1. Introduction

1.1 Introduction

Diabetes mellitus is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period that result from defects in insulin secretion or action or both(WHO , 1980). Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger .If left untreated, diabetes can cause many complications. (WHO, 1999)

Diabetes is due to either the pancreas not producing enough insulin or the body not responding properly to the insulin produced. (Shoback, *et al.* 2011)

There are two major types of diabetes mellitus, Type 1 DM result from the pancreas failure to produce enough insulin previously referred to as "insulin -dependent diabetes mellitus" (IDDM) or "juvenile diabetes". Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly previously referred to as "non-insulin –dependent diabetes mellitus" (NIDDM). Gestational diabetes, occurs when pregnant women without a previous history of diabetes develop a high blood sugar level. (WHO, 1999).

In America as American Diabetes Association (ADA) statistics in 2012, Prevalence about 29.1million of American has diabetes (9.31%) of total population, Diagnosed 21.0 million people, Undiagnosed 8.1 million people Death diabetes remains the 7^{th} leading cause of death in the United State 234.051 death certificate listing diabetes as underlying or contributing cause of death and morbidity (ADA , 2015).

New figures from International Diabetes Federation 2015 suggest that 415 million are living with diabetes worldwide, up from 387million a year ago.19.3% of the UAE population are living with diabetes, the UAE is ranked 16^{th} worldwide ,these statistics indicate that the region has high risk factors for diabetes mostly related to rising obesity rates and physical inactivity this sedentary life style and unhealthy diet have contribute to the rise in obesity and diabetes prevalence in the region (International Diabetes Federation , 2015).

Diabetes the most common non- communicable disease in Sudan is having an increase impact on rates of morbidity and mortality (Ahmed and Ahmed, 2000). The spread of sedentary life style and adoption of western dietary habits (high in refined carbohydrates and fats) are driving an increasing in the number of people with obesity –related type 2 diabetes (Ahmed, 2001).

Knowledge of the diabetes epidemic in Sudan is limited, the most recent data come from small scale study that was carried out in 1996 the result of study indicate a prevalence of 3.4 % (Elbagir and Eltom, 1996).

Recent estimation place in the diabetes population at around 1 million, around 95%of whom have type -2 diabetes (ADA, 2015). 10% of hospital admission in Sudan the principal cause of admission is diabetes ketoacidosis (inadequate insulin resulting in high blood glucose level with accumulation of organic acids and ketones in blood). Diabetes provokes more death each year in 10%of hospital mortality ketoacidosis is the principal killer, other cause of death is diabetic foot-related septicemia and end stage renal disease (ESRD) (Ahmed and Ahmed, 2000).

Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma,

Serious long-term complications include cardiovascular disease, stroke, chronic kidney failure, foot ulcer and amputation, nerves and eyes damage (Kitabchi, *et al*. 2009)

Diabetic nephropathy is one of the major causes of chronic renal failure, after many years of diabetes the delicate filtering system in the kidney become gradually destroyed, initially becoming leaky to large blood proteins such as albumin which is lost in the urine, serum urea and creatinine are widely used to assess the function of kidney. (Saweirs, 2006).

Uric acid is significant elevate in prediabetes stages and low in diabetes and rise again after the developments of renal insufficiency (Choi and Ford, 2008).

1.2 Rationale

Diabetes mellitus is a medical condition that can be life threatening if not controlled and treated properly, the incidence and prevalence of diabetes mellitus is rising all over the world , despite known roles for obesity, sedentary life style diet and genetic accounts for significant risk in development of diabetes mellitus .

The long term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, neuropathy with risk of foot ulcers and amputation, cardiovascular and cerebrovascular disease, in addition to neuropathy that may lead to renal failure.

Sudan has a limited data or statistical studies for diabetes and the prevalence in the Sudanese, some studies held in 2000 showed about 10% of hospital admissions is diabetes which is a high rate of hospitalization, and about 10% of death certificate listing diabetes as on underlying or contributing cause of death and morbidity.

Many studies reported abnormal results for the serum level of uric acid and creatinine is association with type 2 diabetes mellitus in different countries.

This study aims to underlying any significant changes in the serum levels of uric acid and creatinine in Sudanese reside in UAE diagnosed with type-2 diabetes mellitus, and to evaluate any relationship between the disease and the levels of hemoglobin A1C, serum uric acid and creatinine, further more to take evidence for diabetes type -2 as risk factor to renal impairment.

1.3 Objectives

1.3.1 Genereal objective:-

To study the levels of the glucose, HbA1C, uric acid and creatinine in Sudanese with diabetes mellitus in UAE comparison with healthy subjects as a control group

1.3.2 Specific objectives:-

1. To measure and compare the levels of glucose, HbA1C, uric acid and creatinine in Sudanese with diabetes mellitus type 2 reside in UAE with healthy Sudanese volunteers
2. To correlate between glucose and the levels of HbA1C, uric acid and creatinine among diabetic patients type 2
3. To compare the levels of uric acid and creatinine between >10 years diabetic and $\leq$10 years diabetic duration.

2. Literature Review

2.1 Diabetes Mellitus

2.1.1 Definition of Diabetes Mellitus

Diabetes Mellitus is a heterogeneous group of syndrome characterized by an elevation of fasting blood glucose that caused by relative or absolute deficiency of insulin, which enables cells to absorb glucose in order to turn it into energy.(Pamela, *et al*. 2008)

Insulin is a hormone made by beta cells of the pancreas in response to the elevated glucose in the blood after a meal. Insulin binds to receptors on the body cells to allow the passage of glucose into the cells to metabolize and convert to energy and stimulate cells to remove glucose from the blood to maintain glucose level as normal. Diabetic have either a deficiency of insulin or defective insulin receptor blinding unable glucose entry to the cells remains in the blood causing high blood glucose(hyperglycemia) (Lillioja, *et al*. 1993)

2.1.2 Classification of Diabetes Mellitus

The first widely accepted classification of diabetes mellitus was published by WHO in 1980 and in modified form in 1985, the 1980 and 1985 classification of diabetes mellitus and allied categories of glucose intolerance included clinical classes. (National Diabetes Data Group.1979), (WHO. 1980)

The 1980 Expert Committee proposed two major classes of diabetes mellitus. IDDM or type 1 and NIDDM or type 2. In both the 1980 and 1985 reports other classes of DM include other types and impaired glucose. Tolerance (IGT) as well as Gestational Diabetes Mellitus (GDM) these were reflected in the subsequent International Nomenclature of Disease (IND) in 1991, and the tenth revision of the International Classification of Disease (ICD-10) in 1992. (Alberti and Zimmet, 1998)

The 1985 classification was widely accepted and is used internationally. It represented a compromise between clinical and aetiological classification and allow patients in a clinically useful manner even when the specific cause or etiology was unknown. The recommended classification based on clinical descriptive criteria and a complementary aetiological classification, the classification encompasses both clinical stages and aetiological types of diabetes mellitus and others categories of hyperglycemia as suggested by Kuzuya and Matsuda (Kuzuya and Matsuda, 1997)

2.1.2.1 Type 1 diabetes mellitus

Type 1 diabetes was formerly called juvenile onset diabetes because it is usually first identified in children and young adults .it was also known as brittle Diabetes and insulin –dependent Diabetes mellitus (IDDM).Type 1 diabetes it is a condition of autoimmune disease in which a body immune system has attacked and destroyed the beta cells of pancreas .As a result is a shortage of insulin, and glucose cannot enter the cells. Bodily processes involving the storage of glucose as energy and the utilization of glucose are adversely affected (Whtby, *et al*. 1998).

Type 1 diabetes constitutes only 10-20% of all diabetes and commonly occurs in childhood and adolescence. (Michael, *et al*. 2010)

Sign and symptoms include polydipsia (excessive thirst), polyphagia (increased food intake), polyuria (excessive urine production), rapid weight loss, hyperventilation, mental confusion and possible of consciousness (due to increase glucose to brain).Complications include micro vascular problems such as nephropathy, neuropathy, and retinopathy. (Michael, *et al*. 2010).

2.1.2.2 Type 2 diabetes mellitus

Type 2 diabetes formerly called Adult onset diabetes because is usually develops in adult over 40^{th} age .However, individuals can develop type 2 diabetes at any age. Also known as non-insulin dependent diabetes mellitus (NIDDM). (Whtby, *et al*. 1998).

Type 2 characterized by hyperglycemia as result of individual resistance to insulin with insulin secretory defect. This resistance results in a relative, not an absolute insulin deficiency. Type 2 constitutes the majority of diabetes cases .Most patients in this type are obese or have an increase percentage of body fat distributed in the abdominal region. This type of diabetes often goes undiagnosed for many years and is associated with strong genetic predisposition with patients at increased risk with in an age, obesity, and lack of physical exercise, characteristics usually include adult onset of disease and milder symptoms than type 1, ketoacidosis seldom occurring; however these patients are more likely to go into a hyperosmolar coma and increased risk of developing macrovascular and microvascular compilications. (Michael, *et al*. 2010).

2.1.2.3 Gestational Diabetes Mellitus (GDM)

“Is any degree of glucose intolerance with onset or first recognition during pregnancy”, causes of GDM include metabolic and hormonal changes. Patients with GDM frequently return to normal postpartum, this disease is associated with increased prenatal complications and increased risk for development of diabetes is at increased risk respiratory distress syndrome, hypocalcemia and

hyperbilirubinemia .fetal insulin secretion is stimulated in the neonate of a mother with diabetes. When the infant is born and the umbilical cord is served, the infant's oversupply of glucose is abruptly terminated causing a sever hypoglycemia. (Michael, *et al*. 2010).

2.1.3 Laboratory Diagnosis of Diabetes Mellitus

The diagnosis of type1 diabetes and many cases of type 2, is usually prompted by recent-onset symptoms of excessive urination (polyuria) and excessive thirst (polydipsia), and often accompanied by weight loss. These symptoms typically worsen over days to weeks, about a quarter of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis (Ketoacidosis is a type of metabolic acidosis which is caused by high concentrations of ketones bodies, formed by the breakdown of fatty acids and the deamination of amino acids), by the time the diabetes is recognized. Diabetes is often detected when a person suffers a problem that is frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia. Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the followings, fasting plasma glucose level at or above 126 mg/dL (7.0 mmol/L), plasma glucose at or above 200 mg/dL (11.1 mmol/L) two hours after a 75 g oral glucose load as in a glucose tolerance test. The symptoms of hyperglycemia appear at or above blood glucose 200 mg/dl (11.1mmol/L). (WHO, 1999), (Saydah, *et al*. 2001)

2.1.3.1 Blood glucose test

Fasting blood glucose test is the preferred way to diagnosis diabetes it is easy to perform and convenient. After the person has fasted overnight (at least 8 hours), a single sample of blood is drawn and send to the laboratory for analysis . (ADA, 2007).

Normal fasting blood glucose level are less than 100 mg/dL .Fasting plasma glucose levels of more than 126mg/dL on two or more tests on different days indicate diabetes. (Harris, 1993)

A random blood glucose test can also be used to diagnosis diabetes, a blood glucose level of 200 mg/dL or higher in two different occasions indicates diabetes. (Harris,1993).

American Diabetes Association (ADA) recommended diabetes screening when a person is age 45 or older or has risk factors as overweight ,obese, physically inactive, close relative with diabetes (first degree relative),woman who delivered baby weighting more than 9 pounds or with history of gestational diabetes high blood pressure (hypertension),low HDL cholesterol level less

than 35 mg /dl or high triglyceride level more than 250 mg/dl or HbA1c equal or above 5.7% , history of cardiovascular disease (CVD).If the screening test result within normal limits the ADA recommending testing within 3 years while the(USPSTF) United States Preventive Services Task Force recommends yearly testing (ADA, 2007).

2.1.3.2 Oral glucose tolerance test (OGTT)

The oral glucose tolerance test (OGTT) is the golden standard for the diagnosis of type 2 diabetes. It is still commonly used for diagnosing Gestational Diabetes Mellitus (GDM) and in conditions of pre-diabetes ,With an oral glucose tolerance test, the person fasts overnight (at least 8 hours and not more than 16 hours)then the fasting plasma is tested , after this the person receives 75 grams of oral glucose (100 grams for pregnant women) (ADA, 2007).

The classic oral glucose tolerance test measures blood glucose levels five times over a period of two hours, In a person without diabetes levels is rise within the normal and then fall , In someone with diabetes ,glucose levels is rise higher than normal and fail to come back as fast. (ADA, 2007), (Harris, 1993).People with levels between normal and diabetic have Impaired Glucose Tolerance (IGT), people with impaired glucose tolerance do not have diabetes, but are at high risk for progressing to diabetes (Walid, *et al*.2009).

2.1.3.3 Glycated hemoglobin (HbA1C)

Also known as glucosylated hemoglobin or HbA1c is formed in blood when glucose attached to hemoglobin, the higher level of glucose in blood the more glycated hemoglobin is formed. The rate of combination is directly proportional to the plasma glucose concentration. Because the average red blood cell lives approximately 120 days, the glycated hemoglobin level at any one time reflect the average blood glucose level over the previous 2-3 months. HbA1c test may be used to screen or diagnose diabetes and prediabetes in adult (Michael, *et al*. 2005).

The American Diabetes Association guidelines are similar to others in advising that the glcosylated hemoglobin test be performed at least two times a year in patients with diabetes who are meeting treatment goals (and who have stable glycemic control) and quarterly in patients with diabetes whose therapy has changed or who are not meeting glycemic goals, also it added the A1c $\geq$ 6.5% as another criteria for the diagnosis of diabetes (ADA, 2007), (Walid, *et al*. 2009). HbA1c in screening and diagnosis some results may seen A1C non diabetic less than 5.7%, Diabetic person will have A1C higher than 6.5%, 5.7% to 6.5% level for the risk of developing diabetes in future. (ADA, 2007)

2.1.3.4 Fructosamine

Fructosamine is the name given to ketoamine products formed from the non-enzymatic attachment of a carbohydrate to a protein. The reaction between glucose and plasma proteins forms unstable Schiff bases that are converted to stable ketoamine products (Fructosamine). (Armbruster, 1987). Advocated as tool for the assessment of glycaemic control in patients with diabetes mellitus. As the mean half –life of plasma proteins is approximately 2-3 weeks for Fructosamine provides a shorter term presentation of glycaemic control than HbA1c.
(Armbruster, 1987).

2.1.3.5 C.peptide

C-peptide is a polypeptide consisting of 31 amino acids (MW~3000), is stored in the secretory granules of the beta cells and released into circulation in equimolar amounts with insulin. C-peptide plays an important role in the synthesis and functionality of insulin. C-peptide ensures the correct structure of insulin by aligning the A and B chains of the insulin molecule so that the correct interchain disulfide bonds form. (Sacks, *et al*. 1994), (Dods, *et al*. 1996)

The determination of C-peptide provides an assessment of endogenous insulin secretory reserves in patients with diabetes mellitus and is considered a more reliable indicator of insulin secretion than insulin itself. (Wahren, *et al*. 2000) .

C-peptide measurement is primarily used for the evaluation of fasting hypoglycemia. Urinary and fasting C-peptide levels have been used clinically to assist in the classification of diabetes mellitus and to differentiate insulin-dependent patients from non-insulin-dependent patients. (Cha, *et al*. 1991)

2.1.4 Complication of Diabetes Mellitus

Patient education, understanding, and participation are vital since the complications of diabetes are far less common and less severe in people who have well-controlled blood sugar levels. Wider health problems accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.
(Nathan , *et al*.2005)

Diabetes mellitus affects many organ system, the morbidity and mortality associated with diabetes are related to the short term (acute), and long term complications (chronic) which include the following .(Marshal, 1995)

2.1.4.1 Acute glycemic complications

2.1.4.1.1 Diabetes Ketoacidosis (DKA)

Lack of insulin causes the inability to store fat and protein along with breakdown of existing fat and protein stores with increase in plasma glucose (hyperglycemia), this dysregulation results in the process of ketosis and the release of ketones into the blood which turn the blood acidic. (Marshal, 1995).Diabetic ketoacidosis can be caused by infections, stress, or trauma, all of which can increase insulin requirements. In addition, missing dose of insulin is also an obvious risk factor for developing diabetic ketoacidosis. (Marshal, 1995).DKA may be the first symptom of previously undiagnosed diabetes, but it may also occur in known diabetics due to a variety of causes, such as intercurrent illness or poor compliance with insulin therapy. Vomiting, dehydration, deep gasping breathing, confusion and occasionally coma are typical symptoms (Dunger, *et al*. 2004).Morbidity associated with DKA relates to the severity of the acid-base and electrolyte disturbances. These disturbances may result in coma and death.. It is important to correct slowly the hyperglycemia, acidosis, and electrolyte disturbances to prevent precipitating cerebral edema. (Durr, *et al*. 1992)

2.1.4.1.2 Hyperosmolar Non ketotic coma (HNC)

Type of diabetic coma associated with a high mortality seen in diabetes mellitus type 2. The preferred term used by the American Diabetes Association is hyperosmolar nonketotic state (HNS), Other commonly used names are hyperosmolar hyperglycemic nonketotic coma (HHNKC) or hyper osmotic non-ketotic coma (HONKC). It is also called Hyperglycemic Hyperosmolar State (HHS). (Stoner, 2005). A relative insulin deficiency leads to a serum glucose that is usually higher than 33 mmol/l (600 mg/dl) and a resulting serum osmolarity that is greater than 350 mOsm. This leads to polyuria (an osmotic diuresis), which in turn leads to volume depletion and hemoconcentration that causes a further increase in blood glucose level. Ketosis is absent because the presence of some insulin inhibits lipolysis, unlike diabetic ketoacidosis. (Tintinalli and Judith, 2004). Although the emergency treatment guidelines recommend early restoration of the intravascular volume, correction of fluid and electrolyte deficits, hyperglycemia and hyperosmolarity. (S. Kodama, *et al*.2009)

2.1.4.1.3 Hypoglycemia

Hypoglycemia is the medical term for a state produced by a lower than normal level of blood glucose level below approximately 60 mg/dL. Hypoglycemia can produce a variety of symptoms

and effects but the principal problems arise from an inadequate supply of glucose as fuel to the brain, resulting in impairment of function (neuroglycopenia), other symptoms associated with adrenergic symptoms (apprehension, tremors, sweating, or palpitations) (Philip , *et al.* 2001).

The most common forms of moderate and severe hypoglycemia occur as a complication of treatment for diabetes mellitus with insulin or oral medication. (CarrolandMatz, 1993)

The major morbidity associated with hypoglycemia is temporary neurologic deficit and coma, seizures with central nervous system injury, and permanent neurologic impairment if treatment is delayed or omitted.The key, again, is careful monitoring and adjustment of insulin dosage to avoid the extremes of hyperglycemia and hypoglycemia. Death related to hypoglycemia in diabetes occurs rarely. (Diabetes Control and Complication Trial Research Group, 1993)

2.1.4.2 Chronic glycemic complications

2.1.4.2.1 Kidney disease (Diabetic nephropathy)

Kidney disease (diabetic nephropathy) is a very serious complication of diabetes causes by damage to small blood vessels in the kidneys act as the tiny filters in kidney called glomeruli, this damage leads to kidney dysfunction and leak of proteins and useful gradients in urine, and microalbuminuria is important markers for kidney damage which may develop to renal insufficiency and chronic renal failure CRF. (Jawa, *et al*. 2004)

Diabetic nephropathy represents a distinct clinical syndrome characterized by albuminuria, hypertension, and progressive renal insufficiency. Diabetic nephropathy can lead to end-stage renal disease (ESRD), a serious condition in which a patient's survival depends on either dialysis or kidney transplantation. (Mogensen, *et al*. 1983)

2.1.4.2.2 Cardiovascular Complications

Diabetes accelerates hardening of the arteries (atherosclerosis) of larger blood vessels, leading to coronary heart disease, angina, stroke, and heart failure (Marshal, 1995).

2.1.4.2.3 Eye disease (Diabetic retinopathy)

The most common eye disorder in diabetes is retinopathy, diabetic retinopathy is a condition in which the retina in the eye becomes damage which can eventually lead to blindness.

(Jawa, *et al*. 2004).

2.1.4.2.4 Nerve disease and foot problem (Diabetic neuropathy)

Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body. Some people with nerve damage

have no symptoms. Others may have symptoms such as pain, tingling, or numbness—loss of feeling—in the hands, arms, feet, and legs. Nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs. (Bishop, *et al*. 2005)

2.2 Uric Acid (UA)

UA is the end-product of purine nucleotide metabolism in humans. In contrast to many lower vertebrates, human lack UA oxidase (uricase), an enzyme which further catalyses UA to allantoin, more soluble end product .Humans have higher serum UA levels when compared to other mammals due to the lack of uricase (Sautin and Johnson.2008)

2.2.1 Uric Acid Metabolism

UA is produced by breakdown of purines. Purines are Nitrogen containing compounds found in the body's cells including our DNA which purine nucleotides are essential compounds in Nucleic acids (adenosine and guanine), when the cells die and breakdown they release purines, sub extent purines may come from the digestion of certain foods ,organ meat such as , liver ,kidneys, dried beans , sardines and mushroom all are rich sources of purines (Brule, *et al*.1988). A diet rich in animal protein contributes significantly to the purine pool and subsequentUA formation by a series of enzymatic reaction involving xanthine oxidase as the final step.(Sachez,*et al*.2006),(Gawa, 1999)

2.2.2 Uric Acid Excretion

UA is primarily excreted via the urine. The balance between dietary intake, endogenous metabolism of purines and the urinary excretion rate of UA determines plasma UA levels. (Kutzing and Firestein, 2008) . Solubility of UA in urine is primarily determined by urinary PH. The super saturation of urine with UA occurs when urinary pH is less than **5.5**. Increased urinary sodium concentrations promote formation of the monosodium urate complex, which is more soluble than undissociated UA. (Finlayson, 1974)

2.2.3 Plasma urate

Plasma urate concentration in general higher in men than in women, tend to high with age and usually elevated in people in the higher socioeconomin group and theobese.There is considerable variation in plasma urate concentration between different ethnic groups. (Marshal, 1995)

2.2.3.1 Hyperuricemia

Almost all serum UA is present in the ionized form, monosodium urate, and only about 5% of urate is protein bound at physiological pH. The definition of hyperuricemia is increase of plasma

urate greater than (416µmol/l). (Hak and Choi, 2008)Increase plasma urate may be attributable to one of the several mechanisms but must be either overproduction or defective elimination of urate. (Marshal, 1995)

2.2.3.1.1 Over production of Urate Increased purine synthesis due specific enzyme defects (e.g. PRPP-synthase"5-phosphoribosyl-1-pyrophospkate"). Increased turnover of preformed purine as in Myeloproliferative disorders (e.g.polycythaemiaruber Vera), Lymph proliferative disorders (e.g lymphoma)·(Smith,*et al*.1994)

2.2.3.1.2 Defective elimination of urate

Due to renal disease (e.gchronic renal failure), metabolic acidosis (e.g.lacticacidosis, ketoacidosis), drugs (e.g. diuretics). (Marshal, 1995)

2.2.4 Uric acid and acute renal failure

Uric acid, as the end-product of purine metabolism in humans, presents a clinical impact since its has a relative insolubility, particularly in the acidic environment of the distal nephron. As a result, states of enhanced purine catabolism increases the urate load on the kidney, leading to internal precipitation. Major causes of increases on purine metabolism are malignancies with rapid cell turnover, such as leukemia and lymphomas, and the added acceleration of cell lyses that occurs with chemotherapy and radiation. Serum urate levels rise rapidly, and acute renal failure occurs as a consequence of tubular deposition and obstruction of urate and uric acid. The keys to the diagnosis of acute uric acid nephropathy are the appropriate clinical settings as cell lyses increases, oliguria, marked hyperuricemia, and hyperuricosuria (Hyperuricosuria is defined as a mean 24-hour urinary UA excretion of more than 600 mg/24 hr) .(Conger, 1990)

2.2.5 Uric acid, metabolic syndrome and diabetes

The relationship between hyperuricemia, hypertension, and the metabolic syndrome has long been debated. Recent evidences from animal studies and epidemiology suggest that hyperuricemia has a recently clinical studies focusing on UA, albuminuria and diabetic kidney disease have been published .The new evidence suggests that UA could be a risk factor for the development of diabetic nephropathy; however, the significance of serum UA as pathogenic factor in the development of diabetic nephropathy is not yet fully clarified. (Hovind, *et al*. 2011)

2.2.6 Uric acid, Gout

Gout is an inflammatory process initiated by tissue deposition of monosodium urate (MSU) crystals. (So A, 2008).Multiple risk factors may interact and lead to development of gout. Gender

, Age and Diet. Monogenic disorders that result in overproduction of UA via enzyme defects in purine metabolism is extremely rare, historically gout has long been linked with a rich lifestyle involving excesses of meat and alcohol . (Choi, *et al*. 2004)

2.3Creatinine

Creatinine is product from creatine which is synthesized primarily in liver from argenine, glycine and methionine. It is then transported to other tissue, such as muscle, where it is converted to phosphocreatine, which serves as high energy source. Creatine phosphate loses phosphoric acid and water to form creatinine which passes into plasma. Formation of creatinine is anon enzymatic reaction and free creatinine is not reused in metabolism and thus functions as a waste product of creatine. Creatinine formation has relationship to muscle mass, freely filtered by the glomeruli and excreted in the urine. (ADA, 2007), (Marshal, 1995)

2.3.1 Serum creatinine

Serum creatinine is relatively constant, and some greater in males than females. It is interpreted as a measure of golmerular filteration rate and it used as an index of renal function in clinical practice, Elevated creatinine concentration with reduced renal excretion is associated with abnormal renal function, especially as it relates to golmerular function .(Burtis, *et al*. 2001)

Serum or plasma creatinine concentration and urinary excretion are increased significantly by skeletal muscle disease necrosis or atropy and hyperthyroidism. (Burtis, *et al*. 2001)

2.3.1.1 High serum creatinine due non pathological significance

Diet has also been shown to influence creatinine excretion. Approximately 10% of daily urinary creatinine excretion is of exogenous origin. Long term low-protein consumers, such as vegetarians, have urinary creatinine excretion that is lower than the 10% allowed for exclusion of exogenous creatinine sources ((Bosch, *et al*. 1983)

2.3.1.2 High serum creatinine due pathological significance

Renal cause as any disease in which there is impaired renal perfusion (e.g. reduced blood pressure, fluid depletion, renal artery stenosis).Most disease in which there is loss of functioning nephrons (e.g. acute and chronic glomerulonephritis and renal failure).Diseases where pressure is increased on tubular side of the nephrons(e.g. urinary tract obstruction due to prostatic enlargement).Skeletal muscle necrosis or atropy. Hyperthyroidism. (Burtis, *et al*. 2001), (Kassirer, 1071)

3. Materials and Methods

3.1 Materials

3.1.1 Study Design

This is a descriptive, cross sectional and hospital based study

3.1.2 Study area and period

The study was conducted in United Arab of Emirates (UAE), patients enrolled in this study meets in Sudanese cultural clubs located in Abu Dhabi and Dubai. The study was carried during the period from July 2015 up to June 2016

3.1.3 Study population and sample size

The target population of this study was patients with type 2 diabetes mellitus categorized into study group of 50diabetes patients and 50of healthy subjects (non diabetic) as a control group.

3.1.4 Ethical Consideration

Permission of this study was obtained from the local authorities in the area of the study which is the Sudan Embassy and Sudanese Cultural club Administration.

The objectives and benefits of the study were explained to the participants, samples taken after participant's agreement as questionnaire (Appendix –I) and consent to participate were filled. (Appendix -II).

3.1.5 Inclusion Criteria

Sudanese patients with type 2 diabetes mellitus were included as a test group and healthy subjects (non diabetic) as a control.

3.1.6 Exclusion Criteria

Study and control group had been excluding those with gout, Rheumatoid Arthritis, renal impairment patients and any other disorders that may affect the level of uric acid and creatinine.

3.1.7 Data collection and clinical examination

Interviews with the test group and controls were done to obtain the clinical data as well as fulfillments of questionnaire.

3.1.8 Sample Collection

After inform consent and questionnaire were filled blood sample 7ml were collected from participants using disposable syringe, accordingly to patients safety, quality control applied.

Collected samples were drawn into three container, Heparin, EDTA and fluoride oxalate, hemolysed samples were rejected and exclude from the study

3.2 Methods

3.2.1 Measurement of Glucose

Principle

GLU reagent is used to measure the glucose concentration by a timed endpoint method. In the reaction, Hexokinase (HK) catalyses the transfer of a phosphate group from adenosine triphosphate (ATP) to glucose to form adenosine diphosphate (ADP) and glucose-6-phosphate. The glucose-6-phosphate is then oxidized to 6-phosphogluconate with the concomitant reduction of β-nicotinamide adenine dinucleotide (NAD) to reduced β-nicotinamide adenine dinucleotide (NADH) by the catalytic action of glucose-6-phosphate dehydrogenase (G6PDH). (Young, 2000), (Tietz, 1990) (Appendix- III)

3.2.2 Measurement of HbA1c

Principle

The system utilizes two unique cartridges, Hb2 and A1c2, to determine hemoglobin A1c2concentration as a percentage of total hemoglobin A1c2

Reagent is used to measure the hemoglobin A1c2 concentration by a turbidimetric immunoinhibition method. In the reaction, hemoglobin A1c2 antibodies combine with hemoglobin A1c2 from the sample to form soluble antigen-antibody complexes. Polyhaptens from the reagent then bind with the excess antibodies and the resulting agglutinated complex is measured turbidimetrically. (Niederau, *et al*. 1998), (Jeppsson, *et al*. 2002) (Appendix -IV)

3.2.3 Measurement of Uric acid

Principle

URIC reagent is used to measure the uric acid concentration by a timed-endpoint method. Uric acid is oxidized by uricase to produce allantoin and hydrogen peroxide. The hydrogen peroxide reacts with 4-aminoantipyrine (4-AAP) and, 3,5-dichloro-2-hydroxybenzene sulfonate (DCHBS) in a reaction catalyzed by peroxidase to produce a colored product. (Fossati P, *et al*. 1980), (Tietz, 2006) (Appendix -V)

3.2.4 Measurement of Creatinine

Principle

CR-S reagent is used to measure the creatinine concentration by a modified rate Jaffé method. In the reaction, creatinine combines with picrate in an alkaline solution to form a creatinine-picrate complex. (Red colored complex). (Jaffe, 1886), (Bowers and Wong, 1980), ((Appendix-V I)

4. Results

The study applied on 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.

90 %(n=50) are $\geq$ 40years age and 10% (n=50) are< 40years age from test group, while 70% (n=50) are $\geq$ 40 years age and 30% (n=50) are < 40 years age from control group, SPSS used for data analysis and results as follow

Glucose

Table(4-1) shows significant difference between mean of Blood Glucose levels in test group and control group (9.7 ± 3.1)versus(5.4 ± 0.7) p=0.000

HbA1c

Table (4-1) shows significant difference between the mean of HbA1c levels in test group and control group (8.5 ± 1.9) versus (5.5 ± 0.7) p=0.000

Creatinine

Table (4-1) shows significant difference between the mean of Creatinine levels in test group and control group (102 ± 58) versus (77 ± 14) p=0.000

Uric Acid

Table (4-1) shows significant difference between the mean of Urate levels in test group and control group (295$\pm$123) versus (358$\pm$61) p=0.000

Table (4.1) Comparison of means plasma levels Glucose, Hba1c, Creatinine and Uric acid between test group and control group

Variable	Test Group (n=50)	Control Group (n=50)	P .value
Glucose	(9.7 ± 3.1) mmol/L	(5.4 ± 0.7) mmol/L	**0.000**
HbA1c	(8.5 ± 1.9) %	(5.5 ± 0.7) %	**0.000**
Creatinine	(101 ± 59) µmol/L	(77 ± 14) µmol/L	**0.000**
Uric Acid	(295 ± 123) µmol/L	(358 ± 61) µmol/L	**0.000**

- The table shows the mean ± Std deviation in brackets and probability (P).
- Independent t-test was used for comparison
- P-value $\leq$ 0.05 is considered significant

Table (4.2) Comparison of means and std deviation levels Glucose, HbA1c, Creatinine and Uric acid between test group with $\leq$ 10years duration and test group with >10 years duration

Variable	Test Group with≤10Yrs Duration(n=11)	Test Group with>10Yrs Duration (n=39)	P .value
Glucose	(9.6 ± 2.7) mmol/L	(9.7 ± 3.2) mmol/L	**0.000**
HbA1c	(8.0 ± 1.5) %	(8.6 ± 2.0) %	**0.000**
Creatinine	(88 ± 27) µmol/L	(106 ± 64) µmol/L	**0.000**
Uric Acid	(270 ± 90) µmol/L	(303 ± 131) µmol/L	**0.000**

- The table shows the mean ± Std deviation in brackets and probability (P).
- Independent t-test was used for comparison
- P-value $\leq$ 0.05 is considered significant

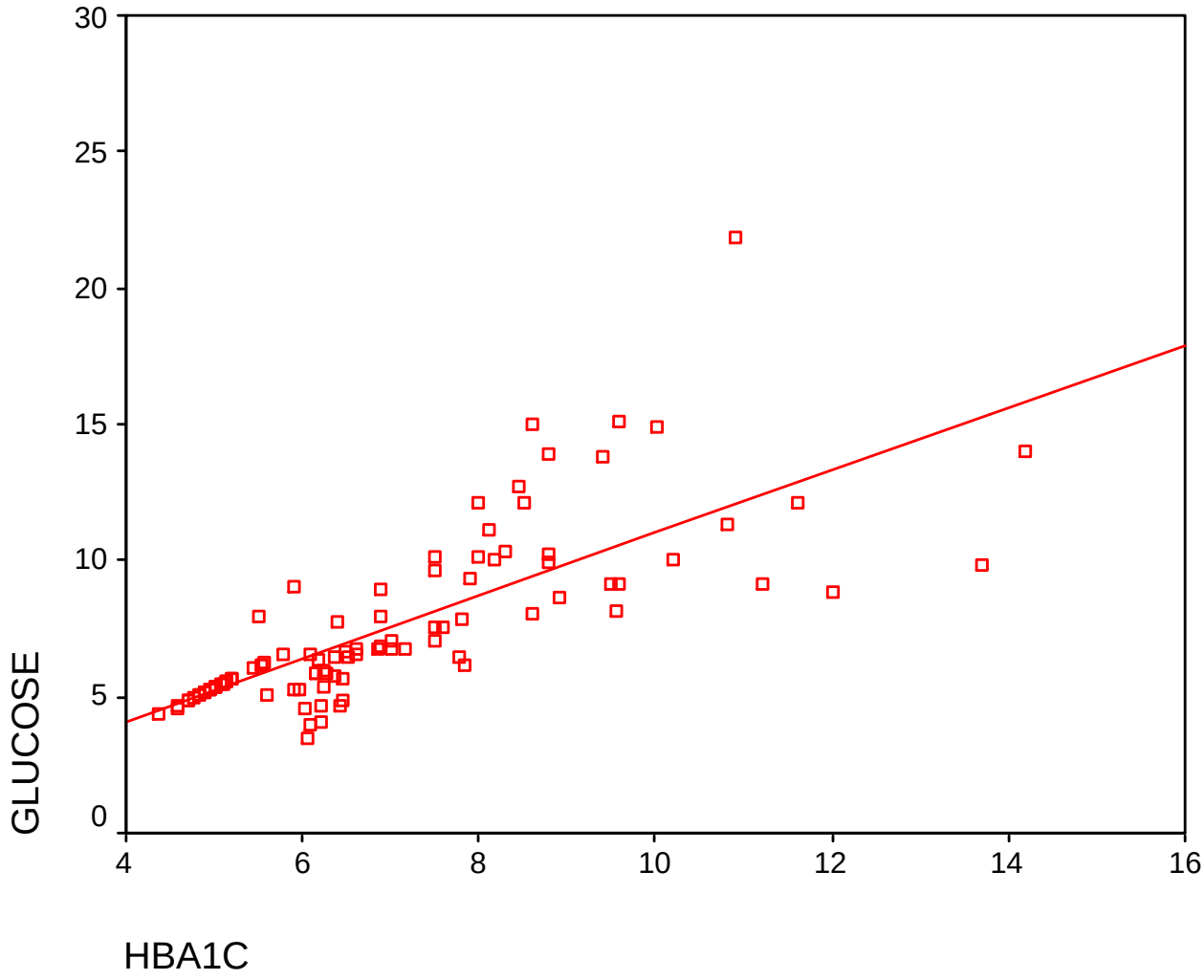

Fig (4.1) Relationship between levels of Glucose in mmol/L and HbA1c in % r=0.760 p=0.000

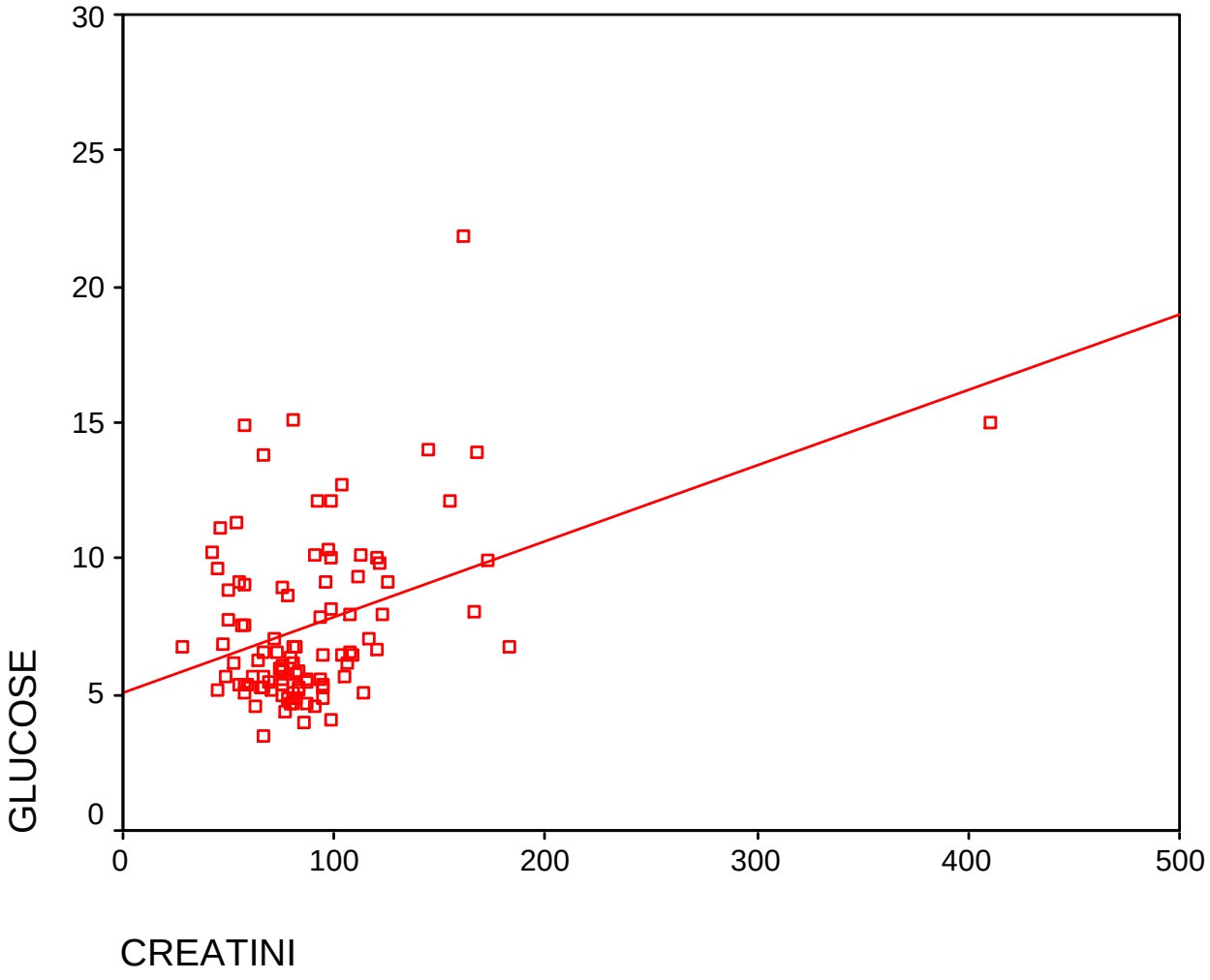

Fig (4.2) Relationship between levels of Glucose in mmol/L and Creatinine in µmol/L

r= 0.399 p=0.000

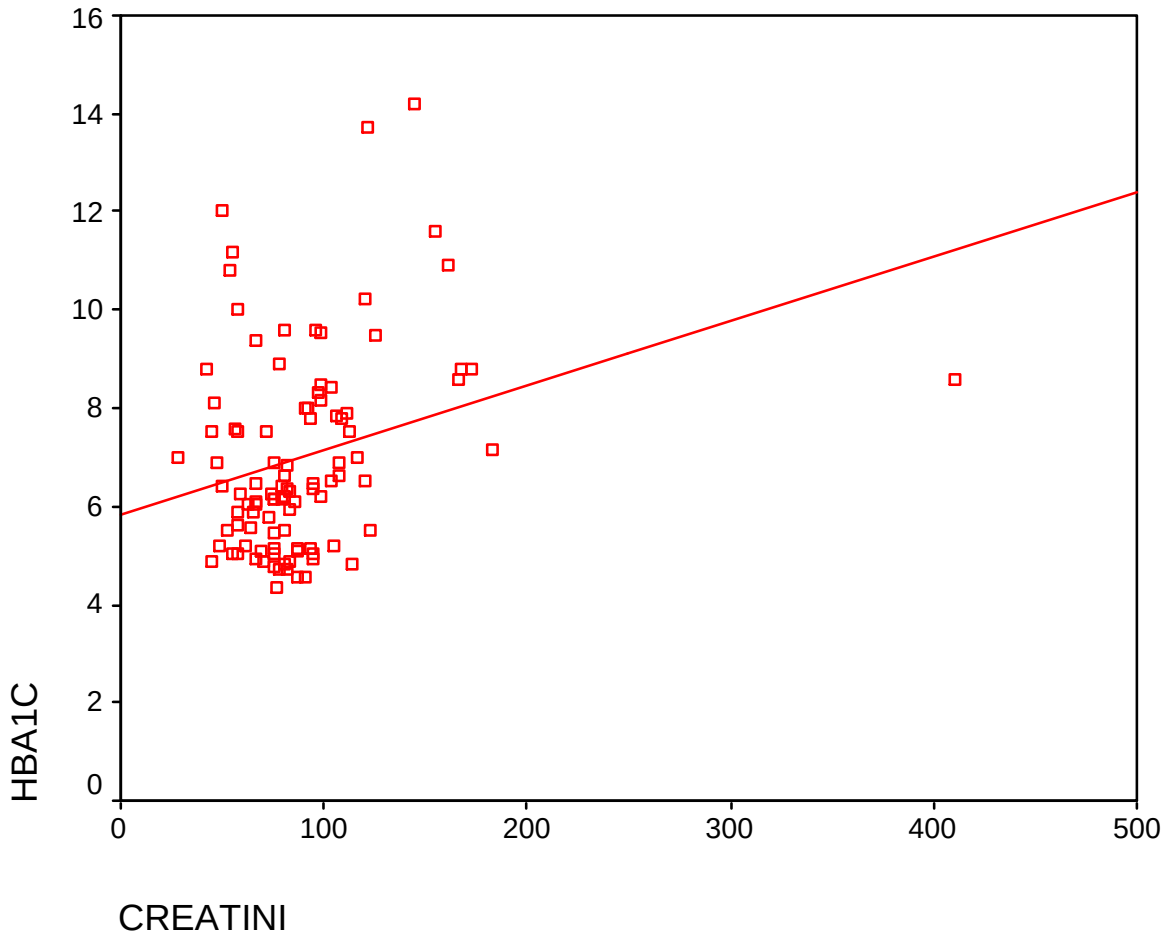

Fig (4.3) Relationship between levels of HbA1c in % and Creatinine in µmol/L r= 0.286 p=0.004

5. Discussion, Conclusion and Recommendation

5.1 Discussion

In the present study there is a significant increase in the mean of creatinine for the test group when it compared with control group (p=0.000), this result is compatible with the results obtained by Aldler , Judykay and Clausen in their report submitted that raised plasma creatinine and urea levels in diabetic patient may indicate a pre-renal problem such as volume depletion. (Alder, *et al*. 2003), (Judkay, 2007), (Clausen, *et al*.1998)

Judykay in his submission suggested that high creatinine levels observed in diabetic patient may be due to impaired function of the nephrons**.** (Judkay, 2007)

The current study shows moderate positive significant correlation between plasma levels of creatinine and glucose (r=0.399 , p=0.000) this agree with that reported by Khawaja AK, Aldler AI, Stevens RJ and Judykay T , study said that the impairment of renal function due to type 2 diabetes mellitus was assessed by measurement of plasma concentration of urea and creatinine. In our study we found an increases in levels of FPG, and plasma creatinine when compared with normal contorls. (Judkay, 2007), (Khawaja, *et al*.2004)

These findings revel that there is strong relationship of blood sugar level with creatinine level . As there is increase in blood sugar levels and increase in creatinine levels has been detected. The plasma creatinine and urea are established markers of GFR, though plasma creatinine is a more sensitive index of kidney function. (Alder, *et al*. 2003).

This study shows a significant correlation between plasma levels of creatinine and Hba1c% (r=0.286 , p=0.004) agree with Rao SS, Disraeli P and Mcgregor T, in their studies said a strong correlation between creatinine and HbA1c was observed, “The level of creatinine was also significantly associated with age in Impaired Glucose Tolerant (IGT) subjects”. (Rao, *et al.* 2004)

For some time, it has been recognized that serum uric acid (UA) is positively associated with serum glucose levels in healthy subjects. (Clausen, *et al*. 1998)

Recent studies have demonstrated that UA levels are higher in subjects with prediabetes and early Type 2 diabetes than I n healthy controls. (Wun, *et al.*1999), (S.Kodama, *et al*.2009)

Furthermore, and elevated serum UA levels was found to increase chances for developing Type 2 diabetes in individuals with impaired glucose tolerance. (Niskanen, *et al*. 2006)

Hyperuricemia has been also added to the set of metabolic abnormalities associated with insulin resistance and/or hyperinsulinemia in metabolic syndrome. (Zavaroni, *et al*, 1993).

The present data clearly demonstrated t hat there is a significant difference between the plasma levels of uric acid in diabetic group and the control group (p=0.000), this result is compatible with the result obtained by A. Dehghan, M. Van Hoek, E. J. G. Sijbrands, A. Hofman, and J. C. M. Witteman , studies reported that there is a positive association between elevated serum uric acid levels and diabetes. (A.Dehghan, *et al*.2008)

The present study shows a weak negative correlation between plasma levels of uric acid and glucose (r= -0.323, p=0.001). Whereas some other studies as Lilliojia S, Mott DM , Spraul M , Ferraro R and Foley JE,shows a negative correlation between hyperglycemia and uric acid, reported no positive association between serum uric acid and diabetes mellitus.

(Lillioja, *et al*.1993)

Also, some studies as Y.Taniguchi, T.Hayashi, K.Tsumura, G.Endo, S.Fujii and K.Okada, reported that serum uric acid is inversely associated with diabetes mellitus. (Y.Taniguchi, *et al*. 2001), (E. Oda, *et al*.2009)

The exact reason for why previous studies found a positive relation between uric acid and diabetes is not clear. Most of these studies were limited by small sample sizes, including either men or women and not both, not having data on confounding factors, or were from selected populations such as industrial workers as opposed to general population samples.

(H.Nan , *et al*.2007)

The present study shows a weak positive significant correlation between plasma levels of creatinine and uric acid (r=0.216, p=0.031) these results agree with that reported by SperlingO, Eilam .G, who observed a significant positive correlation between 24 hour urinary creatinine and uric acid excretion. (Sperling, *et al*.1972)

The current study shows a weak negative correlation between plasma levels of uric acid and Hba1c% (r= -0.305, p =0.002).

This study shows strong positive significant correlation between plasma level of Glucose and Hba1c% (r=0.76o, p=0.031) these results agree with that reported with Yudkin JS, Forrest RD and Jackson CA k, the study said the increasing use of HbA1c to monitor long-term glycemic control in diabetic patients is largely the result of data from the DCCT and the U.K. Prospective Diabetes Study showing that HbA1c is strongly correlated with PG .(DCC,1993), the relationship

between HbA1c and PG is complex. Many studies have shown that HbA1c is an index of MPG over the preceding weeks to months. Erythrocyte life span averages 120 days, the level of HbA1c at any point in time is contributed PG levels. (Yudkin, *et al*. 1990)

In summary, there is a predictable relationship between PG and HbA1c, understanding this relationship will allow patients with diabetes and their healthcare providers set appropriate day-to-day PG targets based on HbA1c goals .(Curt , *et al*,2002)

In this study there was a significant positive correlation between the duration of diabetes mellitus and the serum levels of creatinine and uric acid (figure 4.2) **)** shown the comparison of means and std deviation levels of Glucose, HbA1c, Creatinine, and Uric acid between test group with ≤ 10years duration and test group with >10 years duration which agree with ,Thomas MC, Cooper ME ,Shahinfar S and Brenner BM. in their studies reported that because diabetic nephropathy is associated with gradual and progressive golmerular damage that can leads to renal insufficiency and kidney failure . (Thomas, *et al*. 2003)

5.2 Conclusion

From the study, it was concluded that; in Sudanese patients in UAE with type -2 diabetes mellitus:

1- Serum creatinine and uric acid increased in diabetic patients and this increasing is directly proportional with the duration of diabetes.

5.3 Recommendations

It was recommended that:

1- Microalbuminuria as a parameter is more sensitive with diabetes as well as good marker for kidney damage and dysfunction .
2- Large sample size, Body mass index (MBI) and the equal percentage of the gender are more valuable if included in the study.

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Appendix-1

سم الله الرحمن الرحيم

التبرع بعينة دم لاغراض البحث والدراسة

الموافقة علي المشاركة

انا الباحث / ابراهيم حسن حمزه

أرغب في أخذ عينة دم لغرض البحث والدراسة

موضوع البحث / تقويم مستويات الكرياتنين وحمض اليوريك للسودانيين المقيمين بدولة الامارات العربية ومصابين بداء السكري النوع الثاني

اسم المتبرع .....

اوافق ☐ **لااوافق** ☐

التوقيع .....

Appendix -II

بسم الله الرحمن الرحيم

Sudan University of Science and TechnologyCollege of Graduate Studies

Questionnaire

Serum levels of Uric acid and Creatinine in Sudanese Reside in UAE Diagnosed with Diabetes Mellitus Type 2

Name: ……Tele: ……... Age:……years Gender

male ( ) female ( )

Duration of diabetes since diagnosis ……. Years

Complications of diabetes

According to medical records and physical examination:

Renal disease Yes ( )

Heart attach Yes ( ) Stroke Yes ( )

Foot problem Yes ( ) Eye disease Yes ( )

Hypertension Yes ( ) Others …….

Treatment and Drug history:

1-Diet control ( ) 2- Insulin ( ) 3- Oral hypoglycemic drugs ( ) 4-Lipid lowering drugs ( ) 5-Multivitamins ( )

Investigations:

- Fasting Blood Glucose ……. ……mg/dl
- Hemoglobin A_{IC} ……%
- Plasma Creatinine …….. µmol/L
- Serum Urate ……. µmol/L