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Relationship between Urea and Creatinine with Diabetes Mellitus type 2

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

وَأَن لَّيْسَ لِلْإِنسَٰنِ إِلَّا مَا سَعَىٰ (39) وَأَنَّ سَعْيَهُۥ سَوْفَ يُرَىٰ (40)
ثُمَّ يُجْزَىٰهُ ٱلْجَزَآءَ ٱلْأَوْفَىٰ (41)

صَدَقَ ٱللَّهُ ٱلْعَظِيمُ

الإهداء

أولا وقبل كل شيء، نشكر

الله لأنه منحنا الصبر والقوة لتحقيق انجاز

هذا العمل، الى رفاق الخطوة الاولى و الخطوة ما قبل الاخيرة

الى كل اساتذتي واخص منهم بالذكر مشرف البحث: د. دعاء

عظيم تقديرنا وشكرنا لجميع أعضاء هيئة التدريس في كلية الصيدلة

على مدى السنوات الخمس الماضية.

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Abstract

Diabetes mellitus is a metabolic disease that is marked by an increase in blood glucose levels exceeds normal limits. One of the effects of diabetes mellitus is kidney function disorder. Many researches about diabetes mellitus found that patients have uncontrolled levels of urea and creatinine. The purpose of this study was to determine urea and creatinine levels in patients with diabetes mellitus.

His disease of Type-2 DM rapidly had become a problem of health globally due to a fast-growing and aged population, urbanization and increasing obesity prevalence due to decreasing physical activity. The case of diabetic-nephropathy is concerned with the most important reasons for chronic kidney failure. For assessing kidney function, all of the serum urea, as well as creatinine, are mostly use.

Chapter One

1.1.Introduction

Diabetes mellitus (DM) is a major public health issue affecting more than 400 million people worldwide[1]. This metabolic disorder progressively leads to chronic micro vascular, macro vascular and life threatening complications. Diabetes mellitus is caused either by deficiency of insulin secretion, damage of pancreatic β cell or insulin resistance. Inclination to sedentary lifestyle may be the major reason for the continual rise in the number of patients Diabetes globally which is expected to strike 366 million in 2030 in the elderly population (>65years) [2]. .The various complications associated with DM includes nephropathy, neuropathy, cardiovascular and renal complications, retinopathy.

1.2.Creatinine with diabetes

Creatinine is found in serum, plasma, and urine and is excreted by glomerular filtration at a constant rate and in the same concentration as in plasma. Creatinine is a more reliable indicator of renal function than BUN because it is less influenced by other factors such as diet and hydration.
Here are the normal values by age: 0.9 to 1.3 mg/dL for adult males. 0.6 to 1.1 mg/dL for adult females. 0.5 to 1.0 mg/dL for children ages 3 to 18 years.
Creatinine is found in serum, plasma, and urine and is excreted by glomerular filtration at a constant rate and in the same concentration as inplasma. Creatinine is a more reliable indicator of renal function than BUN because it is less influenced by other factors such as diet and hydration[3].

Levels of creatinine can indicate that your kidneys aren't working well. There are many possible causes of high creatinine, some of which may be a one-time occurrence. Examples can include things such as dehydration or intake of large amounts of protein[4].

1.3.Urea with diabetes

The concentration of urea (urea) or the concentration of nitrogen in the blood urea (blood urea nitrogen) is checked. Urea is the end product of protein metabolism in the body, produced in the liver from ammonia, and in the liver from ammonia.
Urea and creatinine are nitrogenous end products of metabolism. Urea is the primary metabolite derived from dietary protein and tissue protein turnover. Creatinine is the product of muscle creatine catabolism.
Higher levels of urea may increase insulin resistance and suppress insulin secretion. However, whether higher levels of blood urea nitrogen (BUN) are associated with increased risk of incident diabetes mellitus in humans is not known [5].
Correlation in diabetic and non-diabetic subjects in a tertiary hospital and study the variation in serum urea and creatinine levels in relation to blood sugar levels in type 2 diabetic patients in comparison with the levels in non–diabetic control subjects. The variations in serum urea and creatinine levels in type 2 diabetic patients in relation to duration of disease were studied. We studied the usefulness of estimation of the serum creatinine and urea levels in type 2 diabetics as a simple easily available tool for diagnosis and prognosis of diabetic nephropathy[6].

The relationship between Urea and Creatinine with type 2 diabetes mellitus is not as straight forward as one might think. Although a rise in urea levels can lead to an increase in creatinine level, this relationship changes depending on when the kidney starts having problems processing Urea. If the kidneys stop being able to process Urea well, the level of Creatinine will elevate even if there is a decrease in Urea levels.

1.4. Classification of Diabetes Mellitus

According to the American Diabetes Association (ADA) and most national and international diabetes organizations, diabetes can be classified into the following general categories
- Type 1 diabetes (T1DM) (due to autoimmune beta cell destruction, usually leading to absolute insulin deficiency) [7].
- Type 2 diabetes (T2DM) (due to a progressive loss of beta-cell insulin secretion usually with a background of insulin resistance) .
- Gestational diabetes mellitus (GDM)
- Specific types of diabetes due to other causes (8).

1.5. Diagnosis of Diabetes Mellitus

Diagnosis of DM is depended on many different tests after clinical examination and complete history to document the physician suspicion of DM , like HbA1c (glycated hemoglobin), blood fasting glucose and oral glucose tolerance test (OGTT) [9].
American diabetes associated (ADA)
criteria for diagnosing DM are shown in the figure 1-1 [10].

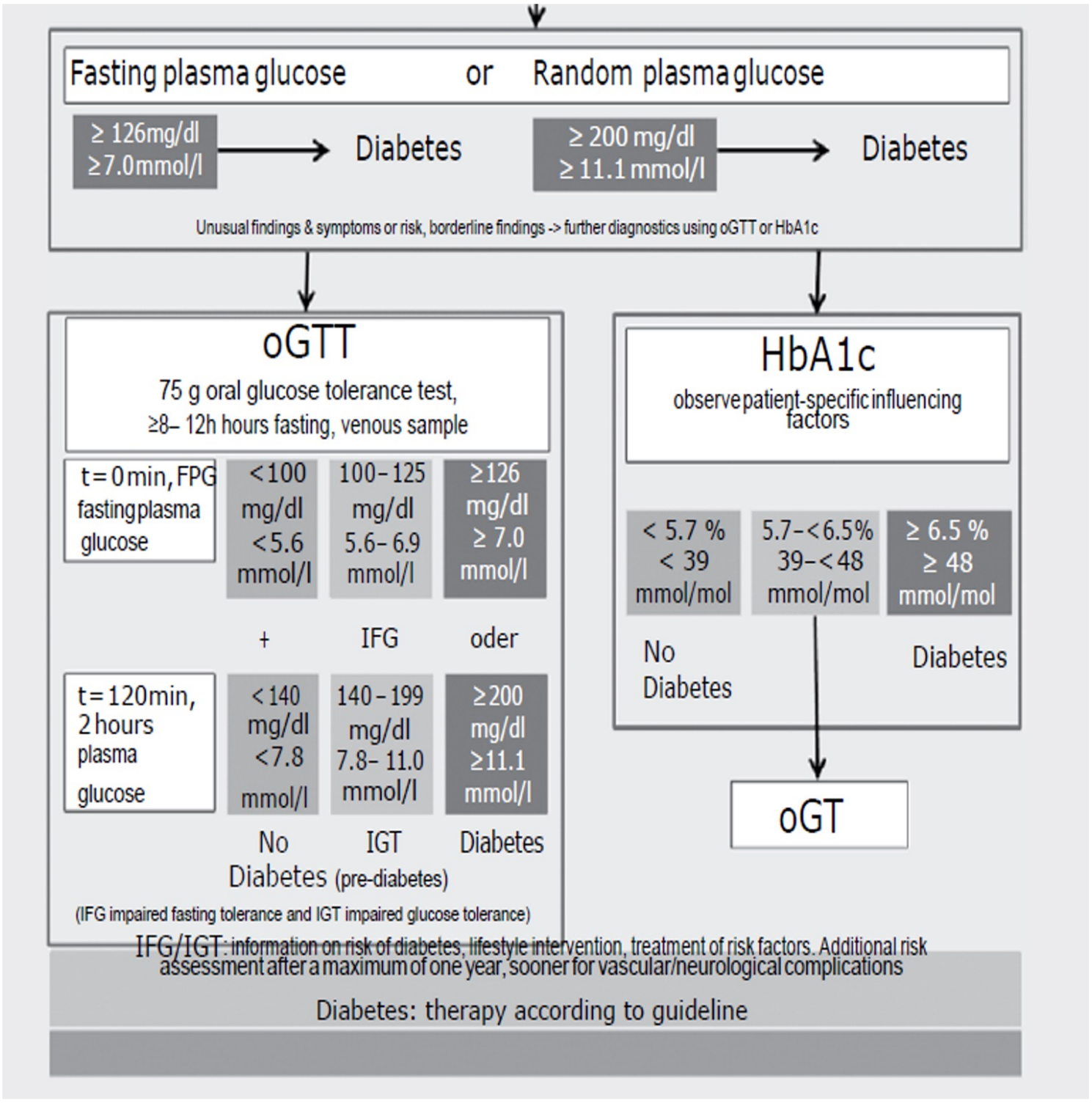

Fig.1- 1 Diagnostic approach for diagnosing diabetes

1.6.Type 2 Diabetes Mellitus (T2DM)

Diabetes mellitus comprises a series of metabolic disorders featured by abnormally high glucose level in blood. [11].

Type 2 DiabetesMellitus T2DM develops because of insulin resistance of human organs.and insufficient secretion of insulin from pancreatic β-cells [12]. Patients with T2DM may proceed with severe long-term complications including heart, kidney, retinopathy, and foot problems that increase the risk of mortality [13].

Kidneys: Increased Glucose Production And Reabsorption

The kidneys have an impact on glucose homeostasis by way of three main functions:-

1. Release glucose directly into the plasma by way of gluconeogenesis.

2. Take up glucose from the circulation to meet energy needs.

3. Reabsorb glucose from the glomerular filtrate, returning glucose to plasma circulation

In the pathogenesis of T2DM, there are 2 manifestations observed in the kidneys: increased gluconeogenesis and increased glucose reabsorption [14].

These 2 shortcomings directly affect blood glucose levels and exacerbate hyperglycemia.

1.7.The reasons

Type 2 diabetes is primarily caused by two interrelated problems.

Cells in muscle, fat, and liver become resistant to insulin. Because these cells do not react normally to insulin, they do not absorb enough sugar .

The pancreas becomes unable to produce enough insulin to control blood sugar levels .The exact reason for this is still unknown, but one of the main factors that contribute to this condition is being overweight and not exercising .How does insulin work ?Insulin is a hormone produced by the gland behind and below the stomach (pancreas). Insulin regulates the way the body uses sugar in the following ways :The sugar in the bloodstream stimulates the pancreas to secrete insulin .Insulin moves into your bloodstream, allowing sugar to enter your cells .The amount of sugar in the bloodstream decreases .In response to this decrease, the pancreas secretes less insulin.

1.8.Type2 Diabetes Mellitus Management

Modification of lifestyle, including weight loss, increasing physical activity and adopting a healthy diet, remain one of the first-line strategie for the management of T2DM [16].

The treatment of T2DM safeguards patient-centered therapeutic individualization and is initiated by the alteration of the individual lifestyle, counterworking sedentarism, and obesity through the increase of physical activity and adoption of a balanced diet [17].

However, withprogressive decline of pancreatic β _-cells function, medication is required generally for extended periods of time [18].

The pharmacological therapies are mainly based on increasing insulin availability either by direct administration of insulin or via agents promoting insulin secretion, improving insulin sensitivity, delaying gastrointestinal absorption of carbohydrates, and/or increasing glucose excretion [19].

The administration of insulin allows glycemic control, but is related to weight gain due to an increase in body fat mass, especially abdominal obesity, with consequent increase in insulin resistance, as well as episodes of hypoglycemia when the treatment is not performed properly[20].

Diet influences body weight, glucose, and insulin homeostasis being recognized as a risk factor for the development of T2DM [21].

There is unanimity on the importance of body weight control, reduction of energy intake coupled with exercise, and healthy diet with low intake of processed foods (rich on refined sugars and flour) and high consumption of whole grains, fiber, polyunsaturated fatty acids, fruits, vegetables, and low-fat dairy products for the control and prevention of T2DM [22].

In addition to lifestyle modification, social support has an important role in T2DM management as it directly affects the performance of diabetes mellitus self-care behaviours and indirectly affects glycaemic control[23].

For example, patients whose family members exhibit non-supportive behaviours have reduced adherence to diabetes mellitus medication regimens[24].

1.9.Aim of study

The aim of our study was to measure serum urea and serum creatinine levels and evaluate their.

Chapter Two

2.1.Subjects Groups and Study Design

This study was performed at the laboratory of Chemistry and Biochemistry Department, College of Medicine, University of Babylon. The study composed of 30 subjects of type 2 diabetes mellitus patients and 15 subjects were represented as healthy controls .All samples were collected from Marjan and Imam Al-Sadiq teaching Hospitals.

2.2.Materials and Methods

Kinetic test without deproteinization. Reagent for the quantitative determination of creatinine in human plasma and urine. The tools used in this study include equipment blood sampling (syringes, non-anticoagulant .
vacuum tubes, alcohol swabs, plasters, tourniquet, and label), centrifuge and micropipette. The ingredients used in this study include serum blood.
Creatinine is produced after the breakdown of creatine (muscle protein) by the kidneys. The creatinine level provides information on the functioning of the kidneys and on the patient's muscle mass. A high creatinine level is often a sign of kidney failure. The measurement of its clearance is therefore an indicator of the glomerular filtration rate. A low level of creatinine can be a sign of myopathy (severe muscular atrophy).
Creatinine forms a colored complex with picric acid in an alkaline medium. The rate of formation of this complex is proportional to the concentration of creatinine

Reagents

Reagents 1	**Sodium hydroxide**	**1.6 mmole/L**
Reagents 2	Picric acid	17.5 mmole/L
Reagents 3 standard	Standard creatinine	2 mmole/L 20 mmole/L 176.8 mmole/L

Working Reagent
Mix proportionally 1:1; the reagent R1 and R2.
Stability; 1 month at 20-25˚C.
Blood samples
Five ml of venous blood sample were collected from the patients serum will separated by centrifugation.

2.3.Creatinine test

A creatinine test is used to see if your kidneys are working normally.

2.3.1.Principle :

Creatinine reacts with picric acid in an alkaline solution to form a reddish colored complex. The reaction is commonly known as the Jaffe reaction and the red colored product as the Janovski complex.

2.3.2.Materials required for this test :

•Sample
•Blank tube
•Mechanical pipette
•Spectrophotometer
•Rack
•Creatinine kit contain (R1, R2, standard)

2.3.3.Procedure

1. Take three blank tubes and name the first the (sample), the second (standard), and the third (blank) with a pen.
2. Put in each tube 500 µl of R1.
3. Put in each tube 500 µl of R2 and mix it.
4. Put 100 µl of distill water in the blank tube to clear the Spectrophotometer.
5. Put 100 µl of standard in the standard tube and mix it Then we put it directly in the Spectrophotometer and take the first reading (A1) after 30 seconds and take the second reading (A2) after two minutes and 30 seconds.
6. Put 100 µl of serum into the sample tube and mix it Then we put it directly in the Spectrophotometer and take the first reading (A1) after 30 seconds and take the second reading (A2) after two minutes and 30 seconds.
7. The wavelength of the Spectrophotometer is 490 λ.

2.4.Urea test

The concentration of urea (urea) or the concentration of nitrogen in the blood urea (blood urea nitrogen) is checked. Urea is the end product of protein metabolism in the body, produced in the liver from ammonia, and in the liver from ammonia.

Principle:

The principle of the test is the ability of H. pylori to secrete the enzyme urease, the sample (e.g. gastric biopsy) is placed in a gel containing urea. The urease produced by H. pylori rapidly hydrolyzes urea, producing ammonia, which causes the indicator to change color.

2.4.1Materials required for this test:

1. Sample (serum)
2. Blank tube
3. Pipette
4. Water bath
5. Spectrophotometer
6. Rack
7. Urea kit contain (R1, R2, standard)

2.4.2.Procedure:

1. I take three blank tubes and name the first the (sample), the second (standard), and the third (blank) with a pen.
2. Put in each tube 1000 µl of R1.
3. Put 10 micrometers of serum into the sample tube and mix it.
4. Put 10 µl of standard in the standard tube and mix it.
5. Put 10 µl of distill water in the blank tube and mix it.
6. We put tubes in the water bath at 37C° for 5 minutes.
7. After 5 minutes, we take it out of the water bath and add 1000 µl of R2 to all tubes.
8. We return it to the water bath for 5 minutes at 37 °C.
9. Then we put it in the spectrophotometer to read the results

Chapter Three

Results and Discussion

3.1 Demographic characteristics of Studied groups:

The results of the current comparative study of the patient and control groups were calculated statistically using the t-test to determine the difference in mean between the control and patient groups as well as the correlation between the different parameters of all patients. The total number of study groups was 45 adults (male and female) .The results of demographic data are shown in Table

investigations	Controls No.(15) Mean ±SD	Diabetics No.(30) Mean ±SD	Significance
Age of the individuals	43 ± 3.2	45.46 ± 8.2	NS
Fasting Blood Sugar (FBS) mg/dl	93.95 ± 13.46	223.16 ± 85.07	S
Serum Urea mg/dl	23.06 ± 5.96	23.96± 31.06	NS
Serum Creatinine mg/dl	0.75 ± 0.12	1.63 ± 1.28	S

3.2. Discussion

Affected kidney function resulting from type 2 DM was estimated by testing the plasma levels of creatinine and blood urea in diabetics and non-diabetic controls. Although the plasma creatinine is the more responsive index for kidney dysfunction, plasma creatinine and blood urea are well-known markers for GFR. An increment in urea value is observed whenever there was kidney damage or ineffective kidney function. Raising of urea concentration with the raising of sugar level determines that the augment blood sugar concentration results in renal damage. Research carried out by Anjanaeyulu et al -2004 had noticed that elevated urea and serum creatinine in diabetic rats indicates progressive kidney damage[25].

Study observations found that blood glucose concentration, plasma creatinine and urea concentrations were noticed to be greater in type 2 DM subjects [26],[27]. This showed that increased plasma creatinine and urea levels in diabetic patients would indicate a pre-renal disorder. A Saudi study carried out by Abdulrahman Aldukhayl in 2017 showed a comparison between many Arabian countries in regards to the prevalence of diabetic nephropathy

clarifying that Iraq had a medium prevalence of DN while UAE had the highest prevalence when Bahrain had the lowest[28].
This study outcome showed that poorly controlled levels of blood sugar would cause rising levels of blood urea which would increase the probability of the patients suffering from diabetic nephropathy. This agrees with the results of previous study findings which found that hyperglycemia is the main reasons for progressive kidney damage [29].
All of the serum creatinine and blood urea were greater (although insignificantly which may because of the small sample size of this study) in males than females. The same finding was reported by an Iraqi study conducted by Ali A Ali 2013 [30].

3.3.Conclusion

One of the ways to prevent chronic kidney failure is to control the level of blood glucose which assists the prevention of progressive kidney impairment as well as diabetic nephropathy. To prevent the development of diabetes mellitus into diabetes nephropathy there is a need to monitor the serum urea and creatinine.
Diabetic nephropathy, especially related to type 2 diabetes, has become the single most important cause of diabetes, end-stage renal disease (ESRD), growing recognition that nontraditional risk factors such as increased S. urea, elevated serum creatinine levels, may also be important in individuals with chronic kidney disease. The importance of the identification of levels of S. urea as well as serum creatinine to predict the development of (ESRD) in patients with type 2 diabetes and nephropathy.
Good control of blood glucose level helps to prevent progressive renal impairment and diabetic nephropathy is one of major cause of chronic renal failure. In order to prevent the progression of diabetes mellitus to diabetic nephropathy, vigilant monitoring of serum urea and creatinine are simple biomarkers available in patients with proteinuria if micro albuminuria screening test cannot be performed. We would like to conclude that blood urea and serum creatinine levels are simple tests helpful in diabetics who are poorly controlled to assess the renal function.

3.4.Recommendations

Good control of blood sugar levels is necessary to prevent the development of kidney nephropathy in patients. We suggest a larger population for the next research for exact results.

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