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Evaluation of Cystatin C Levels in the Early Stage for Diagnosis of the Patients with Disbetic Nephropathy in Babylon Governorate , Iraq

A Graduation Research Project Submitted to the Council of Faculty of Pharmacy in the Partial Fullfillment of the Requirement for the University of Babylon

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(وَأَن لَّيۡسَ لِلۡإِنسَٰنِ إِلَّا مَا سَعَىٰ وَأَنَّ سَعۡيَهُۥ سَوۡفَ يُرَىٰ ثُمَّ يُجۡزَىٰهُ ٱلۡجَزَآءَ ٱلۡأَوۡفَىٰ)

صدق الله العلي العظيم

سورة النجم الآية (39–41)

Dedication

This thesis dedicated to our parents, and to my beloved sister who have always loved us unconditionally and have been a constant source of support and encouragement during the challenges of graduation and life

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We would like to express our special thanks to our supervisors assistants lecturers **(Sabreen Hassan**) and **(Zahraa Majid**) for their support and guidance during the study.

We are very grateful for them for their efforts in managed their times for us to make it convenient for us through the study.

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LIST OF ABBREVIATIONS

Abbreviation	
ADA	American Diabetes Association
AER	Albumin Excretion Rate
BCG	Bromo Cresol Green
BGL	Blood Glucose Level
BMI	Body Mass Index
CBVD	Cerebro Vascular Disease
CCr	Creatinine Clearance
CKD	Chronic Kidney Disease
CKF	Chronic Kidney Failure
CVD	Cardio Vascular Disease
DM	Diabetes Mellitus
DN	Diabetic Neuropathy
DNP	Diabetic Nephropathy
DR	Diabetic Retinopathy
ECM	Extra Cellular Matrix
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme Immunoassay Technique
ESRD	End Stage Renal Disease
ESRF	End Stage Renal failure
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
HNS	Hyperosmolar Non ketotic States

IDDM	Insulin Dependent Diabetes Mellitus
IDMS	Isotope Dilution Mass Spectrometry
MAU	Micro Albumin Urea
MDRD	Modification of Diet in Renal Disease
NIDDM	Noninsulin Dependent Diabetes Mellitus
OHA	Oral Hypoglycemic Agents
PVD	Peripheral Vascular Disease
ROC	Receiver Operating Characteristic
Scr	Serum Creatinine
STZ	Strep To Zotocin
T1DM	Type 1 Diabetes Mellitus
T2DM	Type II Diabetes Mellitus
TKF	Terminal Kidney Failure
UAE	Urinary Albumin Excretion
UTI	Urinary Tract Infection

Summary

Background: Diabetic nephropathy is a significant cause of morbidity and mortality in patients with diabetes mellitus (DM). The condition is characterized by persistent albuminuria and decline in the glomerular filtration rate (GFR). Serum cystatin C has been proposed as a simple and accurate.

Diabetic nephropathy (DNP) is typically defined by microalbuminuria—that is, a urinary albumin excretion of 30-300 mg/ml or macro albuminuria and abnormal renal function as represented by an abnormality in serum creatinine, calculated creatinine clearance, or glomerular filtration rate (GFR). Clinically, diabetic nephropathy is characterized by a progressive increase in proteinuria and a decline in GFR and hypertension.

Changes in albuminuria are considered a hallmark of onset or progression of DNP. However, some patients with diabetes have advanced renal pathological changes and progressive kidney function decline even if urinary albumin levels are in the normal range, indicating that albuminuria is not the perfect marker for the early detection of DNP. Creatinine are considered the gold standard methods for estimating GFR. Serum creatinine demonstrates an inadequate sensitivity, particularly in the early stages of renal impairment.

Cystatin C is a plasma protein that has a low molecular mass freely filtered through the glomerulus and reabsorbed completely by tubular cells. It has been proposed as a new and very sensitive serum marker of changes in GFR.

Aim of the study: - To assess serum levels of cystatin C to compare with some biochemical parameters and to a predictor of early stage type2

diabetic nephropathy. Serum cystatin C has been proposed as an endogenous marker of glomerular filtration rate (GFR) because it shows a correlation with the albumin to creatinine ratio (ACR) in diabetic nephropathy.

Method:-In this study, 100 patients with diabetes mellitus type II (50 patients with diabetic nephropathy and 50 patients without diabetic nephropathy). Body mass index(BMI) were measured for each participant .Blood samples were obtained in the morning for measurement of serum cystatin C, creatinine, blood urea, blood glucose, cholesterol, and urine sample for measured microalbuminuria .

Results : -The two groups of diabetic patients were separate depending on the presence or absence of microalbuminuria in urine 30-300mg/ml(patients with nephropathy and without nephropathy) respectively. Results showed a significant increase $P \leq 0.05$ in cystatin c ,creatinine, blood urea, GFR, albumin, cholesterol in diabetic patients with early nephropathy compare with diabetic patients without nephropathy. There were no significant differences between females and males, as well as between normal and overweight for the studied tests. The percentage of patients with abnormal parameter in diabetic patients with nephropathy was cystatin c 46%, creatinine 2%, urea 30%,GFR 46%,albumin2%,

cholesterol 74% while the percentage of other group cystatinc, creatinine, GFR, and albumin was zero ,and for urea4%,cholesterol 46% . There were a significant positive correlation between serum creatinine and cystatin C among diabetic patients (N= 100, r =0.281, P= 0.005*) , between blood urea and cystatin C (N= 100, r =0.25, P= 0.012*), positive correlation between serum cholesterol and cystatin C (N= 100, r =0.237, P= 0.018*) and positive

correlation between Cystatin C and micro albuminuria(N= 50, r =0.315, P= 0.026*) in diabetic patients type II. There were a significant negative correlation between Cystatin C and GFR (N= 100, r = -0.363, P= 0.001*).

No significant correlation between serum albumin and cystatin C among diabetic patients (N= 100, r =0.187, P= 0.062).

Conclusion :- The results of this study suggest that Cystatin C measurement in serum is a useful and practical test for the evaluation of early stage type II diabetic nephropathy.

Chapter One

Introduction and litreture Review

1. *Introduction*

1.1 Diabetes Mellitus:-

Diabetes mellitus (DM) is a metabolic systemic disorder characterized by a tendency to chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolisms that are high from a defect in insulin secretion or action or both. It is a common condition in Iraq (1) .The prevalence of diabetes in Iraq is approximately 19.7%. There are two distinct types: in type 1 DM, there is a destruction of pancreatic cells due to a decrease in, and eventually cessation of insulin secretion. Approximately ,10% of all patients with diabetes have type I. They have an absolute requirement for insulin. In type 2 DM, insulin secretion is defective and delayed, and there is a resistance to its action. The prevalence of both types of diabetes is increasing (2).

The long-standing high of blood glucose causes the chronic complications of diabetes level including atherosclerosis, retinopathy, nephropathy, and neuropathy. Hyperglycemia causes chronic complications in cells where entry of glucose is not dependent on insulin, increase blood glucose due to increased intracellular glucose and its metabolites. Hyperglycemia promotes the condensation of glucose with cellular proteins in a reaction similar to the formation of HbA1c .

Micro albuminuria is defined as albumin excretion of 30–300mg/ml. Without intervention, diabetic patients with micro albuminuria typically progress to proteinuria and overt diabetic nephropathy. As many as 7% of patients with type II diabetes may already have micro albuminuria at the time they are diagnosed with diabetes. In the united kingdom prospective diabetes study (UKPDS), the incidence of micro albuminuria was 2% per year in patients with type II diabetes, and the 10-year prevalence after diagnosis was 25% (3). Assessment of diabetic nephropathy the most tests used to determine renal function are those that assess either GFR or the integrity of the

glomerular filtration barrier, and detection of GFR can be made by measuring the urinary excretion of substance that is completely filtered from the blood by the glomeruli and is not secreted, reabsorbed or metabolized by the renal tubule (clearance) (4). Cystatin C has been identified as a new, promising, and easily measurable marker for prompting detection of early kidney failure (5).

Cystatin C is produced at a constant rate by nucleated cells and released into the blood stream with a half-life of 2 h (6). Cystatin C is freely filtered and is almost completely taken up and degraded, but not secreted, by proximal tubular cells. Several studies have used direct measures of GFR as the gold standard to compare cystatin C with creatinine and creatinine- derived estimates of Glomerular Filtration Rate GFR (7).

1.1.1. Type I Diabetes Mellitus:-

It was formerly termed insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes, and it usually occurs in children or young adults, It accounts for 5-10% of diabetes adult, but it can occur at any age (8). It is characterized by severe insulin deficiency as common by low or undetectable levels of plasma C-peptide. It is further divided into type 1A, which is immune mediated, and type 1B, which has no defined etiology for the insulin deficiency (Idiopathic) (9). Immune mediated form of disease results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas(10).This autoimmune process is due to genetic and environmental factors(8). Markers of the immune destruction of the β-cell include islet cell autoantibodies, insulin autoantibodies, glutamic acid decarboxylase autoantibodies, and autoantibodies to insulinoma antigen IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85-90% of individuals when fasting hyperglycemia is initially detected (10).

There is ample evidence suggesting that autoimmune diseases, such as Addison’s disease, pernicious anemia, and autoimmune thyroid disease are

involved in the etiology of T1DM (11). Idiopathic diabetes has no known etiologies and a minority of patients with T1DM falls into this category. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity .This form of diabetes is strongly inherited (10).

1.1.2 .Type II Diabetes Mellitus:-

This type of diabetes previously referred to as noninsulin dependent diabetes mellitus (NIDDM), or adult onset diabetes (12). It comprises approximately 90-95% of all patients with diabetes(8) .It is characterized by insulin resistance in muscle, liver and adipose tissue and usually individuals have relative (rather than absolute) insulin deficiency (i.e. patients secrete insulin, but not enough to overcome the insulin resistance)
(13).while patients with this form of diabetes may have insulin levels that appear normal or increase, the high blood glucose levels in these diabetic patients would be expected to result in even increase insulin values had their β-cell function been normal (10).

Some individuals have essentially normal insulin action,but markedly impaired insulin secretion (12).In contrast to T1DM, patients with T2DM do not depend on exogenous insulin to survive. However, they may require insulin for correction of fasting hyperglycemia if this cannot be achieved with the use of diet or (OHA) (9)**.**Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection (10)**.** In most patients with T2DM diagnosis made in adult years, the disease also occurs in young people who do not require insulin, not ketotic, and hence could not be considered to have T1DM. The average age at diagnosis of T2DM is much earlier in very high prevalence groups, and somewhat earlier in medium prevalence groups **(9)**.

The disease due to develop slowly, and most patients of this condition are undiagnosed for many years because the hyperglycemia is often not severe enough to provoke noticeable symptoms of diabetes. Such patients are at increased risk of developing macrovascular and microvascular complications for a long period of time before diabetes is detected (12).Type 2 DM is strongly associated with genetic predisposition, more so than is the autoimmune form of T1DM (10). However, the etiology of disease is heterogeneous because a variety of lifestyle and environmental factors has been identified as being risk factors for the condition (9).The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity (12).

1.1.2.1.Insulin Resistance:-

Is a state in which a given concentration of insulin produces a less than expected biological effect. Insulin resistance has also been arbitrarily defined as the requirement of 200 or more units of insulin per day to attain glycemic control and to prevent ketosis (14). The syndromes of insulin resistance actually make up a broad clinical spectrum, which includes obesity, glucose intolerance, diabetes, and the metabolic syndrome, as well as an extreme insulin-resistant state. Many of these disorders are associated with various endocrine, metabolic, and genetic conditions. These syndromes may also be associated with immunological diseases and may exhibit distinct phenotypic characteristics (15).

1.1.3. Other Specific Types of Diabetes:-

These groups of DM include various etiologies in which the cause is established or at least partially known. The causes include known genetic

defects of β-cell function or insulin action, diseases of the exocrine pancreas, drug or chemical induced pancreatic changes, infections, genetic syndromes and other endocrinopathies (10).Such types of diabetes account for 1-5% of all diagnosed cases(16).

1.1.4. Signs and Symptoms of DM:-

The classic symptoms of untreated diabetes are weight loss, polyuria (increase urination), polydipsia (increased thirst), and polyphagia (increase hunger) (17). Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may subtle or absent in type 2 DM. Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes (18).

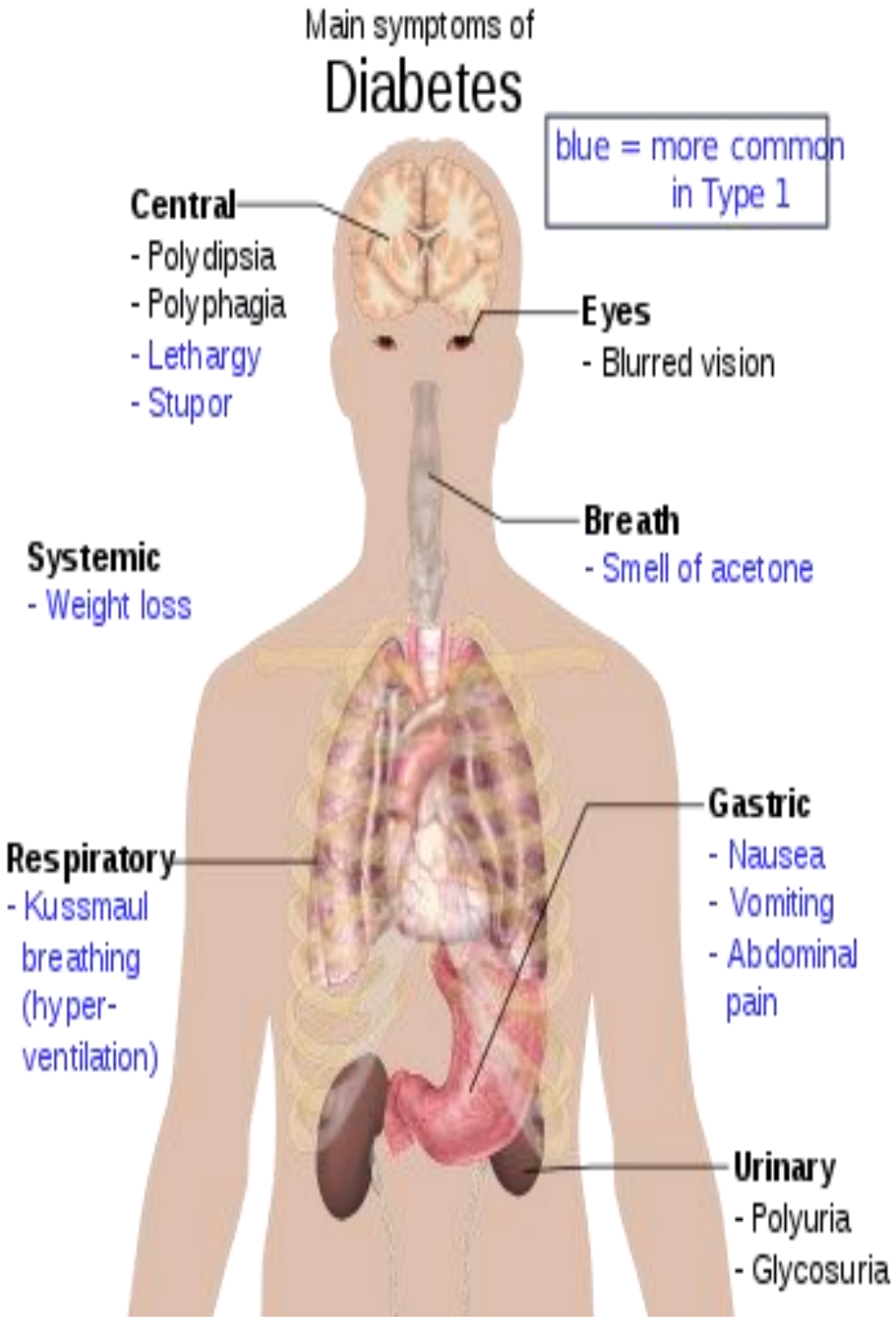


Figure (1.1):-overview of the most significant symptoms of diabetes.

1.1.5. Diagnosis of Diabetes Mellitus:-

Symptoms of hyperglycemia (e.g. polyuria, polydipsia, unexplained weight loss, visual blurring, genital thrush, lethargy) and raised venous glucose detected once – fasting as follows:-

1- HbA1c ≥ 6.5%.

2- Random plasma glucose ≥200 mg⁄dl (11.1 mmol/l).

3- Fasting plasma glucose ≥ 126 mg⁄dl (7.0mmol/l).

or two- hours plasma glucose level≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test OGTT (ADA, 2011).

1.1.6. Epidemiology of Diabetes Mellitus:-

Diabetes is world-wide in distribution and the incidence of both types is rising. However, the prevalence of both varies considerably in different parts of the world and this is probably due to differences in genetic and environmental factors. Diabetes affects 1–2% of the population worldwide (19). The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (20).Diabetes is a leading cause of both mortality and early disability; in the United States, it is the leading cause of blindness among working-age adults, end-stage renal disease, and non-traumatic limb amputations (21).

1.1.7. Diabetic Complications:-

Diabetes as a chronic condition requires a careful control. Without proper control, management and follow-up, it can lead to various complications. These complications may be divided to short and long term complications.

1.1.7.1. Short-term DM Complications

It is acute metabolic complications manifested by increased lipolysis with fatty acid release and accumulation of fat in parenchymal organs further aggravates the metabolic disturbance:-

***Ketoacidosis :-**Insulin is principal signal in converting many of metabolisms from a catabolic to anabolic direction and vice versa. Lack of insulin with excess of glucagons permits to gluconeogenesis and lipolysis .β - Hydroxybutyrate and Acetone lead to decreases the blood's pH . Diabetic ketoacidosis can cause severe dehydration, electrolyte disturbances, hypotension, shock, and death may occur. Individuals with type-1 have tendency to produce ketones while it is rare in type 2, as still producing insulin, which has a greater tendency to develop hyperosmolar non ketotic states (HNS),resulting in concomitant loss of water and if it is prolonged, it will result in electrolyte imbalances and may progress to coma (22).

***Hypoglycemia:-** involves decreased plasma glucose levels. Excess insulin(if the glucose intake does not match the treatment) results in blood glucose level(BGL) below normal fasting level leading to mental confusion and possible loss of consciousness, coma and/or seizures, or even brain damage and death.

***Infections:-** bacterial/fungal: diabetics increased the risk of cystitis and more important of serious upper urinary tract infection as well as ear, nose, and throat infections, necrotizing otitis externa principally occurs. Skin and soft tissue infections are common in DM and may spread to adjacent bone causing osteomyelitis infection (23).

1.1.7.2. Long-term DM complications

Many patients with type 2 diabetes are asymptomatic, and their disease is undiagnosed for many years. Therefore, interfering with the cardio-renal axis is an important therapeutic objective. The duration and intensity of high BGL play an important role in glycosylation of proteins and leads to changes in the shape of the endothelial cells lining the blood vessels, glycoprotein formation, basement membrane become thickening and weak (24). The complications of

DM can be divided into macro-vascular damage (the arteries) and micro-vascular (damage to small blood vessels) diseases:

- Micro-vascular diseases including:

-Nephropathy.

-Neuropathy.

-Retinopathy.

- Macro-vascular diseases (cardiovascular disease) are more common among patients with type-2 DM (USRDS,2007) including:

-Cerebro-vascular disease.

-Coronary artery disease.

-Peripheral vascular disease .

1.2. Diabetic Nephropathy :-

Is a clinical syndrome characterized by persistent albuminuria >300 mg /ml or >200 microgram /minute that is confirmed on at least 2 occasions 3-6 months apart associated with decline in the glomerular filtration rate ,and elevated arterial blood pressure in absent of stressful conditions (25).

Diabetic nephropathy is an important cause of morbidity and mortality, and is now among the most common causes of end –stage renal failure (ESRF) in developed countries(26). About 30% of patients with type I DM have developed diabetic nephropathy 20 years after diagnosis (27).The principal feature of diabetic nephropathy is proteinuria. This develops insidiously, starting as intermittent microalbuminuria before progressing to constant proteinuria and occasionally nephritic range proteinuria (28).

Microalbuminuria is defined albumin excretion from 30–300 mg/ml. It is most reliable as an indicator of incipient diabetic nephropathy within the first 10 years of type 1 DM, when the majority of patients with microalbuminuria will progress to overt nephropathy within a further 10 years. It is a less reliable predictor of nephropathy in older patients with type 2 DM, in whom it may be

accounted for by other diseases, although it is a potentially useful marker of an increased risk of macrovascular disease (29).

The risk factors of diabetic nephropathy is related either to chronic hyperglycemia (poor control of blood glucose), or a family history of diabetic nephropathy, long duration of diabetes, presence of other microvascular complication, pre-existing hypertension and genetic factors also play a role (30). Moreover, smoking accelerates the decline in renal function. Additional susceptibility factors remain unidentified, because only 20–40% of patients with diabetes develop diabetic nephropathy (31).

1.2.1.Epidemiology of Diabetic Nephropathy:-

In the industrialized world, diabetes mellitus is the single leading cause of ESRF. Both the incidence and prevalence of ESRF secondary to diabetes continue to rise. In the United States, more than 30% of patients undergoing either dialysis therapy or renal transplantation have ESRD as a result of diabetic nephropathy, and 40% of the new (incident) cases of ESRF are attributable to diabetes more than 90% of patients with diabetes have type 2 rather than type 1 (insulinopenic) (32). Correspondingly, over 80% of the ESRD secondary to diabetes is also seen in patients with type 2 diabetes. The demographics of ESRD secondary to type 2diabetes mirror the prevalence of type 2 diabetes in the U.S. population (33).

1.2.2.Development of Diabetic Nephropathy:-

There are multi stage conditions that take several years to develop (ESRD).

There are five stages in the development of diabetic nephropathy.

Stage I: Hypertrophic hyper filtration. In this stage, GFR is either normal or increased. Stage I lasts approximately for five years from the onset of the

disease. The size of the kidneys increases by approximately 20% and renal plasma flow increased by 10%-15%, while albuminuria and blood pressure remain within the normal range.

Stage II: The quiet stage. This stage starts approximately two years after the onset of the disease and is characterized by kidney damage with basement membrane thickening and mesangial proliferation. There are still no clinical signs of the disease. GFR returns to normal values. Many patients remain in this stage until the end of their life.

Stage III: The microalbuminuria stage (albumin 30-300 mg/ml) or initial nephropathy. This is the first clinically detectable sign of glomerular damage. It usually occurs five to ten years after the onset of the disease. Blood pressure may increase or normal. Approximately 40% of patients reach this stage.

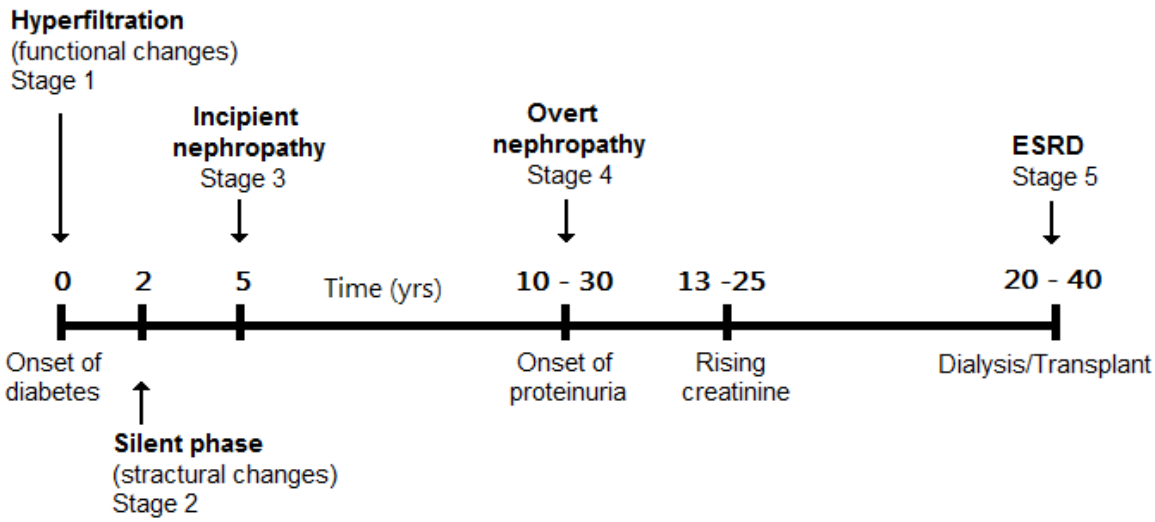
Stage IV: Chronic kidney failure (CKF) is the irreversible stage. Proteinuria develops (albumin > 300 mg/ml), GFR decreases below 60 ml/min, and blood pressure increases above normal values.

Stage V: terminal kidney failure (TKF) (GFR < 15 ml/min). Approximately 50% of patients with TKF require kidney replacement therapy (peritoneal dialysis, hemodialysis, kidney transplantation) (34).In the initial stages of diabetic nephropathy, increase kidney size and change Doppler indicators may be the early morphological signs of renal damage, while proteinuria and GFR are the best indicators of the degree of the damage **(35)** .Depending on the values of microalbuminuria and based on the assumption the rate of UAE ,diabetic nephropathy is divided primary into 5 stages: the two stages hyper filtration and silent phase are normo-albuminuria, MAU is stage 3 and proteinuria stage 4 and ESRD is the last one normo albuminuria is a primary step includes both hyper filtration and silent phase stages, in this step there may be a functional (glomerular hypertension and hyper filtration) and structural changes (detectable glomerular basement membrane thickening on biopsy but no clinical manifestations). Patients usually have normal renal

function and albumin excretion rate concentration < 20 µg per minute (less than 30 mg/ml, or < 20 mg/l) (36) MAU stage; an early manifestation of DNP is the presence of MAU, which is defined as an elevation of urinary albumin excretion rate from 20 to 200µg per minute in an overnight urine sample (albumin-creatinine ratio of 30 to 300 mg/ml in a random urine specimen), it is considered as the first stage of renal involvement in type 2 diabetes (37). In this stage, there is a normal renal function, blood pressure may increase and microalbuminuria is undetected by dipsticks which show a negative result for albuminuria. It is was found that after years of follow-up for a group of DM patients, the risk of diabetic nephropathy was 29 times greater in patients with diabetes type 2 with urinary albumin excretion values >10µg/ml (3). Microalbuminuria affects the proportion of type 2 DM patients (about 7%) shortly after the diagnosis is made; some of them already have MAU at that time, and about 40% of them after 10 years of having the disease .American diabetes association (10) recommends screening for microalbuminuria 5 years after the onset of type I and at the time of diagnosis in type II DM. As the disease progresses filtering function usually begins to drop, and development to the later more albumin leaks into the urine, the kidneys stage which is the presence of macro albuminuria or proteinuria the overt nephropathy stage, hypertension is found, serum creatinine is normal or raised, urinary albumin excretion rate >200 µg/ml, and MAU can detected by commercial dipsticks (38). This stage is irreversible, which leads to increase in blood pressure that develops more and more damage to the kidneys with leakage of more protein leading to ESRD, last stage kidney failure occurs, serum creatinine is > 500 mmol/l, that requires dialysis or transplant to maintain life (36).

Current evidence suggests that both genetic and environmental factors determine the risk for and susceptibility to develop DNP. Many studies have identified factors associated with a high risk of diabetes nephropathy hyper glycaemia, progressive microalbuminuria, increase serum lipids or lipid

disorders blood pressure levels, glycosylated hemoglobin, smoking, physical inactivity older ages, high level of insulin resistance and origin (the amount and source of dietary protein also seem to play a role as diabetic nephropathy risk factors(38). Some medications may harmful to the kidneys, especially non-steroidal anti-inflammatory drugs and some antibiotics. X-ray tests such as angiograms intravenous pyelography, and some CT scans requires IV contrast material (IV dye) can cause further kidney damage (36).



Figure(1.2) Natural history of diabetic nephropathy (Breyer,1992).

(Clinically, the natural history of kidney involvement in DM is described to consist of five stages :-**Stage 1** is characterized by hyper filtration and hypertrophy of the glomerulus, leading to elevated GFR and renal enlargement. **Stage 2** is clinically similar to stage 1, but morphological lesions (glomerular basement membrane thickening and mesangial expansion) are present in the kidney on biopsy. Stages 1 and 2 are generally clinically silent. By **stage 3,** microalbuminuria (incipient DNP) is present with mild to moderate decrease in GFR. It is usually occurring at least *5-10* years after the onset of diabetes. Without treatment, however, patients may progress to stage 4, with overt DNP (also referred to as macro albuminuria or proteinuria). **Stage 4** is associated with moderate to severe decrease in GFR. Subsequently, some patients evolve to stage 5 which defined as ESRD a stage in which patients require dialysis or kidney transplantation).

1.2.3. Risk Factors for Diabetic Nephropathy:-

There are several risk factors for the development of diabetic nephropathy. They can be divided into those that cannot be altered (genetic factors, age, and race) and those that can and must be changed (hyperglycemia, hypertension, dyslipidemia, and GFR) (39).The risk factor are as the following:-

1.2.3.1. Hyperglycemia

Hyperglycemia is a prerequisite for the development of DNP, and it is a significant risk factor for the development of microalbuminuria in T1DM (40) and T2DM (41). Microalbuminuria is closely associated with glycated hemoglobin(HbA1c) levels over 8.0% in T1DM (42) ,and in T2DM patients (43). In T2DM patients, tight glycemic control reduced the development of overt DNP(44). Patients with T2DM and microalbuminuria, intensive glycemic control is associated with a decreased rate of progression of AER, but not renal function as measured by creatinine clearance(45). Diabetic nephropathy often develops in patients with poor glycemic control. The degree of glycemic control is an important predictor of terminal kidney failure (46).

1.2.3 .2. Dyslipidemia

Type 2 DM is one component of the metabolic syndrome, which includes impaired glucose tolerance, insulin resistance, central obesity, hypertension, combined dyslipidemia, impaired fibrinolysis and hyperuricemia(47).

Microalbuminuria has also been linked to this pattern of metabolic disturbances (48). Microalbuminuria is associated with hyper triglyceridaemia and low HDL (44). Total cholesterol predicts the risk of development of microalbuminuria and total cholesterol also predicts a decline in renal function (49).In T1DM patients increased serum triglycerides, cholesterol and LDL are associated with micro- and macro albuminuria (50). High serum cholesterol also seems to be a risk factor for GFR loss in macro albuminuria T1DM subjects (51).The determinants of progression of microalbuminuria to overt

DNP include serum cholesterol in T1DM (50) and serum triglycerides in T2DM (52).

1.2.3.3. Overweight

High Body Mass Index (BMI) increases the risk of development of chronic kidney disease in patients with DM (39) adequate diet and reduction in body weight decrease proteinuria and improve kidney function in these patients (28).

1.2.3. 4. Age

In patients with type 2 DM, age and duration of DM increase the risk for albuminuria (39). In type 2 DM, subjects diagnosed with DM before age 20 years had a higher risk of developing terminal kidney failure .The risk of terminal kidney failure in patients with type 1 DM was low if the disease was diagnosed by the age of 5 years (53).

1.2.3.5. Blood Pressure

There is a relationship between the increased arterial pressure and diabetic nephropathy (54).Three factors have been shown to contribute to the development of increased arterial pressure in this metabolic disorder including hyper insulinemia, excessive extracellular fluid volume, and increased arterial rigidity. Hyper insulinemia contributes to the development of increased arterial pressure via insulin resistance in type 2 DM or via administration of insulin (55).

1.2.3.6. Smoking

Some studies have shown an association between smoking and the progression of diabetic nephropathy; however, a large prospective study by (56) did not confirm the association between smoking and decreased GFR rate in patients with DM with or without ACEI therapy.

1.2.4. Pathophysiology and Pathogenesis of Diabetic Nephropathy:-

Diabetic Nephropathy is a major micro-vascular complication caused by diabetes mellitus it differs from other causes of chronic kidney disease (CKD) in its predictability of functional progression from hyper filtration, to MAU, Macro-Albuminuria and renal failure (57).Glomerular hypertrophy and hyper filtration are early renal abnormalities (first step) in diabetic nephropathy patients.Functional abnormalities take place in the glomerulus filter apparatus include glomerular hypertrophy, thickening of (GBM),and expansion of mesangial extracellular matrix with development of proteinuria and subsequent (GFR), (58).

Morphological and structural changes take place in the glomerulus of diabetic nephropathy patients; Glomerular hypertrophy is one of the histological changes seen in diabetic nephropathy (59). Earliest changes take place in the capillary of GBM and become more thick; a loss of glomerular basement membrane charge selective properties (due to decrements in the anionic components of the glomerular capillary wall); mesangial expansion with extra cellular matrix (ECM) accumulation, a subsequent increase in pores size leading to loss of filtration surface area podocytes (57). By time, a glomerulus with dilated afferent and constricted efferent arterioles and abnormal basement membrane permeability will cause damage to the glomerular capillary, proceeds to mesangial and GBM injury, and in-turn it will stimulate the release of different cytokines. These effects can produce further relentless injury to the cells and cause further nephron loss (60).

Ultimately, there are irreversible changes such as loss of podocytes and development of arteriolar hyalinosis, glomerulosclerosis, and tubule interstitial fibrosis occur (57), this means progression to the latest step of diabetic nephropathy. The increased thickening of glomerular basement

membrane is associated with increased microalbuminuria, and eventually the (GFR) begins to fall (61). The early finding affected cells (morphological substrates) through DNP by podocyte depletion, these cells found to be crucial during the disease pathogenesis. Podocytes, elaborately shaped visceral epithelial cell, are highly differentiated glomerular epithelial cells and appear to be incapable to divide (62).

These cells are essential for glomerular structure and function, they are surrounding the glomerular capillaries and appear to form foot -like processes contributing to the filtration barrier and responsible for maintaining and supporting the glomerular basement membrane so as to facilitate efficient filtration (63). Loss of podocytes is an early feature of diabetic nephropathy(DNP), a clear loss was found after onset of hyper glycaemia and contributes to the progression of albuminuria in type 2 DM (57). Hence, the onset of DNP can be predicted, and can be significantly ameliorated, at an early stage when MAU is detected (64).And his colleagues discuss genomic strategies to find new diagnostic and therapeutic targets in DNP “of StrepToZotocin (STZ) induced mouse model so type 1 and type 2 diabetes” . They demonstrate that podocyte apoptosis increase sharply with onset of hyperglycemia. In an induction of a 30 mmol /l glucose solution in both STZ model and cell cultured experiment, the podocytes show increase apoptosis with exposure to the elevated glucose levels (65).

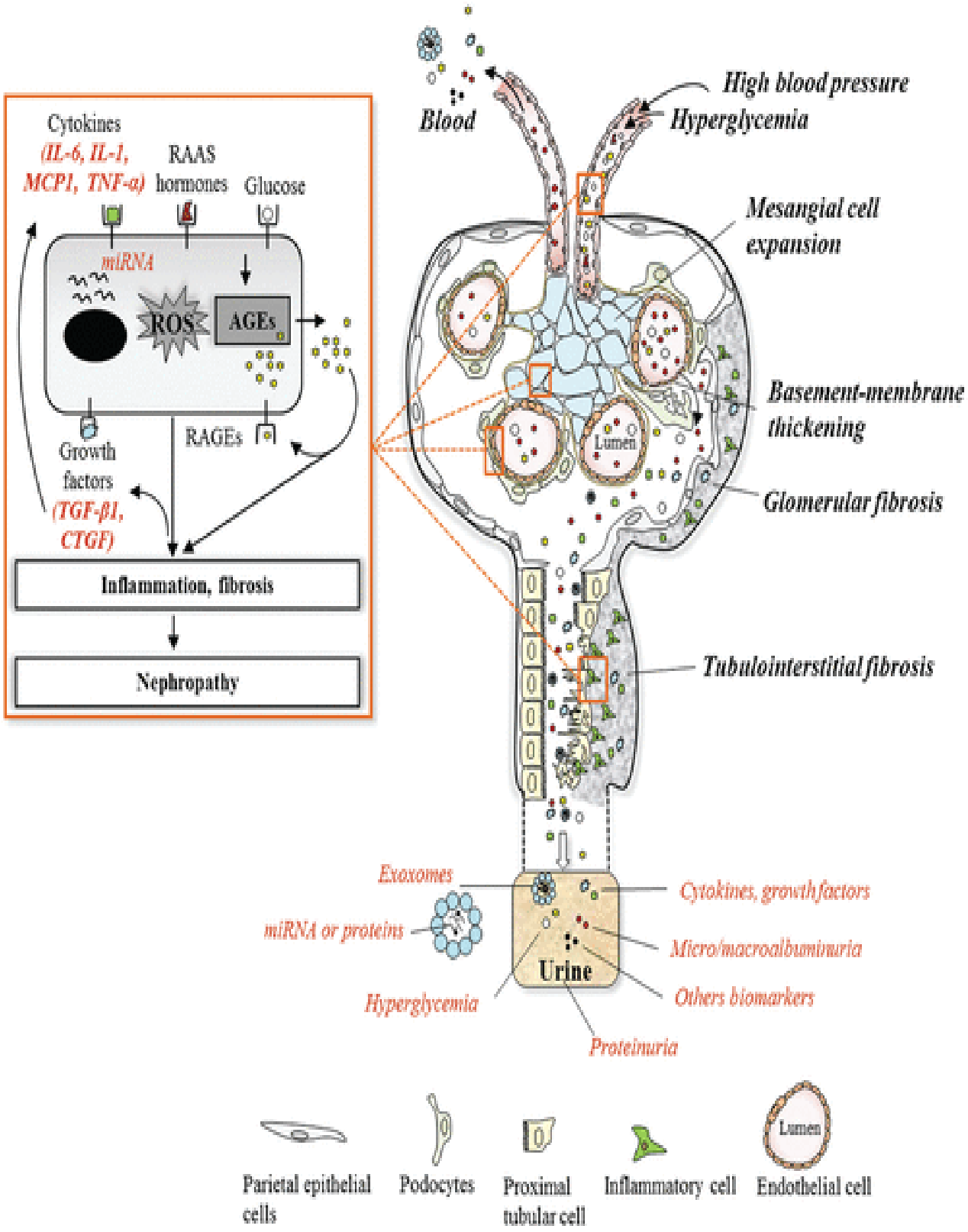


Figure (1.3). Overview of DN pathogenesis and associated biomarkers(Hall *et al.*, 2004).

Three major histologic changes occur in the glomeruli of a person with diabetic nephropathy. First, mesangial expansion is directly induced by hyperglycemia, perhaps via increased matrix production or glycation of matrix

proteins. Second, thickening of the GBM occurs. Third, glomerular sclerosis is caused by intra glomerular hypertension (induced by dilatation of the afferent renal artery or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli). These different histologic patterns appear to have similar prognostic significance (66).

Glomerular hyper perfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the GFR. During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5–10 years of DM type 1, ~40% of individuals begin to excrete small amounts of albumin in the urine. Although the appearance of microalbuminuria in DM type 1 is an important risk factor for the progression to overt proteinuria (>300 mg/ml), only ~50% of individuals progress to macro albuminuria over the next 10 years. In some individuals with type 1 diabetes and microalbuminuria of short duration, the microalbuminuria regresses (32).

Once macro albuminuria is present, there is a steady decline in GFR and blood pressure rises slightly and the pathologic changes are likely irreversible. Some individuals with type 1 or type 2 DM have a decline in GFR in the absence of micro- or macro albuminuria. Microalbuminuria arises from the increased passage of albumin through the glomerular filtration barrier. This requires ultrastructural changes rather than alterations in glomerular pressure or filtration rate alone. Compromise of selective glomerular permeability can be confirmed in early diabetic nephropathy but does not correlate well with reported glomerular structural changes.

The loss of systemic endothelial glycocalyx a protein-rich surface layer on the endothelium in diabetes suggests that damage to this layer represents this missing link (67). During the initial stage, there is a high concentration of blood glucose in diabetics. This raises high inflammatory mediators within the kidney (68). These mediators cause the glomerulus to filter albumin and these

get excreted in urine. High blood glucose concentration causes some proteins to bind to the glomerulus which leads to scarring of the glomerulus membrane. This condition develops over a period of years (29).

As the localized scarring process worsens, the kidneys after a period of time lose their ability to filter blood. This results from the replacement of healthy tissues with scarred tissues (5). This gradual 'failing' of the kidneys progressively results in end-stage kidney failure. increased excretion of albumin in urine (where the excreted levels of albumin into the urine is between 30-300 mg/ml) is the initial sign noticed in diabetics with renal conditions. This initial sign when not managed well over a period of time gives rise to excretion of protein in urine (69). Once proteinuria where the amount of albumin that leaks into the urine is more than 300 mg /ml occurs, it is not reversible and, therefore, initiates the start of an insidious functional decline in the kidneys leading to terminal renal failure. Diabetic nephropathy leads to the glomerulus being damaged. This allows more proteins to be excreted in urine. The gradual damage of the kidneys over a period of time leads to the inability of the kidneys to function well and renal failure sets in (70) .

1.3.Cystatin C as a Marker for early Diabetic Nephropathy:-

Cystatin C is a 13 kDa protein with low molecular weight and produced by all nucleated cells and freely filtered by the renal glomeruli and reabsorbed in the proximal tubule. Cystatin C is not affected by age or muscle mass in healthy person. Increased Cystatin C is a marker of renal tubular dysfunction (71). Cystatin C has multiple biological functions including modulation of the immune system and controlling extracellular proteolysis. Cystatin C is reabsorbed by proximal tubule epithelial cells and is not returned to the circulation (72). Cystatin C is highly correlated with GFR and is not influenced by inflammatory conditions, muscle mass, age, body composition and gender (73).

Cystatin c is abundant in the serum and less dependent on extra renal factor compared to creatinine and greater sensitivity for revealing mild renal dysfunction even in presumably healthy individuals compared to conventional renal indictor (74) .Cystatin C levels have been used most commonly to assess kidney function. Serum creatinine and serum Cystatin C are endogenous markers of kidney function. Serum creatinine levels are associated positively with greater muscle mass and dietary meat intake, while, the serum Cystatin C level is less sensitive to inter-individual differences in muscle mass. The levels of these markers are increased in person with higher body mass index, inflammation, and diabetes (75) .

Traditionally, the earliest common of Diabetic Nephropathy (DN) in person with type 2 diabetes is the determination of a little amount of protein albumin in the urine, called microalbuminuria and it is associated with considered renal disorder . However, a proportion significant of alone with type 2 diabetes could have renal damage as known by low GFR to levels < 60 ml/minute without microalbuminuria, the good standard for diagnosis, and these patients can appear progress to a degree significant of renal disorder while remaining normo albuminuric (76). The cystatin C may be high in diabetic patients even before the occurrence of traditional chronic kidney disease signs such as creatinine and albuminuria, and can be used as important signs for determine nephropathy in patients with normo albuminuria early nephropathy .Serum cystatin C is also a sensitive signs for determine early renal impairment and is a stronger standard of early onset of nephropathy and its development than serum creatinine measurements. Conducted levels of serum cystatin C were known high in micro and normo albuminuria as compared to controls. Serum cystatin C and creatinine are significantly higher in patients with DNP than in normoalbuminuric patients (77). evaluated serum cystatin C as a potential new marker of GFR in diabetic patients with early renal impairment (78).

1.4. Urinary Albumin Excretion(UAE):-

Albumin is generally the most prevalent protein circulating in the blood. The kidney normally excretes very little albumin into the urine, as the glomerular filtration barrier prevents passage of the majority of albumin into the urinary space. Normal UAE has been defined as less than 30 mg daily (79).

Microalbuminuria refers to albumin excretion between 30 and 300 mg/ml, “incipient” nephropathy. More advanced disease is known by the occur of macro albuminuria or proteinuria; albumin excretion greater than 300 mg daily.

Micro albuminuria is measure in people with diabetes mellitus and people with GFR less than 60 ml/minute and people with strong chronic kidney disease (80) .Micro albuminuria is used as screening and diagnostic diabetic nephropathy. It is a marker of early diagnosis of kidney disease and also used as a predictor for development coronary heart disease and mortality(81).

1.5. Glomerular Filtration Rate:-

Glomerular filtration rate(GFR) is the size of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time. Central to the physiologic maintenance of GFR is the differential basal tone of the efferent and afferent arterioles (82). GFR is similar to the clearance rate when any solute is freely filtered and is neither secreted nor reabsorbed by the kidneys.

A commonly used surrogate marker for the estimation of createnine clearance is the Cockcroft-Gault formula, which in turn estimates GFR in ml/min. It is named after the scientists who first published the formula, and it employs serum createnine measurements and a patient's weight to predict the createnine clearance. The formula, as originally published, is:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

This formula expects weight to be measured in kilograms and createnine to be measured in mg/dl, as is standard in the USA. The resulting value is multiplied by a constant of 0.85 if the patient is female and 1 if the patients is male (83).

If serum createnine is measurement in µmol/l:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women (84).

And other method for estimated GFR Modification of Diet in Renal Disease (MDRD):

Estimated glomerular filtration rate (eGFR) (ml/min/l.73m2) = 186 × ((serum creatinine (mg/dl) -1.154 × age (years) -0.203 × (0.742 if a woman) × (1.21 if African- American)) (45).

1.6.Blood urea :-

Synthesized in the body of many organisms as part of the urea cycle, either from the oxidation of amino acids or from ammonia. Urea production occurs in the liver and is regulated by N-acetylglutamate. Urea is found dissolved in blood and is excreted by the kidney as a component of urine. In addition, a small amount of urea is excreted (along with sodium chloride and water) in sweat (85).

The handling of urea by the kidneys is a vital part of human metabolism. Besides its role as carrier of waste nitrogen, urea also plays a role in the countercurrent exchange system of the nephrons, that allows for re-absorption of water and critical ions from the excreted urine. Urea is reabsorbed in the inner medullary collecting ducts of the nephrons, thus raising the osmolarity in the medullary interstitium surrounding the thin ascending limb of the loop of Henle, which in turn causes water to be reabsorbed. By action of the urea transporter 2, some of this reabsorbed

urea will eventually flow back into the thin ascending limb of the tubule, through the collecting ducts, and into the excreted urine (5).

This mechanism, which is controlled by the antidiuretic hormone, allows the body to create hyperosmotic urine, that has a higher concentration of dissolved substances than the blood plasma. This mechanism is important to prevent the loss of water, to maintain blood pressure, and to maintain a suitable concentration of sodium ions in the blood plasmas (86).

1.7. Serum Creatinine:-

Creatinine is a waste product that is made when the body breaks down protein and also, when muscles are injured (87). A high serum creatinine level then implies kidney damage. However, creatinine levels vary somewhat, even when the kidneys work normally (88). Creatinine levels tend to be higher in men and people with large muscles. Measuring creatinine is therefore, a step to finding the level of kidney function. Measurement of urea or creatinine in plasma or serum has been used to assess renal function. Both are suitable but insensitive (about 50% of the kidneys have to be destroyed before a significant rise in serum creatinine becomes apparent) (75). Serum concentrations of creatinine are affected by different analytical interferences, and depend critically on muscle mass, age, sex, ethnicity, body habitus and diet (89). Diet may have a rapid and transient effect on creatinine concentration and there is evidence that consumption of cooked meat, in particular, may affect CKD categorization based on estimated glomerular filtration rate (eGFR).

1.8. Serum albumin:-

Often referred to simply as blood albumin, is an albumin (a type of globular protein) found in vertebrate blood. Human serum albumin is encoded

by the ALB gene. Other mammalian forms, such as bovine serum albumin, are chemically similar.

Serum albumin is produce by the liver, occurs dissolve in blood plasma and is the most abundant blood protein in mammals. Albumin is essential for maintaining the oncotic pressure needs for proper distribution of body fluids between blood vessels and body tissues; without albumin, the high pressure in the blood vessels would force more fluids out into the tissues. It also acts as a plasma carrier by non-specifically binding several hydrophobic steroid hormones and as a transport protein for hemin and fatty acids. Too much or too little circulating serum albumin may harmful. Albumin in the urine usually denotes the presence of kidney disease. Occasionally, albumin appears in the urine of normal persons following long standing (postural albuminuria) (90) .Albumin functions primarily as a carrier protein for steroids, fatty acids, and thyroid hormones in the blood and plays a major role in stabilizing extracellular fluid volume by contributing to oncotic pressure (known also as colloid osmotic pressure) of plasma.

1.9.Serum Cholesterol:-

Cholesterol is a waxy, fat-like substance that's found in all the cells in your body. Your liver makes cholesterol, and it is also in some foods, such as meat and dairy products (91).

The test of cholesterol level gives this information:-

- Total cholesterol - a measure of the total amount of cholesterol in your blood. It includes the two types - low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol.
- LDL (bad) cholesterol - the main source of cholesterol buildup and blockage in the arteries.

- HDL (good) cholesterol - HDL helps remove cholesterol from your arteries.
- Triglycerides - another form of fat in your blood that can raise your risk for heart disease, especially in women.

The most important plasma lipids are triglyceride, free and esterified cholesterol, phospholipids, and free fatty acids. The water insoluble lipids are made soluble in plasma by their association with certain proteins, the apolipoproteins (92).

Lipoproteins fall into four relatively discrete classes i.e, chylomicrons, very low density lipoprotein-triglycerides (VLDL-triglycerides), low density lipoprotein-cholesterol (LDL-cholesterol), and high density lipoprotein (HDL) (93). Hypertriglyceridemia, elevated fatty acid concentration and increased level of low-density lipoprotein (LDL) have been reported in diabetic patients. Among these abnormalities, hypertriglyceridemia is the most common, in which a defective clearance of triglycerides is implicate. Individuals with DM may have several forms of dyslipidemia. Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be assessed aggressively and treated as part of comprehensive diabetes care. DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation (21).

Aim Of Study : To assess serum levels of cystatin C to compare with some biochemical parameters and to a predictor of early stage type2 diabetic nephropathy. Serum cystatin C has been proposed as

an endogenous marker of glomerular filtration rate (GFR) because it shows a correlation with the albumin to creatinine ratio (ACR) in diabetic nephropathy.

CHAPTER TWO

Patients , Materials and Methods

2.MATERIALS AND METHODS

2.1 Materials

Table(2.1): Instruments and tools:-

Instrumental	Supplied Company	Country
Spectrophotometer	Apel	Japan
Centrifuge	Sigma	Germany
ELIZA	Beckman coulter	Austria
Disposable syringe	Witeg	Malaysia
Micropipette	Ataco	China
Plain tube	Afma – Dispo,	Jordan

Table(2.2): Chemical materials and sources:-

No.	Chemical materials	Sources
1	Cystatin c	Germany
2	Urea kit	Biomerieux , France
3	Albumin kit	Biomegreb(Tunis)
4	Cholesterol	(Diasys, Halzheim, Germany)
5	Creatinine Kit	Human, Germany

Table(2.3)The normal value of parameters:

No.	Parameter	Normal Value
1	Cystatin C	0.51-0.98 Ng/ml
2	Blood glucose	3.6-6.1 mmol/l
3	Blood urea	3.3-7.5 mmol/l
4	Serum creatinine	62-124 mmol/l
5	Serum albumin	3.6-5.5 mmol/l
6	Cholesterol	3.9-6.5mmol/l
7	GFR	90-120ml/minute
8	Microalbuminuria	30-300 μg/ml

2.1.1. Data collection-

The present study is an observational retrospective case control design . The study lasted from January 2017 to June 2017. The study was conducted in general words in Merjan teaching hospital in AL-Hilla City and AL-Mussayb General Hospital .

2.1.2. Patients:-

The total number of subjects involved 100 patients in the study. They were classified into 50 patients with diabetic nephropathy and 50 patients without diabetic nephropathy .

2.2. Inclusion criteria and exclusion.

2.2.1 Inclusion criteria

*Duration of type2 DM for more than 7 years.

*Age of patients from 35 to 71 years.

2.2.2 Exclusion criteria

1-Thyroid dysfunction

2-Patients on glucocorticoid therapy

3-Cardiovascular disease.

4- end stage renal disease

5-Diabetic patient with macro albuminuria

2.3. Methods

The clinical assessment for microalbuminuria in urine and biochemical test (blood sugar ,serum cystatin c, blood urea ,serum creatinine, serum albumin ,serum cholesterol) to all DM patients (with and without nephropathy)

2.4. Clinical Assessment:-

a. Questionnaire

A full history was taken from each patient regarding personal data like name, age, gender, height ,weight ,duration of DM ,Dialysis operation , any symptoms of renal dysfunction as fatigue, nausea and vomiting ,poor appetite and swelling of the legs.

b. Urine Sampling and Processing:-

Generally, diabetic nephropathy is considered after a routine urinalysis and screening for microalbuminuria in the setting of diabetes.

Figure(2.1):-show urine sampling for measurement microalbuminuria .

c. Measurement of Body Mass Index:-

Body mass index (BMI) was calculated as person's weight in kilograms divided by height in meters squared (BMI=kg/m2)according to the world health organization (94). People with body max index =18.5-24.9 seemed to have normal weight, people with BMI=(25.0-29.9) were

classified over weight, people with BMI=(30.0-34.9) were considered obese of type1, and those with BMI=(35.0-39.9)were obese of type 2, and people with BMI ≥40 were classified as obese of type 3.

2.5.Biochemical Assessment:-

Blood Collection:

Venous blood samples were collected from each patient ,5milliliter (ml) the serum was recovered by centrifugation at 3000 rpm for 10 minutes and transferred into plain plastic tubes and stored at −20°C until time of usage. Serum samples were used for measurement of blood sugar, blood urea, serum albumin, serum creatinine ,serum cholesterol, GFR and serum cystatin c.

A.Serum albumin measurment:

The determination of albumin in serum or plasma was usually based on the binding behavior of the protein with anionic dyes, such as bromocresol green (BCG), in a manual or automated procedure. Electrophoretic and immunochemical methods were also available for the analysis of albumin (95).

B.Serum createnine measurement:

The serum createnine is prepared by adding 0.5 ml of tri chloroacetic acid to 0.5 ml serum and centrifugation for 5 minutes, taking 0.5 ml of the precipitant that form after centrifugation and adding to 0.25 of NaOH and 0.25 ml of picric acid and letting it heated to about 20 minute , at 25 C°. At 520 nm by using spectrophotometer the result multiplied by the factor (4.9), according to procedure recommended by the company Randox, united kingdom (11).

C. Cystatin C

Principle and Method

This cystatin C ELISA Kit is an intended laboratory for research use only and is not for use in diagnostic or therapeutic procedure .The spot solution changes the color from blue to yellow and the intensity of the color is measured at 450 nm using a spectrophotometer .In order to measure the concentration of cystatin C in the sample, this cystatin C ELISA Kit includes a set of calibration standards . This assay employed the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for human Cystatin C had been pre-coated onto a microplate from RnD systems. 100ul of Standards and samples were pipetted into the wells and any Cystatin C present is bound by the immobilized antibody. After washing away any unbound substances, 100ul of enzyme-linked monoclonal antibody specific for human Cystatin C was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, 90ul of substrate solution was added to the wells and color developed in proportion to the amount of Cystatin C bound in the initial step. The color development was stopped and the intensity of the color was measured at 450nm.

D.blood Glucose measurement:

The absorbance of standard and sample are measured against reagent blank at 546nm according to the procedure recommended by the Human company, Germany (95).

E.Blood urea measurement:

In the first step of preparation of urea ,1ml of reagent 1 urease was added to 0.01 ml of serum and let for 5 minutes to complete reaction.

The second step, added 0.2 ml of reagent phosphate buffer sodium salicylate, sodium nitroprusside and EDTA were added to the mixture. In an alkaline median, the ammonium ions react with salicylate and hypochlorite to form a green colored indophenols (2,2 _dicarboxylindophenol) and the reaction is catalyzed by sodium nitroprusside. And read at 580 nm by using spectrophotometer, according to procedure recommended by the urea kit from the Biomerieux company, France (96).

F.Serum Cholesterol measurment :

The quantity of red dye quinoneimine formed was proportional to the cholesterol concentration, and was measured by spectrophotometer at 505nmwavelength (44).

2.6. Statistical Analysis

Statistical analysis was carried out using SPSS version 20. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Student t-test was used to compare between the two groups. Correlation coefficient (r) was used to assess the relationship between two continuous variables. A *p*-value of ≤ 0.05 was considered as significant and ROC test (97).

2.7. Ethical Approval

All subjects involved in this work are informed and the agreement was obtained verbally from each one before the investigation.

CHAPTER THREE

RESULTS

3.Results

The two groups of diabetic patients were separate depending on the presence or absence of microalbuminuria in urine 30-300mg/ml(patients with nephropathy and without nephropathy) respectively. Results showed a significant increase $P < 0.05$ in cystatin c ,creatinine, blood urea, GFR, albumin, cholesterol in diabetic patients with early nephropathy compare with diabetic patients without nephropathy. There were no significant differences between females and males, as well as between normal and overweight for the studied tests. The percentage of patients with abnormal parameter in diabetic patients with nephropathy was cystatin c 46%, creatinine 2%, urea 30%,GFR 46%,albumin2% cholesterol 74% while the percentage of other group cystatinc, creatinine, GFR, and albumin was zero ,and for urea4%,cholesterol 46% . There were a significant positive correlation between serum creatinine and cystatin C among diabetic patients (N= 100, r =0.281, P= 0.005*) , between blood urea and cystatin C (N= 100, r =0.25, P= 0.012*), positive correlation between serum cholesterol and cystatin C (N= 100, r =0.237, P= 0.018*) and positive correlation between Cystatin C and micro albuminuria(N= 50, r =0.315, P= 0.026*) in diabetic patients type II. There were a significant negative correlation between Cystatin C and GFR (N= 100, r = -0.363, P= 0.001*) **No significant correlation between serum albumin and cystatin C among diabetic patients (N= 100, r =0.187, P= 0.062)**

3.1 Demographic distribution of diabetic patients

(Table1)shows distribution of diabetic patients according to study variables including (age, BMI, blood sugar, duration of diabetes and GFR)

(Table 3.1): Distribution of diabetic patients according to (age, gender, BMI and duration of diabetes). (n=100)

Study variable	(Mean ± SD)	Range
Age (years)	(55.40 ± 8.78)	(35-71)
BMI (Kg/m^2)	(26.46 ± 3.55)	(21-34)
Blood sugar (mmol/l)	(14.53 ± 3.31)	(8.7- 23.0)
Duration (years)	(16.83 ± 6.35)	(7-35)
GFR (ml/minute)	(88.46 ± 25.89)	(35-184)

The Distribution of Diabetic Patients According to Gender

(Figure 1) shows distribution of diabetic patients according to gender. (51%) of patients were female

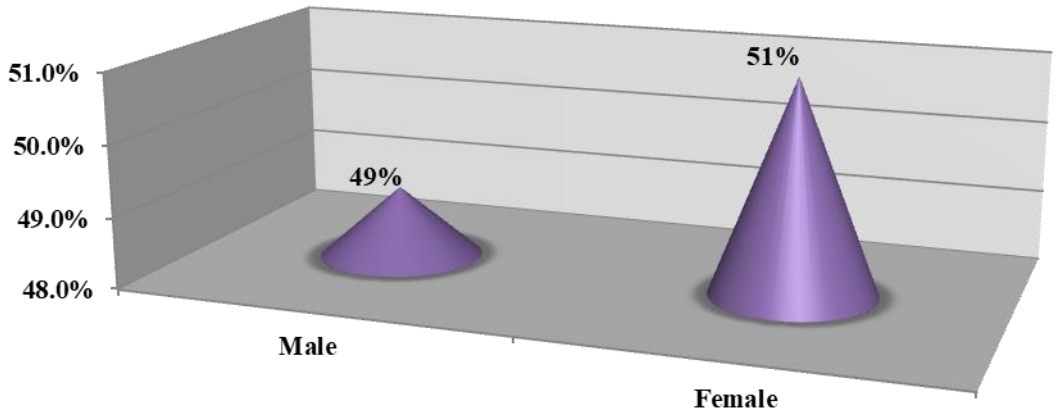


Fig (3.1) Distribution of diabetic patients according to gender. (n=100)

3.2 Mean Differences of Blood Urea, Serum Creatinine and GFR According to Study Group

(Table 2)shows mean differences of blood urea, serum creatinine and GFR according to study group including (diabetic patients with nephropathy and diabetic patients without nephropathy). There were significant differences between means of blood urea, serum creatinine and GFR by study group.

Table 3.2: The mean differences of blood urea, serum creatinine and GFR according to study group

Parameters	**Diabetic patients with micro-albuminuria** NO.= (50), Mean ± SD	**Diabetic patients without micro-albuminuria** NO.=(50)**,** Mean ± SD	**P value**
Blood urea (mmol/l)	7.57 ± 3.5	5.68 ± 1.43	0.001*
Serum creatinine (mmol\l)	78.06 ± 21.44	67.38 ± 10.11	0.002*

*P value < 0.05 was significant**.**

3.3 Mean Differences of Blood Sugar and Duration of Diabetes According to Study Group

(Table 3) shows mean differences of blood sugar and duration of DM according to study group including (diabetic patients with nephropathy and diabetic patients without nephropathy). There were significant differences between means of diabetes duration by study group

Table 3.3: The mean differences of blood sugar and duration of DM according to study group

Study markers	**Diabetic patients with micro-albuminuria** NO.= (50), Mean ± SD	**Diabeticpatients without microalbuminuria** NO.=(50), Mean ± SD	**t-test**	**P value**
Blood sugar (mmol/l)	13.95 ± 3.07	15.11 ± 3.46	-1.773	0.079
Duration (Years)	21.30 ± 5.19	12.36 ± 3.70	**9.91**	**<0.001***

*P value < 0.05 was significant .

3.4 Mean Differences of Serum Albumin, Serum Cholesterol and Cystatin C According to Study Group

(Table 4) shows mean differences of serum albumin, serum cholesterol and cystatin C according to study group including (diabetic patients with nephropathy and diabetic patients without nephropathy). There were significant differences between means of serum albumin, serum cholesterol and cystatin C by study group.

Table 3.4: The mean differences of serum albumin, serum cholesterol and cystatin C according to study group

Study markers	**Diabetic patients with micro-albuminuria** NO.= (50), Mean ± SD	**Diabetic patients without microalbuminuria** NO.=(50)**,** Mean ± SD	**t-test**	**P value**
Serum albumin (mmol/l)	40.54 ± 6.57	38.34 ± 4.24	**1.988**	**0.05***
Serum cholesterol (mmol/l)	5.80 ± 0.74	5.40 ± 0.86	**2.451**	**0.016***
Cystatin C (ng/l)	110.07 ± 19.92	66.62 ± 15.34	**12.217**	**<0.001***

*P value < 0.05 was significant.

3.5 Mean Differences of Study markers According to BMI among Patients with Diabetic Nephropathy

(Table 5) shows mean differences of study markers including (blood urea, serum creatinine, GFR ,serum albumin, serum cholesterol and cystatin C) according to BMI among patients with diabetic nephropathy.There were no significant differences between means of study markers by BMI.

Table 3.5: The mean differences of study markers according to BMI (n=50)

Study markers	Over-weight or obese Mean ± SD NO(35)	Normal Mean ± SD NO(15)	t-test	P value
Cystatin C (ng/l)	109.75 ± 20.36	110.81 ± 19.52	**-0.171**	**0.865**
Serum creatinine (mmol/l)	77.77 ± 19.20	78.73 ± 26.70	**-0.144**	**0.886**
GFR (ml/minute)	79.74 ± 24.80	79.60 ± 22.50	**0.019**	**0.985**
Serum albumin (mmol/l)	40.08 ± 6.95	41.60 ± 5.66	**-0.742**	**0.461**
Serum cholesterol (mmol/l)	5.86 ± 0.77	5.66 ± 0.67	**0.835**	**0.408**
Blood urea (mmol/l)	7.36 ± 3.53	8.08 ± 3.50	**-0.659**	**0.513**

*P value $<$ 0.05 was significant.

4.6 The number and percentage of patients with abnormal parameters in both groups (diabetic patients with nephropathy and diabetic patients without nephropathy

(Table6) shows distribution (the number and percentage) of patients with abnormal parameters (blood urea, serum creatinine, GFR ,serum albumin, serum cholesterol and cystatin C in both to study groups

Table 3.6:The number and percentage of patients with abnormal parameters in both groups (diabetic patients with nephropathy and diabetic patients without nephropathy)

Study markers	diabetic patients with nephropathy	diabetic patients without nephropathy
Cystatin C(ng/l)	23 (92%)	0 (0%)
Serum creatinine (Mmol/l)	1 (2%)	0 (0%)
GFR (ml/min)	23 (92%)	0 (0%)
Serum albumin (g/l)	1 (2%)	0 (0%)
Serum cholesterol Mmol/l)(	37 (74%)	23 (46%)
Blood urea (mmol/l)	15 (30%)	2 (4.0)

3.7 The number and percentage of patients with abnormal parameters in diabetic patients with micro-albuminuria according to gender groups

(Table7):shows the number and percentage of diabetic patients with micro-albuminuria patients distribution of study markers (blood urea, serum creatinine, GFR ,serum albumin, serum cholesterol and cystatin C) according to gender among diabetic patients with nephropathy

(Table 3.7): The number and percentage of patients with abnormal parameters in diabetic patients with micro-albuminuria according to gender groups

Study markers	Male with abnormal value of microalbuminuria	Female with abnormal value of microalbuminuria
Cystatin C	23 (92%)	0 (0%)
Serum creatinine	0 (0%)	1 (3.6%)
GFR	23 (92%)	0 (0%)
Serum albumin	0 (0%)	1 (3.6%)
Serum cholesterol	16 (72.7%)	21 (75%)
Blood urea	10 (45.5%)	5 (17.9%)

3.8 The Correlation Between Blood Urea and Cystatin C among Diabetic Patients

(Figure 2) shows correlation between blood urea and cystatin C among diabetic patients. There were significant positive linear correlation between blood urea and cystatin C among diabetic patients. (N= 100, r =0.25, P= 0.012*).

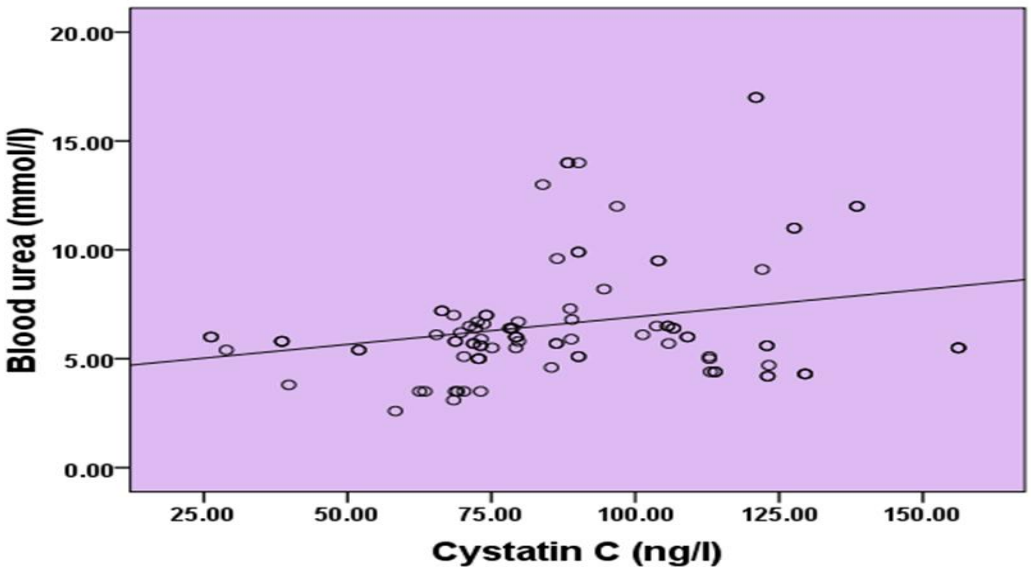


Figure 3.2:The correlation between blood urea and cystatin C among diabetic patients

3.9 The Correlation Between Serum Creatinine and Cystatin C among Diabetic Patients

(Figure 3): shows correlation between serum creatinine and cystatin C among diabetic patients. There were significant positive linear correlation between serum creatinine and cystatin C among diabetic patients. (N= 100, r =0.281, P= 0.005*).

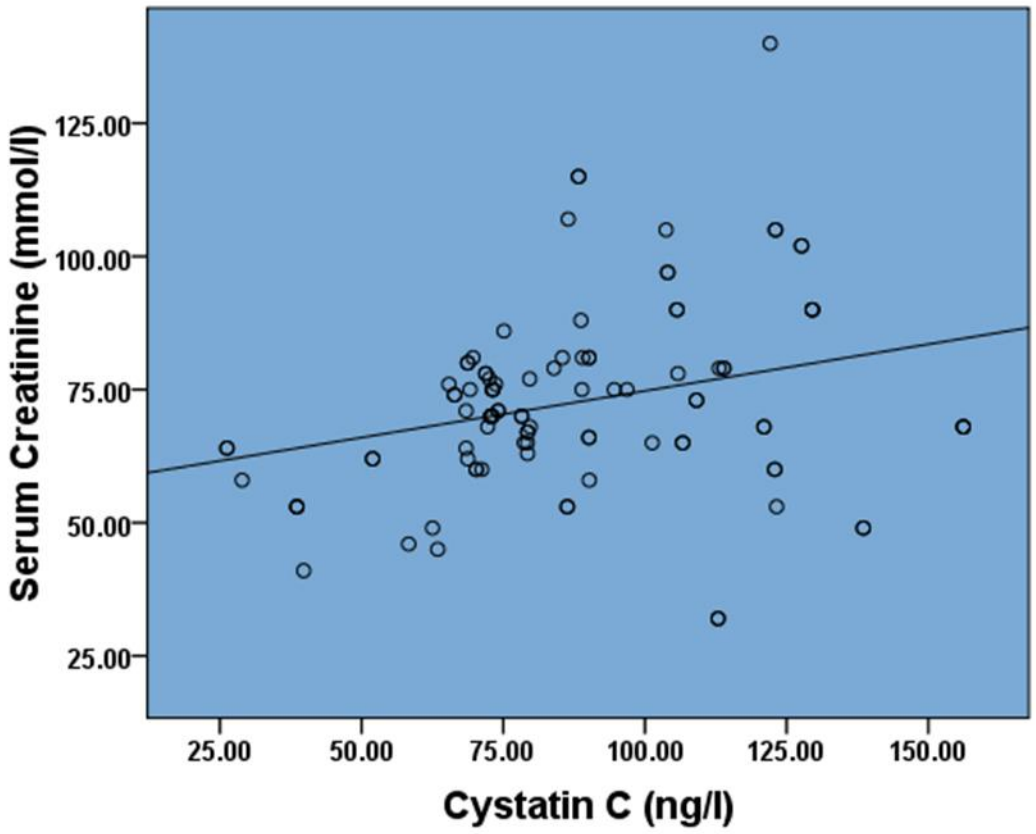


Figure 3.3:The correlation between serum creatinine and cystatin C among diabetic patients

3. 10 The Correlation Between Serum Albumin and Cystatin C among Diabetic Patients

(Figure 4) shows correlation between serum albumin and cystatin C among diabetic patients. There were no significant correlation between serum albumin and cystatin C among diabetic patients. (N= 100, r =0.187, P= 0.062).

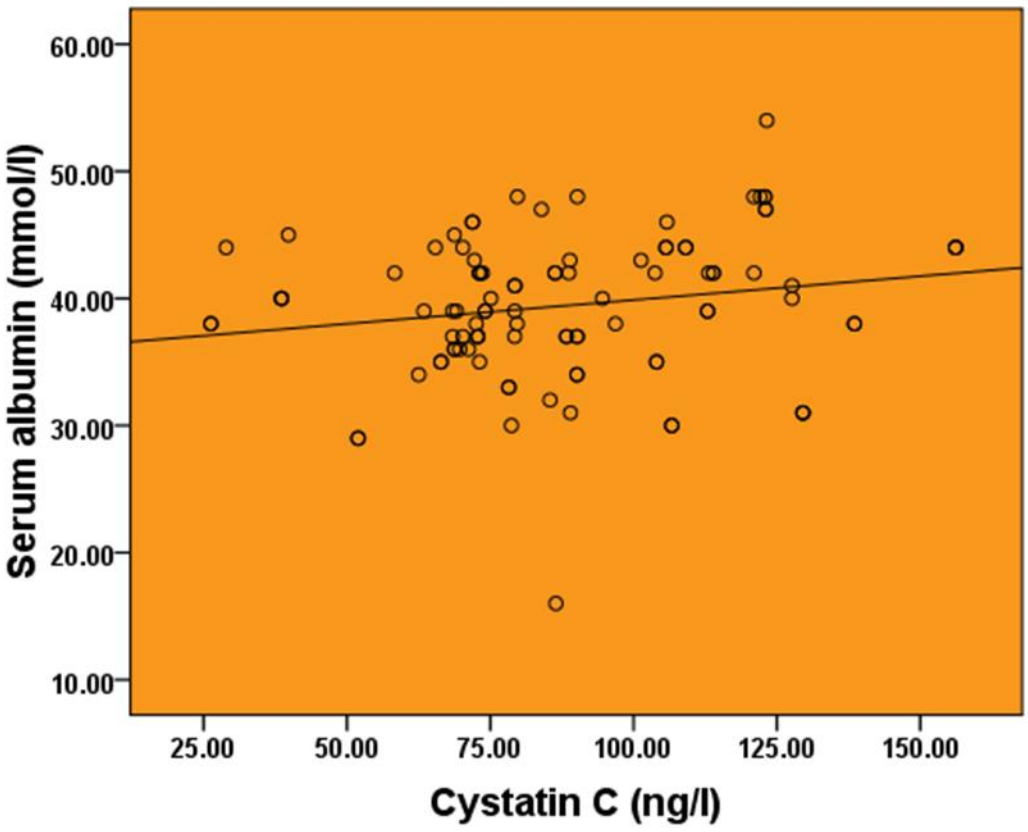


Figure 3.4:The correlation between serum albumin and cystatin C among diabetic patients

3.11 The Correlation Between GFR and Cystatin C among Diabetic Patients

(Figure 6)shows correlation between GFR and cystatin C among diabetic patients. There were significant negative linear correlation between GFR and cystatin C among diabetic patients. (N= 100, r = -0.363, P= <0.001) *

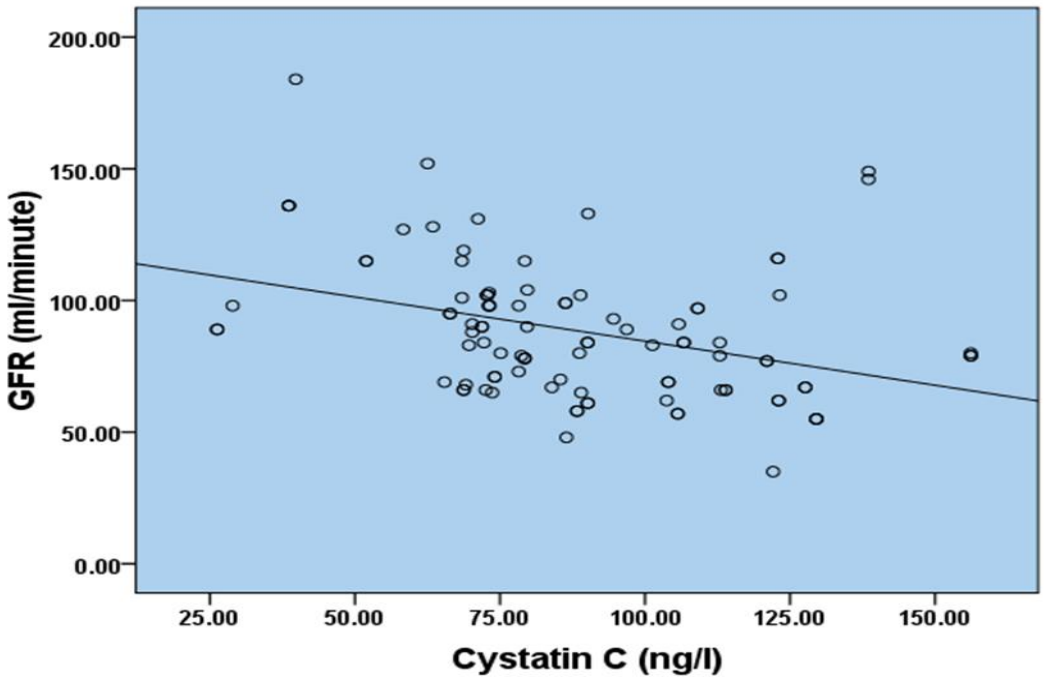


Figure 3.5: Correlation Between GFR and Cystatin C among Diabetic Patients

Chapter Four

Discussion

4.Discussion

4.1. Excretion of albumin in urine:-

The presence of micro albuminuria is considered as indicator or warning signal to renal disease in patients with type 2 diabetes mellitus, and also considered as the earliest marker of diabetic nephropathy and associated with significant glomerular damage. The result of this study agree with (98) which he explained that reduced risk factors lead to decrease level of micro albuminuria and decrease in renal diseases .while (73) disagree with our study where he studied that the micro albuminuria does not necessary reflect renal impairment in addition to the early structure damage in both tubular structure and glomerular that may be present in normal albuminuria. So, there is a need to find biomarkers that help in identification of the patients' risk of the disease and monitoring preventive and therapeutic effects.

The reason is due to appearance of microalbuminuria in urine it could be the earliest detectable change is in the thickening of the glomerular basement membrane (GBM) that filters the blood, the damage to the membrane and the cells next to it in the capillary walls causes albumin to leak from the blood into the urine; this is called albuminuria and proteinuria (38).

4.2. Mean differences of serum cystatin C, Serum Creatinine and GFR and blood sugar ,Blood urea, serum cholesterol ,serum albumin:-

There were significant differences between means of blood urea ,GFR and serum creatinine. This result agree with (99) which found that higher glucose level and long duration of disease in addition to, serum creatinine, GFR, and blood urea.

The blood glucose levels was high in the two groups but there are no significant differences between the means of two groups this concur with (100) found that blood glucose was higher in normoalbuminuric than in microroalbuminuric group. High blood glucose concentration causes some proteins bind to the glomerulus which leads to scarring of the glomerulus membrane. (101) is found this condition develops over a period of years. Hyperglycemia plays a role in the development of diabetic nephropathy. (76) puzzle out the hyperglycemia causes increase hyper filtration and renal injury. The hyperglycemia is considered as the key initiator for kidney damage by activation of other metabolic pathways and formation or increase in oxidative stress.

Increased level of Cyst-C in diabetic patients with micro albuminuria is significant when compared to diabetic patients with normo albuminuria. This result correspond with (102) which found that serum Cystatin C use as a marker to detect early stage diabetic nephropathy and development of acute renal failure earlier than serum creatinine the result as well as(103) accept that Cystatin C as a good marker for diagnosis early diabetic nephropathy than serum creatinine in kidney damage because of serum Cystatin C is not influenced by race, muscle mass, gender and age. Cystatin C considered an excellent marker of GFR this

identify with (104).The reason is attributed that Cystatin C is a small cationic 13.3 kDa protein ,which produced by all nucleated cells at a constant rate and is freely filtered by the glomerulus, it is not secreted in the tubules but mainly reabsorbed by tubular epithelial cells and catabolized completely .

Significant decrease of GFR in microalbuminuria compare with normoalbuminuria this result agree with (Manoorkar *et al.*,2006).Because after 5–10 years of DM, ~40% of individuals begin to excrete small amounts of albumin in the urine. Glomerular filtration rate (GFR) provides an excellent measure of the filtering capacity of the kidneys. A low or decreasing GFR is a good index of kidney disease this result agree with (105). The ideal marker of GFR should be an endogenous molecule, which being produced at a constant rate, is cleared solely by the kidneys via free glomerular filtration, with being neither secreted by tubular cells, nor reabsorbed into peritubular circulation this result agree with (72).

Blood urea was significantly increased in microalbuminuria compared to normoalbuminuria this study agree with(65).The reason has been explained that there change in blood urea and creatinine may be related to disturbance of kidney function toward the development of DNP. (106) (107) (108) found that high blood urea ,serum createnine concentrations in diabetic nephropathy patients as compared to normoalbuminuria groups. These results agree with (52) that found this increases in urea and creatinine level occurs because in diabetic nephropathy the kidney lose its ability to eliminate nitrogenous wastes from the blood results in accumulation of these substances in the blood.

Microalbuminuria group had high cholesterol, than normoalbuminuria group, the difference between the two diabetic groups were significant this result disagree with **(109)** .Total cholesterol

values of diabetic nephropathy patients are higher than those of control groups without statistically significant increase this result proves the results obtained by (94) (110) (47) (111) that found the total cholesterol level is not a risk factor of diabetic nephropathy.

Serum albumin increase in early stage diabetic nephropathy compare with control group this result disagree with (112) (113) which found that serum albumin is significant decreased in diabetic nephropathy patients compared to the control groups. The explanation that hypoalbumineamia may result from protein restriction ,anorexia , protein-lose nephropathy .

4.3. Mean differences of Study markers According to Gender among Patients with Diabetic Nephropathy:-

0There were no significant differences between means of (cystatin C, serum creatinine, serum albumin, serum cholesterol and blood urea) in male and female patients groups with diabetic nephropathy except GFR significant .The ideal marker of GFR should be an endogenous molecule, which being produced at a constant rate, is cleared solely by the kidneys via free glomerular filtration, with being neither secreted by tubular cells, nor reabsorbed into peritubular circulation this result agree with (72).This result consistent with (114) who shows that females are more prone to develop diabetic nephropathy than males. The one of results because of pregnancy , used of oral contraceptive pills and hormonal cause which associated with worsening of diabetic complication as nephropathy (27). (115) disagree with our result which found that there were significant differences between means of (cystatin C, serum creatinine, serum albumin, serum cholesterol and blood urea) in diabetic nephropathy group .

4.4.Mean differences of study markers according to BMI among patients with diabetic nephropathy:-

There is no significant differences between means(cystatin C, serum creatinine, GFR ,serum albumin, serum cholesterol and blood urea) according to BMI among patients with diabetic nephropathy. This result agreement with (116).The percentage of diabetic nephropathy in overweight was more than obese and normal patients this could be due to that increased body weight associated with difficult control of blood sugar and more complication as well as this condition due to HbA1C effect on kidney lead to early stage diabetic nephropathy.

4.5. Correlation between blood urea and cystatin C among diabetic patient:-

There is a significant positive linear correlation between blood urea and cystatin C among diabetic patients. This study agree with (43). The change in blood urea related to disturbance of kidney function toward the development of DNP. This funding could be explained by impairment of kidney function .

4.6. Correlation Between Serum Creatinine and Cystatin C among Diabetic Patient:-

There is a significant positive linear correlation between serum creatinine and cystatin C among diabetic patients.
The present study agreement with (53)**.**We conclude from this that its more accurate in determining the early stages of DNP patients with renal impairment. The change in serum creatinine may be related to disturbance of kidney function toward the development of DNP. This funding could be explained by impairment of kidney function. Serum creatinine levels are associated positively with greater muscle mass and

dietary meat intake, while the serum Cystatin C level is less sensitive to inter-individual differences in muscle mass. The levels of these markers are increased in person with higher body mass index, inflammation, and diabetes (2).

4.7. Correlation between serum albumin and cystatin C among diabetic patients:-

There is no significant correlation between serum albumin and cystatin C among diabetic patients. This study disagree with (112) and (113).

4.8. Correlation between serum cholesterol and cystatin C among diabetic patients:-

There is a significant positive linear correlation between serum cholesterol and cystatin C among diabetic patients. This correlation is in agreement with (117).

4.9. Correlation between GFR and cystatin C among diabetic patients:-

There is a significant negative linear correlation between GFR and cystatin C among diabetic patients**.** The present study shows agreement with (118) (39).We concluded from this relationship that there is close correlation between GFR and Cystatin c and from this result we approval cystatin c as a good marker for early diagnosis of DNP.

4.10. Correlation between cystatin c and microalbuminuria among diabetic patients with nephropathy :-

There is a significant positive linear correlation between Cystatin C and microalbuminuria among diabetic patients with nephropathy .The present study agreement with **(118)**. As well as (102) agreement with this result that suggests cystatin C acts as a marker even before microalbuminuria begins.

4.11. ROC curve for cystatin C between patient and control group:-

The area under the corresponding ROC curve for cystatin was compared between patients and the control group .ROC analysis revealed that the area under the curve (AUC) for cystatin is 0.988, indicating that a threshold of 78 gave sensitivity of 100%and specificity86% . The more cystatin level , predicting early nephropathic changes in patients than the control group.

patient's own healthy and prevent disease progression. According to the results of this study all the patients with diabetes mellitus type 2 female and male having high serum Cystatin C in early stage of diabetic nephropathy. This analyses shows a higher predictive ability to the detection and progression of the diseases.

Conclusion and Recommendation

Conclusion

Serum cystatinc appears to hold promise in predicting early renal dysfunction and move so as an indicator of overt nephropathy cystatinc correlated more closely with standard measure of GFR

Recommendations:

1- Screening for diabetic nephropathy patients in outpatient clinics and hospitals for all diabetic persons by simple procedures including history and examination (blood and urine) is important for signs of possible kidney problems.
2- Control of blood sugar level which is the most important factor in postpone of diabetic nephropathy.
3- Aggressive management of all classical cardiovascular risk factors (hypertension, dyslipidemia) and cessation of cigarette smoking to reduce the rate of progression of kidney disease.
4- Assessment of oxidative stress in diabetic patients may be important in predicting and preventing oxidative stress-related complications .
5- Diabetic patients should be encouraged to eat foodstuffs rich with antioxidants like vegetables, fruits(limited), fish, fiber-containing foods, and other.

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الخلاصة

الخلفية

اعتلال الكلية السكري هو سبب مهم للتسبب بالمرض والوفيات لدى مرضى السكري (DM). تتميز هذه الحالة باستمرار البيلة الزلالية وانخفاض معدل الترشيح الكبيبي (GFR). وقد تم اقتراح مصل السيستاتين C في المصل كمقياس بسيط ودقيق.

يُعرّف اعتلال الكلية السكري (DNP) عادةً بالبيلة الزلالية الدقيقة – أي إفراز زلالي بولي يتراوح بين 30–300 ملغم/مل أو بيلة زلالية كبيرة وبيلة كلوية غير طبيعية كما هو موضح في خلل في الكرياتينين في المصل أو تصفية الكرياتينينين المحسوبة أو معدل الترشيح الكبيبي (GFR). سريريًا، يتميز اعتلال الكلية السكري بزيادة تدريجية في البيلة البروتينية وانخفاض في معدل الترشيح الكبيبي (GFR) وارتفاع ضغط الدم.

تُعتبر التغيرات في البيلة الزلالية علامة مميزة لبداية اعتلال الكلية السكري أو تطوره. ومع ذلك، يعاني بعض مرضى السكري من تغيرات مرضية كلوية متقدمة وتراجع تدريجي في وظائف الكلى حتى لو كانت مستويات الزلال البولي في المعدل الطبيعي، مما يشير إلى أن البيلة الزلالية ليست العلامة المثالية للكشف المبكر عن DNP. يُعتبر الكرياتينينين الطريقة القياسية الذهبية لتقدير معدل الغلوكوز الكلوي المثالي. يُظهر الكرياتينينين في المصل حساسية غير كافية، خاصة في المراحل المبكرة من القصور الكلوي.

السيستاتين C هو بروتين بلازما ذو كتلة جزيئية منخفضة يتم ترشيحه بحرية من خلال الكبيبة ويعاد امتصاصه بالكامل بواسطة الخلايا الأنبوبية. وقد تم اقتراحه كمؤشر جديد وحساس للغاية في المصل للتغيرات في معدل الغلوكوز الكلوي.

الهدف من الدراسة :

تقييم مستويات مصل السيستاتين C في الدم للمقارنة مع بعض المعايير البيوكيميائية الحيوية والتنبؤ بالمرحلة المبكرة من اعتلال الكلية السكري من النوع الثاني. تم اقتراح مصل السيستاتين C في المصل كمؤشر داخلي لمعدل الترشيح الكبيبي (GFR) لأنه يُظهر ارتباطًا مع نسبة الألبومين إلى الكرياتينين (ACR) في اعتلال الكلية السكري.

الطريقة :

في هذه الدراسة، تم إجراء هذه الدراسة على 100 مريض مصاب بداء السكري من النوع الثاني (50 مريضاً مصاباً باعتلال الكلية السكري و50 مريضاً غير مصاب باعتلال الكلية السكري). تم قياس مؤشر كتلة الجسم (مؤشر كتلة الجسم) لكل مشارك، وتم الحصول على عينات الدم في الصباح لقياس سيستاتين C في الدم والكرياتينين واليوريا في الدم والجلوكوز في الدم والكوليسترول وعينة البول لقياس البيلة الكلوية الدقيقة.

النتائج :

تم فصل مجموعتي مرضى السكري بناءً على وجود أو عدم وجود البيلة الألبومينية الدقيقة في البول 30–300 ملجم/مل (المرضى الذين يعانون من اعتلال

الكلية وغير المصابين باعتلال الكلية) على التوالي. أظهرت النتائج زيادة كبيرة $P \leq 0.05$ في السيستاتين ج، والكرياتينين، واليوريا في الدم، ومعدل الغلوكوز في الدم، ومعدل نمو الغدة الدرقية في الدم، والألبومين، والكوليسترول في مرضى السكري المصابين باعتلال الكلية المبكر مقارنة بمرضى السكري غير المصابين باعتلال الكلية. لم تكن هناك فروق ذات دلالة إحصائية بين الإناث والذكور، وكذلك بين الإناث والذكور وكذلك بين الوزن الطبيعي والوزن الزائد في الاختبارات المدروسة.

الاستنتاجات:

تشير نتائج هذه الدراسة إلى أن قياس السيستاتين C في المصل هو اختبار مفيد وعملي لتقييم المرحلة المبكرة من اعتلال الكلية السكري من النوع الثاني.

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

صدق الله العلي العظيم

سورة النجم الآية (39–41)

وزارة التعليم العالي والبحث العلمي
جامعة بابل
كلية الصيدلة

تقييم مستويات السيستاتين سي في المرحلة المبكرة لتشخيص المرضى الذين يعانون من اعتلال الكلى السكري في محافظة بابل، العراق

مشروع بحث تخرج مقدم إلى مجلس كلية الصيدلة في استيفاء جزئي لمتطلبات التخرج من جامعة بابل

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