezos E, Mikhailidis DP. Uric acid anddiabetes: Is there a link? Curr Pharm Des. 2013;19(27):4930-7.
8. Dean L, McEntyre J. The Genetic Landscape of Diabetes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004. Chapter 1, Introduction to Diabetes. 2004 Jul 7. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1671/
9. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World Journal of Diabetes. 2015;6(6):850-867.
10. Asif M. The prevention and control the type-2 diabetes. Journal of Education and Health Promotion. 2014;3:1.

11. Chentli F, Azzoug S, Mahgoun S. Diabetes mellitus in elderly. Indian Journal of Endocrinology and Metabolism. 2015;19(6):744-752.
12. Taylor R. Type 2 Diabetes: Etiology and reversibility. Diabetes Care. 2013;36(4):1047-1055.
13. Bos M, Agyemang C. Prevalence and complications of diabetes mellitus inNorthern Africa, a systematic review. BMC Public Health. 2013 Apr 25;13:387.
14. Grassi D, Ferri L, Desideri G, et al. Chronic Hyperuricemia, Uric Acid Deposit. Current Pharmaceutical Design. 2013;19(13):2432-2438.
15. Rho YH, Zhu Y, Choi HK. The Epidemiology of Uric Acid. Seminars in nephrology. 2011;31(5):410-419.
16. Gustafsson D, Unwin R. The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. BMC Nephrology. 2013;14:164.
17. Jin M, Yang F, Yang I, et al. Uric Acid, Hyperuricemia and Vascular Diseases. Frontiers in bioscience: a journal and virtual library. 2012;17:656-669.
18. Perez-Ruiz F, Dalbeth N, Bardin T. A Review of Uric Acid, Crystal Deposition Disease, and Gout. Advances in Therapy. 2015;32:31-41.
19. Zhang F, Zhang Q, Ke Y, et al. Serum uric acid levels: a meta-analysis. Scientific Reports. 2018;8:1100.
20. Hediger MA. [Physiology and biochemistry of uric acid]. Ther Umsch. 2004Sep;61(9):541-5.
21. Becker BF. Towards the physiological function of uric acid. Free Radic BiolMed. Jun;14(6):615-31.

22. Feig DI, Mazzali M, Kang DH, Nakagawa T, Price K, Kannelis J, Johnson RJ. Serum uric acid: a risk factor and a target for treatment? J Am Soc Nephrol. 2006Apr;17(4 Suppl 2):S69-73.
23. Sebesta I, Krijt J, Schneiderka P. The importance of uric acid examination. SbLek.;95(4):383-9.
24. Das M, Borah NC, Ghose M, Choudhury N. Reference Ranges for Serum Uric Acid among Healthy Assamese People. Biochemistry Research International. 2014;2014:171053.
25. Mikanagi K, Kitamura H. [Uric acid: interpretation of the test results]. NihonRinsho. Mar:Suppl:755-60.
26. Sautin YY, Johnson RJ. URIC ACID: THE OXIDANT–ANTIOXIDANT PARADOX. Nucleosides, nucleotides & nucleic acids. 2008;27(6):608-619.
27. Voruganti VS, Nath SD, Cole SA, et al. Variation in Serum Uric Acid Risk Factors in Mexican Americans. The Journal of Clinical Endocrinology and Metabolism. 2009;94(2):632-638.
28. Johnson RJ. Why focus on uric acid? Curr Med Res Opin. 2015;31 Suppl 2:3-7.
29. Assmalli, Ibrahim Hassan Hamza. Serum Levels of Creatinine and Uric Acid in Sudanese Resident in UAE Diagnosed with Type 2 Diabetes Mellitus. SUST. 2016, sep; 15-6 found in http://repository.sustech.edu/handle/123456789/15399
30. Chakrapani Alavala; Rajendra Prasad Kathula. A study of correlation of serum uric acid levels in diabetes mellitus and its significance in pre-surgical evaluation. Journal of Evidence Based Medicine and Healthcare 2016; 3, 2537-2539.

31. Xu YL, Xu KF, Bai JL, Liu Y, Yu RB, Liu CL, Shen C, Wu XH. Elevation of serum uric acid and incidence of type 2 diabetes: A systematic review andmeta-analysis. Chronic Dis Transl Med. 2016 Nov 2;2(2):81-91.
32. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, Saito A, Sone H. Association between serum uric acid and development of type 2 diabetes. Diabetes. Care. 2009 Sep;32(9):1737-42.
33. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care. 2008Feb;31(2): 361-2.
34. Bhole V, Choi JW, Kim SW, de Vera M, Choi H. Serum uric acid levels and therisk of type 2 diabetes: a prospective study. Am J Med. 2010 Oct;123(10):957-61.
35. Causevic A, Semiz S, Macic Dzankovic A, Cico B, Dujic T, Malenica M, Bego T. Relevance of uric Acid in progression of type 2 diabetes mellitus. Bosn J BasicMed Sci. 2010 Feb;10(1):54-9.
36. Bandaru P, Shankar A. Association between Serum Uric Acid Levels and Diabetes Mellitus. International Journal of Endocrinology. 2011; 2011: 604715.

Shendi university

Faculty of graduate studies & Scientific research

Questionnaire

(The information of this questionnaire is confidential and only for scientific propose)

Personal data:

Date: ……..

Name: ……..……..

- **Age:**

30 – 40 { } 40 – 50 { } more than 50 { }

- **Address:** ……

Social demographic data:

- **Residency:**

In side Shendi { } out side Shendi { }

- **Sex:**

Male { } female { }

- **Level of education:**

Illiterate { } primary { } secondary { } university { }

- **Occupation:**

Worker { } employee { } other { }

- **D.M:**

Yes { } No { }

- **Duration of D.M:**

<5years { } 5 – 10years { } > 10 years { }

- **Pain in small joints:** Yes { } No { }
- **Loin pain:** Yes { } No { }

- **Renal disease:** Yes { } No { }
- **Hypertension:** Yes { } No { }
- **Renal stones:** Yes { } No { }
- **Vesicle stones:** Yes { } No { }

Result:

Serum level of uric acid:

……

……

Appendix II

إقـــرار بالموافقـــة

الاسم:----------

العمر:---------- العنوان:----------

أوافق بمحض إرادتي بالمشاركة في البحث العلمي المتعلق بدراسة العلاقـــة بـــين حمـــض اليوريك أسيد بالبلازما بين المصابين بالسكري من البالغين في منطقة شندي ولاية نهر النيل.

الباحثة: ست البنات إبراهيم أحمد حسين

بعد أن شرحت لي بأنه لا يترتب عليه أي أذى جسدي أو نفسي واعلم أن المشاركة في هـــذا البحث لن تؤثر بأي حال من الأحوال في الرعاية الطبية التي أتلقاها كما أنه يحق لي بـــدون إبداء أسباب الانسحاب من هذا البحث في أي مرحلة من مراحله.

البحث بإشراف:

د. حاج حمد الزين محمد

التوقيع: ---------- التاريخ:----------

SPINREACT

CE

URIC ACID

Uric acid

Uricase +POD. Enzymatic colorimetric

Quantitative determination of uric acid
IVD

Store at 2-8ºC

PRINCIPLE OF THE METHOD

Uric acid is oxidized by uricase to allantoine and hydrogen peroxide ($2H_2O_2$), which under the influence of POD, 4–aminophenazone (4-AP) and 2-4 Dichlorophenol sulfonate (DCPS) forms a red quinoneimine compound:

$$\text{Uric acid} + 2H_2O + O_2 \xrightarrow{\text{Uricase}} \text{Allantoine} + CO_2 + 2H_2O_2$$

$$2H_2O_2 + \text{4-AP} + \text{DCPS} \xrightarrow{\text{POD}} \text{Quinoneimine} + 4H_2O$$

The intensity of the red color formed is proportional to the uric acid concentration in the sample[1,2].

CLINICAL SIGNIFICANCE

Uric acid and its salts are end products of the purine metabolism.
With progressive renal insufficiency, there is retention in blood of urea, creatinine and uric acid.
Elevate uric acid level may be indicative of renal insufficiency and is commonly associated with gout[1,4].
Clinical diagnosis should not be made on a single test result; it should integrate clinical and other laboratory data.

REAGENTS

R 1 Buffer	Phosphate pH 7.4	50 mmol/L
	2-4 Dichlorophenol sulfonate (DCPS)	4 mmol/L
R 2 Enzymes	Uricase	60 U/L
	Peroxidase (POD)	660 U/L
	Ascorbate oxidase	300 U/L
	4 – Aminophenazone (4-AP)	1 mmol/L
URIC ACID CAL	Uric acid aqueous primary standard 6 mg/dL	

PREPARATION

Working reagent (WR): Dissolve (→) the contents of one vial R 2 Enzymes in one bottle R 1 Buffer. Cap and mix gently to dissolve contents. (WR) is stable after reconstitution 1 month at 2-8ºC or 10 days at room temperature.

STORAGE AND STABILITY

All the components of the kit are stable until the expiration date on the label when stored tightly closed at 2-8ºC, protected from light and contaminations prevented during their use.
Do not use reagents over the expiration date.
URIC ACID CAL Once open is stable up to 1 month when stored tightly closed at 2-8ºC, protected from light and contaminations prevented during their use.
Signs of reagent deterioration:
- Presence of particles and turbidity.
- Blank absorbance (A) at 520 nm ≥ 0.16.

ADDITIONAL EQUIPMENT

- Spectrophotometer or colorimeter measuring at 520 nm.
- Matched cuvettes 1.0 cm light path.
- General laboratory equipment.

SAMPLES

- Serum or plasma[1]: Stability 3-5 days at 2-8ºC or 6 months at –20ºC.
- Urine (24 h)[1]: Stability 4 days at 15-25ºC, pH >8. Dilute sample 1/50 in distilled water. Mix. Multiply results by 50 (dilution factor).
  If urine is cloudy; warm the specimen to 60ºC for 10 min to dissolve precipitated urates and uric acid. Do not refrigerate.

PROCEDURE

1. Assay conditions:
   Wavelength: ..... 520 nm (490-550)
   Cuvette: ..... 1 cm light path
   Temperature ..... 37ºC / 15-25ºC
2. Adjust the instrument to zero with distilled water.
3. Pipette into a cuvette:

	Blank	Standard	Sample
WR (mL)	1.0	1.0	1.0
Standard (see IU) (µL)	–	25	–
Sample (µL)	–	–	25

4. Mix and incubate for 5 min at 37ºC or 10 min at 15-25ºC.
5. Read the absorbance (A) of the samples and Standard, against the Blank. The colour is stable for at least 30 minutes.

CALCULATIONS

Serum or plasma

$$\frac{(A)\text{Sample}}{(A)\text{Standard}} \times 6\ (\text{Standard conc.}) = \text{mg/dL uric acid in the sample}$$

Urine 24 h

$$\frac{(A)\text{Sample}}{(A)\text{Standard}} \times 6 \times \text{vol. (dL) urine 24 h} = \text{mg/24 h uric acid}$$

Conversion factor: mg/dL x 59.5 = µmol/L.

QUALITY CONTROL

Control sera are recommended to monitor the performance of assay procedures: SPINTROL H Normal and Pathologic (Ref. 1002120 and 1002210).
If control values are found outside the defined range, check the instrument, reagents and calibrator for problems.
Each laboratory should establish its own Quality Control scheme and corrective actions if controls do not meet the acceptable tolerances.

REFERENCE VALUES[5]

Serum or plasma:

Women	2.5 - 6.8 mg/dL	=	149 – 405 µmol/L
Men	3.6 - 7.7 mg/dL	=	214 – 458 µmol/L
Urine:	250 - 750 mg/24 h	=	1.49 - 4.5 mmol/24 h

These values are for orientation purposes; each laboratory should establish its own reference range.

PERFORMANCE CHARACTERISTICS

Measuring range: From detection limit of 0.03 mg/dL to linearity limit of 25 mg/dL.
If the results obtained were greater than linearity limit, dilute the sample 1/2 with NaCl 9 g/L and multiply the result by 2.
Precision:

	Intra-assay (n=20)		Inter-assay (n=20)	
Mean (mg/L)	4.74	11.4	4.72	11.2
SD	0.03	0.06	0.07	0.15
CV (%)	0.63	0.56	1.58	1.38

Sensitivity: 1 mg/dL = 0.0347 A.
Accuracy: Results obtained using SPINREACT reagents (y) did not show systematic differences when compared with other commercial reagents (x).
The results obtained using 50 samples were the following:
Correlation coefficient (r): 0.99.
Regression equation: y=1.005x + 0.0005.
The results of the performance characteristics depend on the analyzer used.

INTERFERENCES

No interferences were observed to bilirubin up to 170 µmol/L, hemoglobin up to 130 mg/dL and ascorbic acid up to 570 µmol/L[2].
A list of drugs and other interfering substances with uric acid determination has been reported by Young et. al[3].

NOTES

1. Calibration with the aqueous standard may cause a systematic error in automatic procedures. In these cases, it is recommended to use a serum Calibrator.
2. Use clean disposable pipette tips for its dispensation.
3. SPINREACT has instruction sheets for several automatic analyzers. Instructions for many of them are available on request.

BIBLIOGRAPHY

1. Schultz A. Uric acid. Kaplan A et al. Clin Chem The C.V. Mosby Co. St Louis. Toronto. Princeton 1984; 1281-1288 and 418.
2. Fossati P et al. Clin Chem 1980;26:227-231.
3. Young DS. Effects of drugs on Clinical Lab. Tests, 4th ed AACC Press, 1995.
4. Young DS. Effects of disease on Clinical Lab. Tests, 4th ed AACC 2001.
5. Burtis A et al. Tietz Textbook of Clinical Chemistry, 3rd ed AACC 1999.
6. Tietz N W et al. Clinical Guide to Laboratory Tests, 3rd ed AACC 1995.

PACKAGING

Ref: 1001010	Cont.	10 x 20 mL
Ref: 1001011		10 x 50 mL
Ref: 1001012		4 x 125 mL
Ref: 1001013		4 x 250 mL

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