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Al-Hilla University college

Department of Medical Physics

study of blood suger level in patents with kidny failure

Research Submitted To The Council Of Al-Hilla University College It Is Part Of The Requirements For Obtaining A Bachelor's Degree In Medical Physics

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بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَات)

صدق الله العلي العظيم

سورة

الحجرات ايه 11

THANKS AND APPRECIATION

As we take our final steps in university life, we must pause and go back to the years we spent at Hilla University College.

With our esteemed teachers who have given us so much, making great efforts in building tomorrow's generation to revive the nation... Before we proceed, we offer our highest thanks, gratitude, appreciation and love to those who carried the most sacred message in life.

...To those who paved the path of science and knowledge for us, and to all our distinguished teachers

Be a scholar. If you cannot, then be educated. If you cannot, then love scholars. If you cannot, then do not hate them."

We extend our thanks and appreciation to

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Abstract

The kidney is arguably the most important target of microvascular damage in diabetes. A substantial proportion of individuals with diabetes will develop kidney disease owing to their disease and/or other co-morbidity, including hypertension and ageing-related nephron loss. The presence and severity of chronic kidney disease (CKD) identify individuals who are at increased risk of adverse health outcomes and premature mortality. Consequently, preventing and managing CKD in patients with diabetes is now a key aim of their overall management. Intensive management of patients with diabetes includes controlling blood glucose levels and blood pressure as well as blockade of the renin–angiotensin–aldosterone system; these approaches will reduce the incidence of diabetic kidney disease and slow its progression. Indeed, the major decline in the incidence of diabetic kidney disease (DKD) over the past 30 years and improved patient prognosis are largely attributable to improved diabetes care. However, there remains an unmet need for innovative treatment strategies to prevent, arrest, treat and reverse DKD. In this Primer, we summarize what is now known about the molecular pathogenesis of CKD in patients with diabetes and the key pathways and targets implicated in its progression. In addition, we discuss the current evidence for the prevention and management of DKD as well as the many controversies (1)

1.1 INTRODUCTION:

Kidney failure; also called renal failure, is when your kidneys no longer work properly.

Note : Your kidneys' main job is to clean your blood and make urine (wee).

When the kidneys do not work properly, waste and fluid builds up in your body

There are 2 main types of kidney failure:

1. Acute kidney failure (also called acute renal failure, or acute kidney injury)
2. Chronic kidney disease

Acute renal failure (ARF), characterized by sudden loss of the ability of the kidneys to excrete wastes, concentrate urine, conserve electrolytes, and maintain fluid balance, is a frequent clinical problem, particularly in the intensive care unit, where it is associated with a mortality of between 50% and 80% (2)

Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause. It is a state of progressive loss of kidney function ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). Kidney damage refers to pathologic abnormalities either suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates (3)

Diseases and conditions that cause chronic kidney disease include:

- Type 1 or type 2 diabetes
- High blood pressure

- Glomerulonephritis (gloe-mer-u-low-nuh-FRY-tis), an inflammation of the kidney's filtering units (glomeruli)
- Polycystic kidney disease or other inherited kidney diseases

Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people Worldwide (6% population). It is caused by deficiency or ineffective production of insulin by pancreas Which results in increase or decrease in concentrations of glucose in the blood. It is found to damage Many of body systems particularly blood vessels, eyes, kidney, heart and nerves ،Diabetes mellitus has Been classified into two types i.e. insulin dependent diabetes mellitus (IDDM, Type I) and non-insulin Dependent diabetes mellitus (NIDDM, Type II). Type I diabetes is an autoimmune disease characterized By a local inflammatory reaction in and around islets that is followed by selective destruction of insulin Secreting cells whereas Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion The presence of DM shows increased risk of many complications such as Cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, Blindness, amputations etc (4)

Type 1 diabetes is a chronic autoimmune disease characterised by insulin deficiency and resultant hyperglycaemia. Knowledge of type 1 diabetes has rapidly increased over the past 25 years, resulting in a broad understanding about many aspects of the disease, including its genetics, epidemiology, immune and β-cell phenotypes, and disease burden. Interventions to preserve β cells have been tested, and several methods to improve clinical disease management have been assessed. However, wide gaps still exist in our understanding of type 1 diabetes and our ability to standardise clinical care and

decrease disease-associated complications and burden (5).

Type 2 diabetes accounts for more than 90% of patients with diabetes and leads to microvascular and macrovascular complications that cause profound psychological and physical distress to both patients and carers and put a huge burden on health-care systems. Despite increasing knowledge regarding risk factors for type 2 diabetes and evidence for successful prevention programmes, the incidence and prevalence of the disease continues to rise globally. Early detection through screening programmes and the availability of safe and effective therapies reduces morbidity and mortality by preventing or delaying complications. Increased understanding of specific diabetes phenotypes and genotypes might result in more specific and tailored management of patients with type 2 diabetes, as has been shown in patients with maturity onset diabetes of the young (6).

1.1.1 Relationship between diabetic and renal failure:

Nowadays, diabetes mellitus (DM) and hypertension are considered as the most common causes of end-stage renal disease (ESRD). Nephropathy in diabetes is to represent all forms of kidney damage that may occur in temporal or causal relation to diabetes mellitus In the course of the disease, there may be changes in the excretion of protein in the urine, a decrease in kidney function, recognizable by a reduction in the glomerular filtration rate, and the development and/or worsening of concomitant diseases associated with diabetes, such as arterial hypertension and lipid metabolism disorders (7).

Other than presenting the role of DM in ESRD, glucose metabolism and the management of hyperglycemia in these patients are reviewed. Although in

several large studies there was no significant relationship found between tight glycemic control and the survival of ESRD patients, it is recommended that glycemic control be considered as the main therapeutic goal in the treatment of these patients to prevent damage to other organs. Glycemic control is perfect when fasting blood sugar is less than 140 mg/dL, 1-h postprandial blood glucose is less than 200 mg/dL, and glycosylated hemoglobin (HbA1c) is 6-7 in patients with type 1 diabetes and 7-8 in patients with type 2 diabetes. Administration of metformin should be avoided in chronic renal failure (CRF) because of lactic acidosis, the potentially fatal complication of metformin, but glipizide and repaglinide seem to be good choices (8).

1.1.2 The Diabetes

Diabetes is a chronic illness characterized by elevated levels of blood glucose , accompanied by disturbed metabolism of fats and proteins. Blood glucose rises because it cannot be metabolized in the cells, due to lack of insulin production by the pancreas or the inability of the cells to effectively use the insulin that is being produced. There are three major types of diabetes: (1) Type 1, in which the pancreas does not produce insulin; (b) type 2 in which the body cells are resistant to the action of insulin that is being produced and over time the production of insulin progressively decreases; and (c) gestational diabetes which occurs in pregnancy and can cause some complications during the pregnancy, and at birth and increases the risk of type 2 diabetes in the mother and obesity in the offspring. In addition, there are two other categories of glucose intolerance - impaired fasting glucose (IFG) and impaired fasting glycemia (IGT) that are intermediate conditions between normal and diabetic blood glucose levels, although the transition is not inevitable. People with IFG

and IGT are at increased risk of CVD than people with normal blood glucose valuse [Figure (1) shows blood sugar levels]

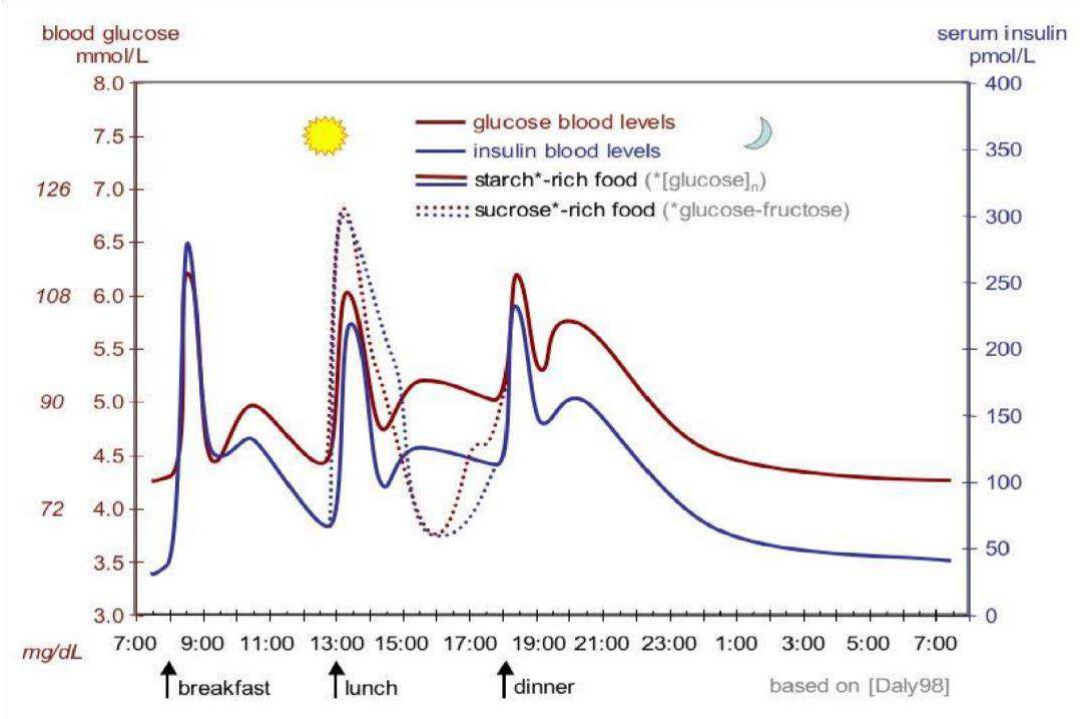


Figure 1

1.1.3 Risk factors for diabetes

Type 1 occurs most frequently in children, adolescents, and young adults. The cause or causes are not known. A combination of genetic susceptibility and environmental factors is believed to lead to type 1 diabetes. Despite extensive research into potential biological, chemical, nutritional, and behavioral causes , none has as yet been identified as the cause of a significant number of cases beyond reasonable doubt. The risk factors for type 2 diabetes are better known . Althou1.1.3gh the genetic component is substantial, the majority of cases occur in the presence of risk factors - age, overweight and obesity and physical inactivity. Smoking has also been shown to increase the risk of diabetes, but by

far the strongest risk factor is increased body fat. Some ethnic groups, such as people of Southeast Asian origin are more sensitive than others to the diabetogenic effect of excess body fat. Several dietary practices, such as a high sugar and fat intake have also been linked to increased risk of type 2 diabetes. The risk factors for gestational diabetes are not only similar to those for type 2 diabetes - family history, age, overweight and obesity, physical inactivity but also include excessive weight gain during pregnancy.

1.1.4 Complications of diabetes

Uncontrolled diabetes leads to complications in many organs. Damage to small and large blood vessels and nerves leads to loss of vision and kidney function, heart attacks, strokes, and lower limb amputations. Diabetes causes disability and shortens lives .

1.1.5 Prevalence of risk factors

The rise in diabetes prevalence mirrors the rise in its main risk factors- overweight and obesity, and physical inactivity. In 2014, more than one in three adults aged over 18 years were overweight (body mass index [BMI] ≥25-29.9), and more than one in 10 were obese (BMI ≥30). The prevalence of being overweight or obese is highest in high-income countries (>50%) and in the WHO Region of the Americas. It is lowest in low-income countries (15% in men and 27% in women) and the WHO Southeast Asian Region (19.3% in men and 25.3%) in women Data from 2010 show that just under a quarter of adults aged over 18 years were classified as insufficiently physically active. It is even

more alarming in adolescents, with about 80% not meeting the minimum requirements for physical activity .

1.1.6 Preventing diabetes

The majority of diabetes cases are type 2 diabetes, which is preventable to a great extent. Unfortunately, the cause of type 1 diabetes is unknown, and it remains unpreventable. Several strategies have been and are being tried, so far with little success. (9.10.11)

1.2 The kidney

In mammals, the kidneys function as a major excretory organ for elimination of metabolic wastes from the body. In most species, death occurs within a week after total cessation of renal function. Partial loss of renal function results in variable deviations from normal, depending on the quantity of functional tissue remaining. The term “azotemia” refers to accumulation of nitrogenous wastes in the blood. Blood concentrations of creatinine and urea are measured as indices of azotemia, although neither imparts significant toxicity because of its accumulation. Animals with moderate to severe azotemia may have a constellation of clinical signs, including lethargy, anorexia, mucosal ulcers, vomiting, diarrhea, weight loss, anemia, and altered urine output. These signs are referred to as renal failure, uremia, or uremic syndrome, and reflect the development of abnormalities in a multitude of tissues secondary to subnormal renal functions. The role of the kidneys in maintaining life is a composite of several functions. Water and many electrolytes are conserved by the kidneys in times of negative body balance and are excreted in times of positive balance. The evolutionary development of the kidney has clinical relevance. In renal

failure, one must deal not only with problems of inadequate excretion because of decreased glomerular filtration but also with problems of excess losses arising from alterations in function of the tubular system reclaiming filtrate (12.13)

[Figure 2 shows the anatomy of the kidney]

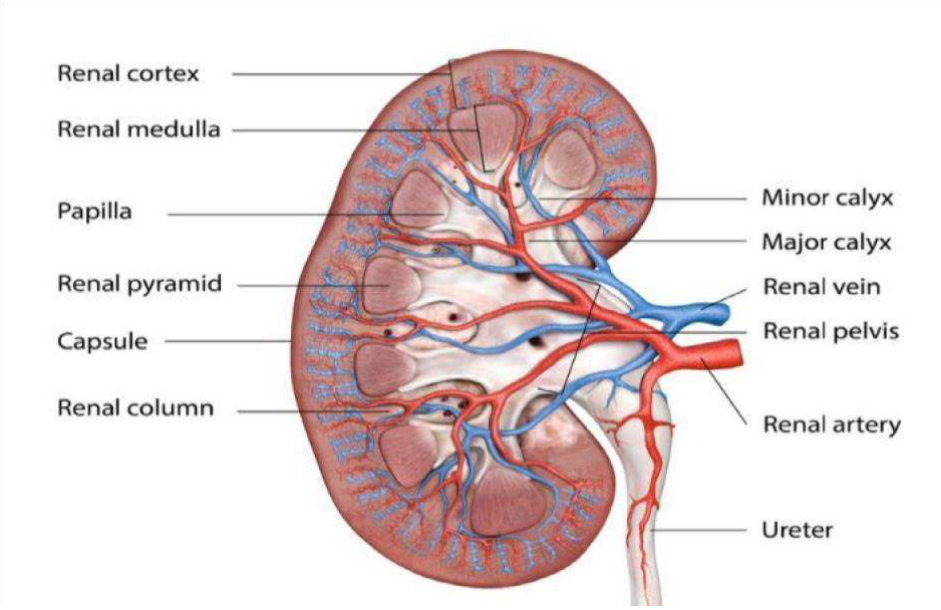


Figure (2)

1.2.1 The Kidney failure

Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2 persisting for 3 months or more, irrespective of the cause. It is a state of progressive loss of kidney function, ultimately resulting in the need for renal replacement therapy (dialysis or transplantation). Kidney damage refers to pathologic abnormalities either suggested by imaging studies or renal biopsy abnormalities in urinary sediment, or increased urinary albumin excretion rates . The 2012 KDIGO CKD classification recommends details about the cause of the

CKD and classifies it into 6 categories based on glomerular filtration rate (G1 to G5 with G3 split into 3a and 3b). It also includes the staging based on three levels of albuminuria (A1, A2, and A3), with each stage of CKD being sub-categorized according to the urinary albumin-creatinine ratio in (mg/gm) or (mg/mmol) in an early morning "spot" urine sample The 6 categories include:

G1: GFR 90 ml/min per 1.73 m2 and above

G2: GFR 60 to 89 ml/min per 1.73 m2

G3a: GFR 45 to 59 ml/min per 1.73 m2

G3b: GFR 30 to 44 ml/min per 1.73 m2

G4: GFR 15 to 29 ml/min per 1.73 m2

G5: GFR less than 15 ml/min per 1.73 m2 or treatment by dialysis

The three levels of albuminuria include an albumin-creatinine ratio(ACR)

A1: ACR less than 30 mg/gm (less than 3.4 mg/mmol)

A2: ACR 30 to 299 mg/gm (3.4 to 34 mg/mmol)

A3: ACR greater than 300 mg/gm (greater than 34 mg/mmol)

Also Individuals with CKD experience substantial physical and mental symptoms . These symptoms can affect quality of life, activities of daily living, social functioning, and mortality . Despite the high burden of symptoms in CKD, many nephrology providers demonstrate limited appreciation of their patients' symptoms . Several factors likely contribute to this, including the limited scientific understanding of symptom etiology, unclear ownership of management, and limited treatment strategies with proven effectiveness in rigorous studies . Fortunately, the shift toward patient-centered care has

reinvigorated the field of symptom research in patients with CKD the pathogenesis of symptoms in patients with CKD remains a critical but poorly understood process. A better understanding of the pathways underlying symptom development in our patients may provide opportunities to develop new treatments or refashion old therapies for new purposes. In this issue of *CJASN*, Wulczyn *et al.* provide epidemiologic evidence to further our understanding of symptoms in patients with CKD. The investigators used longitudinal data from the Chronic Renal Insufficiency Cohort (CRIC) to examine the association between one measure of kidney function, eGFR, and symptom severity in over 3600 patients (including approximately 3300 with longitudinal symptom scores). Symptoms were assessed annually using the symptom items from the Kidney Disease Quality of Life (KDQOL) instrument, which captures how bothersome symptoms are on a five-point Likert scale (from "not at all" to "extremely"). Symptom scores were then scaled from zero to 100, with a one-point Likert scale change representing a 25-point symptom score change. The investigators focused on six symptoms attributable to the accumulation of uremic toxins (fatigue, anorexia, pruritis, nausea, paresthesia, and pain) and examined how longitudinal changes in an individual symptom associated with annual measures of eGFR and other time-varying covariates. The study represents an excellent use of CRIC with its diverse recruitment (Black participants and Hispanic participants comprised 40% and 13% of the cohort, respectively), high prevalence of CKD stages 3a to 4 (approximately 85% of patients) at baseline, and long follow-up (median of 7 years) . As expected, the symptom burden in the cohort was high, with a prevalence of over 40% for pain, fatigue, paresthesia, and pruritis. CKD progression was

common, with an average decrease in eGFR of 1.34 ml/min per 1.73 m^2 per year, and over 500 participants progressed to an eGFR <15 ml/min per 1.73 m^2. (14.15.16.17.18)

1.3 Etiology

The causes of CKD vary globally, and the most common primary diseases causing CKD and, ultimately, end-stage renal disease (ESRD) are as follows

Diabetes mellitus type 2 (30% to 50%)

Diabetes mellitus type 1 (3.9%)

Hypertension (27.2%)

Primary glomerulonephritis (8.2%)

Chronic Tubulointerstitial nephritis (3.6%)

Hereditary or cystic diseases (3.1%)

Secondary glomerulonephritis or vasculitis (2.1%)

Plasma cell dyscrasias or neoplasm (2.1)

Sickle Cell Nephropathy (SCN) which accounts for less than 1% of ESRD patients in the United States (19)

Acute renal failure is caused by ischemic (50%) or nephrotoxic (35%) injury to the kidney. About 15% of acute renal failure is caused by acute tubular interstitial nephritis or acute glomerular nephritis. However, 50% of hospital acquired acute renal failure is frequently multifactorial, for example, sepsis treated with aminoglycosides, radiocontrast in patients receiving angiotensin-converting enzyme inhibitors, or congestive heart failure patients who develop sepsis or are treated with non-steroidal anti-inflammatory agents. Studies from

the 1980s found that the major risk factors for ARF are hypotension, congestive heart failure, septic shock, volume depletion in diabetic patients, aminoglycoside use, or radiocontrast procedures. Acute renal failure also occurs in about 15 to 25% of patients after renal transplantation despite careful attempts to optimize fluid status and increase renal perfusion. There is an increased risk of acute renal failure if the transplanted kidney is obtained from a marginal donor who is either hypotensive with a rising creatinine at the time of transplantation or is greater than 60 years old. Post-transplant acute renal failure has tremendous morbidity, since it prolongs the initial hospitalization and increases the risk of acute and subsequent chronic rejection. If this acute renal failure could be prevented, it would be possible to transplant more kidneys from marginal donors and thus double the size of the donor pool. This would dramatically decrease the waiting time for renal transplantation, which currently averages about three years.(20)

[Figure(3) shows the stages of kidney failure]

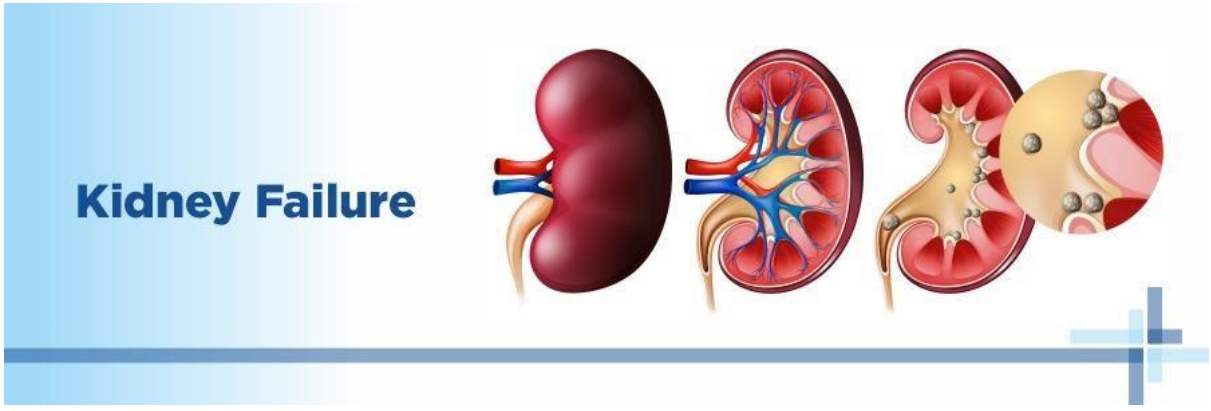


Figure (3)

1.4 The relationship between kidney failure and diabetes

The kidney is arguably the most important target of microvascular damage in diabetes. A substantial proportion of individuals with diabetes will develop kidney disease owing to their disease and/or other co-morbidity, including hypertension and ageing-related nephron loss. The presence and severity of chronic kidney disease (CKD) identify individuals who are at increased risk of adverse health outcomes and premature mortality. Consequently, preventing and managing CKD in patients with diabetes is now a key aim of their overall management. Intensive management of patients with diabetes includes controlling blood glucose levels and blood pressure as well as blockade of the renin–angiotensin–aldosterone system; these approaches will reduce the incidence of diabetic kidney disease and slow its

progression. Indeed, the major decline in the incidence of diabetic kidney disease DKD over the past 30 years and improved patient prognosis are largely attributable to improved diabetes care. However, there remains an unmet need for innovative treatment strategies to prevent, arrest, treat and reverse DKD

Approximately half of all patients with type 2 diabetes and one-third with type 1 diabetes will develop CKD, which is clinically defined by the presence of impaired renal function or elevated urinary albumin excretion, or both The percentage of these patients who can be considered to have CKD as a result of their diabetes is unclear. Invariably, other contributors to renal dysfunction are also present, including hypertension, dyslipidaemia, obesity, intrarenal vascular disease, acute kidney injury, glomerular atherosclerosis, renal ischaemia and ageing-related nephron loss. Accordingly, it is seldom possible to precisely

define ‘diabetic kidney disease’ (DKD) or ‘diabetic nephropathy' in epidemiology or clinical practice, particularly in patients with type 2 diabetes. Consequently, it is more appropriate to identify patients with diabetes and CKD, and to undertake strategies for holistic renoprotection in patients with diabetes. The incidence of CKD in type 1 diabetes differs from that observed in type 2 diabetes. It is estimated that approximately one-third of all people with type 1 diabetes will develop CKD over the course of their lifetime15,22–24. This difference is mostly because subjects with type 1 diabetes are generally younger and healthier at diagnosis and carry fewer co-morbid conditions than those with type 2 diabetes. Consequently, the renal presentation in type 1 diabetes potentially better reflects DKD, rather than the mixed picture of CKD in type 2 diabetes that is confounded by omnipresent other contributors, such as ageing, vascular disease, insulin resistance and obesity.(21) the prevalence and incidence of diabetes mellitus (DM) has increased significantly worldwide, mainly due to a higher prevalence of type 2 DM. Type 2 DM globally affects 18–20 % of adults over the age of 65 years. It is estimated that approximately 285 million people, between 20 and 79 years old, currently have DM, 70 % of whom live in middle- and low-income countries. This increase in type 2 DM (DM2) occurs disproportionately, affecting mainly developing countries, thus bringing enormous challenges in the public health care for these patients. The expectation is for this number to increase by more than 50 % over the next 20 years if preventive programs are not implemented. By 2030, it is estimated that almost 438 million people, or 8 % of the adult population, will have DM Diabetic kidney disease (DKD) is one of the most

frequent and dangerous complications of DM2, affecting about one-third of the patients. In addition to the increasing complexity of outpatient care for patients with DM, DKD results in increased hospitalizations and mortality rates, especially due to cardiovascular complications. DKD also increases the demand for renal replacement therapies, such as dialysis and kidney transplants. The combined economic and social costs of this disease are high and of concern to the world's health systems.(22)

1.5 The current treatment

(RAS inhibitor)

The oldest and most preeminent drug for DKD treatment is the RAS inhibitor. Actually, RAS inhibitors have been shown to be effective in treating DKD in many clinical trials. In 1993, the Captopril Collaborative Study published by Lewis et al. showed that captopril, angiotensin-converting-enzyme inhibitor (ACE-I), inhibited the progression of nephropathy in patients with overt nephropathy in type 1 diabetes mellitus In addition, angiotensin II receptor blocker (ARB) in diabetic patients with manifest nephropathy has been demonstrated in large randomized controlled trials (RCTs), such as the

Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan in Diabetic nephropathy Trial (IDNT)

Moreover, a number of reports on microalbuminuria among DKD patients have been noted. In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA-2), irbesartan was reported to inhibit the progression from microalbuminuria to overt proteinuria by approximately 70% Furthermore, Microalbuminuria reduction with valsartan (MARVAL), which

compared an ARB with a calcium channel blocker, showed that only ARB was effective in lowering microalbuminuria, indicating that RAS inhibitors have an inhibitory effect on nephropathy and a blood pressure-lowering ability RAS inhibitors have been shown to be effective in all stages of DKD. The combination therapy of ACE-I and ARB was also studied in large randomized trials. Although some studies have shown combination therapy to be beneficialthe Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) reported a significant increase in worsening kidney function and mortality in the telmisartan-ramipril combination treatment group Furthermore, in the Veterans Affairs nephropathy in Diabetes (VA Nephron D) study, no significant difference was noted in the efficacy for DKD of the combination treatment group, and the increase in adverse events, such as hyperkalemia and acute kidney injury (AKI), has been reported Based on these results, the combination of ACE-I and ARB is not recommended.(23.24.25)

1.6 Conclusion

In several large studies of patients with ESRD, there was no association between increased survival and strict blood glucose control in the patients. It was suggested that the incidence of hypoglycemia was much higher in patients receiving strict glycemic control. It is recommended that blood sugar control be considered an important goal in the treatment of patients with ESRD diabetes to

prevent additional damage to other organs including the eyes, kidneys and heart. The factors that determine ideal blood sugar control are the following: Lower fasting blood sugar Glipizide is given, It is an oral hypoglycemic agent, at a daily dose of 2.5-10 mg in patients with CRF. Although thiazolidinedione and its metabolites are not retained in renal failure, they can lead to edema and heart failure, especially in patients receiving insulin. Hence, their use has been prohibited in patients with advanced kidney failure, especially if they also have heart failure. Repaglinide is metabolized primarily by the liver, and less than 10% of its metabolites are excreted by the kidneys. Therefore, its use in patients with end-stage renal disease (ESRD) may be permitted with great caution and with regard to the risk of hypoglycemia. Lactic acidosis is a rare but potentially fatal complication of metformin, so this drug should also be avoided in patients with CRF. Insulin can be administered subcutaneously or intraperitoneally in patients undergoing peritoneal dialysis with safe and close monitoring. DM causes kidney failure, which increases oxidative stress and exacerbates oxidative stress. Therefore, the use of antioxidants, especially those that are effective in treating these two diseases, should be beneficial.

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