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END OF STUDY THESIS

In view of obtaining the Academic Master's Degree in Biological Sciences

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THEME

Descriptive study of metabolic indicators in relation to pathological conditions: Case of diabetic nephropathy

Presented by:

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In front of the jury composed of :

President:			University of El Oued
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اهـــــــدا

بسم الله الرحمن الرحيم " (يَرْفَعِ هاللَّهُ اهلذِينَ آمَنُوا مِنْكُمْ وَاهلذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ)

الحمد لله الذي ما تم جهد ولا ختم سعي إلا بفظله وتوفيقه الحمد لله الذي يسر لي البدايات وأكمل لي النهايات وبلغني الغايات

أهدي ثمرة نجاحي وتخرجي.....

إلى من أحمل اسمه بكل فخر أكتب هذه السطور بكامل اشتياقي وحبي وامتناني ، إلى الذي بقيت نغمات مفاتيحه وصوت خطواته في مسمعي هاهي اليوم نغمات نجاحي بدونك يا أبي توصل صداها لروحك الطيبة فشاء القدر
وقدر الله ما شاء فعل ليأخدك بجانبه لحياة يستحقها قلبك الطاهر فروح وريحان وجنة نعيم أبي "إبراهيم"

إلى خير مثال للعزم في أمور الحياة إلى من صبرت وقامت بالدورين معا وزرعت بداخلي القوة والثبات أمام كل العقبات

إلى من علمتني كيف يكون الصبر في الضراء منهج ...والشكر في السراء خلق ؛ وأن التفاؤل والإيمان بفرج الله أمر وليس إختيار أمي الغالية " نجيبة"

إلى رفيق خطواتي سندي ، ذخرتي التي أواجه بها المصاعب أخي الغالي "علاوة"

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ورفيقتا دربي ، إليكن يا من كبرتِن معي حلمًا حلمًا، بذكرياتٍ لا تُنسى "مريم" ؛"خديجة"

أبعث إليكِ يا "وصال " هذه الكلمات محمّلة بكل التقدير والامتنان، لما قدمتِه من جهد واخلاص في إعداد المذكرة. لقد كنتِ بحق مثالًا للتفاني وروح التعاون، ووجودك إلى جانبي أضفى على العمل طابعًا مميزًا وروحًا إيجابية.أتمنى
لكي دوام التألق والنجاح في كل ما تسعين إليه.

إلى كل من له الفضل علي كل بإسمه وجميل وسمه والى كل من أحب

"فـتيـــحة"

اهـــــــدا

يا رب !! لك الحمد كما ينبغي لجلال وجهك وعظيم سلطانك

وكما أن لكل بداية نهاية ،فقد جاءت نهاية هذه الرحلة الطويلة المليئة بالنجاحات والاخفاقات ، سنوات بنيت فيها افقا واسعة لنفسي

.إلى ذلك الجبل الذي لا يميل والظل الذي لا يغيب ابي عامر حفضك الله ورعاك يا غالي.

الى نبض الحنان وسر النجاح ،كل حرف في هذه المذكرة كتب ببركة دعائك ، أمي حميدة ، يا معجزة من طمأنينة ويا مجدا لا يكتبه حبر.

الى اخواتي هدية الرحمان : شهيرة ،فاطمة ،افراح، رنيم ، إلين . بكن تعلمت ان الوقوف لا يكون الا بكرامة وان الحلم يا يصاغ الا بإصرار.لكن الفضل يا غالياتي

الى اخوتي.فارس ، سراج ، أركان ، اهديكم هادا النجاح آمل أن تكونو يوما على عتبته .دمتم ذخرا لي وعزا لا ينكسر.

إلى فتيحة، شريكة الدرب ورفيقة السهر والحروف التي كانت لي

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ونبض الدعابة، وأخت الروح قبل المذكرة وبعدها.

أحببتك فوق الحب حبًا، لأنك ببساطة... استثناء لا يكرر. لكي مني كل التقدير والدعاء بمستقبل مشرق يليق بروحك الراقية ، دمت متميزة كما عهدتك دائما عزيزتي.

"وصـــــال"

ABSTRACTS

Abstract

Diabetes, both types, are among the most common chronic diseases in the world. They are characterized by high blood sugar levels resulting from a defect in insulin production or effectiveness within the body. Type 2 diabetes is more prevalent and has several effects that are not limited to high blood sugar levels, but also lead to chronic complications affecting various organs, most notably the kidneys. This condition is known as diabetic nephropathy, and may gradually develop into chronic kidney failure in advanced stages. The aim of this study is to determine the prevalence diabetic nephropathy and the extent of diabetes's impact on the kidneys. The study was conducted by collecting the results of 400 medical test reports chosen randomly. After that, a selection of 125 diabetic individuals, ranging from 12 to 92 years old was considered as the study sample based on the high blood levels of glycated hemoglobin. The data revealed that women are more likely to be affected by diabetes, with 70 women identified, representing 56% compared to 55 men, who make up 44%. In terms of age, the group most at risk of diabetes complications is those aged 72–62 years, representing 26%, followed by the 52–62 age group at 19%, and then the 72–82 age group at 18%. It was also found that the rate of kidney damage is the highest, with 80 out of 125 individuals affected, representing 64%, based on the results of blood urea and serum creatinine levels. Urine levels of microalbumine was used to determine the level of kidney damage. In the 80 cases of detected kidney damage, a number of 9 cases (11%) was noted as early stages of kidney damage verse 71 cases (89%) of progressed stages of kidney damage. In conclusion, chronically elevated blood sugar levels, lead to kidney damage and are the primary cause of diabetic nephropathy that need to be monitored and prevented.

Keywords: Type 2 Diabetes, Diabetic Nephropathy, Medical tests, Pathophysiology.

ملخص

يُعد داء السكري، بنوعيه، من أكثر الأمراض المزمنة شيوعًا في العالم. يتميز بارتفاع مستوى السكر في الدم نتيجةً لخلل في إنتاج الأنسولين أو فعاليته في الجسم. يُعد داء السكري من النوع الثاني أكثر انتشارًا، وله آثارٌ عديدة لا تقتصر على ارتفاع مستوى السكر في الدم، بل تؤدي أيضًا إلى مضاعفات مزمنة تُصيب أعضاءً مختلفة، أبرزها الكلى. تُعرف هذه الحالة باسم اعتلال الكلية السكري، وقد تتطور تدريجيًا إلى فشل كلوي مزمن في مراحل متقدمة. تهدف هذه الدراسة إلى تحديد مدى انتشار اعتلال الكلية السكري ومدى تأثيره على الكلى. أُجريت الدراسة من خلال جمع نتائج 044 تقرير فحص طبي تم اختيارها عشوائيًا. بعد ذلك، تم اختيار 521 مريضًا مصابًا بداء السكري، تتراوح أعمارهم بين 52 و92 عامًا، كعينة للدراسة بناءً على ارتفاع مستويات الهيموغلوبين السكري في الدم. كشفت البيانات أن النساء أكثر عرضة للإصابة بمرض السكري، حيث تم تحديد 04 امرأة، يمثلن 15٪ مقارنة بـ 11 رجلًا، والذين يشكلون 00٪. من حيث العمر، فإن المجموعة الأكثر عرضة لمضاعفات مرض السكري هي أولئك الذين تتراوح أعمارهم بين 02 و 52 عامًا، ويمثلون 25٪، تليها الفئة العمرية 12-52 بنسبة 59٪، ثم الفئة العمرية 02-22 بنسبة 52٪. كما وجد أن معدل تلف الكلى هو الأعلى، حيث تأثر 24 من أصل 521 فردًا، ويمثلون 50٪، بناءً على نتائج مستويات اليوريا في الدم والكرياتينين في المصل. تم استخدام مستويات الميكروألبومين في البول لتحديد مستوى تلف الكلى. في 24 حالة من حالات تلف الكلى المكتشفة، لوحظت 9 حالات (55٪) كمراحل مبكرة من تلف الكلى مقابل 05 حالة (29٪) من المراحل المتقدمة من تلف الكلى. في الختام، يؤدي ارتفاع سكر الدم المزمن، إلى تلف الكلى، وهو السبب الرئيسي لاعتلال الكلية السكري، الذي يجب مراقبته و الوقاية منه.

الكلمات المفتاحية: داء السكري من النوع الثاني، اعتلال الكلية السكري، الفحوصات الطبية، الفسيولوجيا المرضي.

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List of abbreviations

ACEI: Angiotensin-Converting Enzyme Inhibitor

AGEs: Advanced Glycation End products

ARB: Angiotensin Receptor Blocker

BP: Blood Pressure

BSL: Blood Sugar Level

CTGF: Connective Tissue Growth Factor

DKD: Diabetic Kidney Disease

DM: Diabetes Mellitus

DN: Diabetes Nephropathy

ECM: Extra Cellular Matrix

EGFR: Estimated Glomerular Filtration Rate

EMT: Epithelial-to-Mesenchymal Transition

FPG: Fasting Plasma Glucose

GBM: Glomerular Basement Membrane

HbA1c: Hemoglobin A1C

HDL: High- Density Lipoprotien

HHNS: Hyperosmolar Hyperglycemic Nonketotic Syndrome

IDDM : Insulin-Dependent Diabetes Mellitus

IFG: Impaired Fasting Glucose

IGT: Impaired Glucose in-Tolerance

IL-6: Interleukine 6

JAK: Janus Kinase

MCP-1: Monocyte Chemoattractant Protein-1

NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells

NIDDM : Non-Insulin-Dependent Diabetes Mellitus

NOXs: NADPH Oxidases

NRF2: Nuclear Related- Factor 2

OGTT: Oral Glucose Tolerance Test

PAD: Peripheral Arterial Disease

PKC: Protein Kinase C

RAAS: Renin-Angiotensin-Aldosterone System

RNA: Ribo-nucliec Acid

SGLT2: Soudium- Glucose Linked Transporter 2

STAT: Signal Transducer and Activator of Transcription

T1D: Type 1 diabetes

T2D: Type 2 diabetes

TGF-β: Transforming Growth Factor-beta

TGF-β: Transforming Growth Factor-beta

TNF: Tumoral Neuralgia Factor

TNF-α: Tumor Necrosis Factor alpha

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Chapter III: Results and discussion

INTRODUCTION

Diabetes is a chronic disease with a constantly increasing prevalence worldwide. The global prevalence of diabetes is assessed by the world health organization in 2003 to be 194 million diabetics. Diabetes constitutes a major public health problem due to its frequency and severity. According to the International Diabetes Federation, the number of diabetics in the world continues to increase, with estimation that by 2030, 552 million people worldwide could be diabetic (FID, 2017).

The world health organization (WHO) states that 60% of deaths worldwide are caused by chronic, non-communicable, and non-contagious diseases. In 2005, they caused 35,000 out of 58,000 deaths. Diabetes, due to its insidious nature, prevalence, and incidence, is a polymorphic metabolic syndrome with complications that are often serious, irreversible, costly, and fatal if not taken seriously. This chronic metabolic disease covers different types of diabetes; however type 2 is by far the most common, accounting for approximately 90% of diabetes cases. Its prevalence is underestimated because this glycemic abnormality can develop insidiously and silently over many years. It increases in parallel with aging, urbanization, sedentary lifestyles, diet, and the development of obesity (Goldny et al., 2025; Cristina et al., 2020).

The diagnosis of type 2 diabetes is often made incidentally, even though it has already been present for several years. Thus, these undiagnosed diabetes cases gradually evolve into chronic complications like diabetes nephropathy, diabetic neuropathy, and diabetic foot ulcer. These complications progress insidiously, and those affecting the kidney and the feet are among the most frequent and feared. Persistently elevated blood sugar levels cause widespread vascular damage affecting the heart, eyes, kidneys, and nervous system. Diabetes can cause cardiovascular disease (CVD), blindness, kidney failure, and lower-limb amputation (El Hayek et al., 2021).

Diabetic nephropathy is a kidney disease resulting from diabetes, which affects the body's fluid and salt balance, causing high blood sugar levels that damage the cardiac system and kidneys. This condition is the leading cause of kidney failure in diabetics, affecting nearly a third of them. People with diabetes and kidney disease experience worse overall health compared to those with kidney disease alone (Savant et al., 2022). Therefore, the objective of this work is to study the prevalence of diabetic nephropathy along with some metabolic pointers indicating the onset of this condition.

This work is structured in three chapters, where the first chapter aims at a review on diabetes emphasizing on diabetic nephropathy in particular. The second chapter notes the work methodology followed during the study. The third chapter is devoted to the main results obtained and a discussion about the noted findings. A conclusion, perspectives and some recommendations complete this study.

CHAPTER I

Bibliographic review

This chapter presents an overview about diabetes, with a specific focus on diabetic nephropathy as the first and most common chronic complication.

I.1. Generalities about diabetes

I.1.1. Definition and types of diabetes

It is a metabolic disorder wherein the human body does not produce or properly use insulin, a hormone that is required to convert sugar, starches, and other food into energy. Absence or reduced insulin in turn leads to persistent abnormally high blood sugar and glucose intolerance. It is probably the oldest disease known to man. It is also referred to as the Black Death from the 14th century. In people with diabetes, blood sugar levels remain high. This may be due to insulin not being produced at all, not being made at sufficient levels, or not being as effective as it should be. The most common forms of diabetes are type 1diabetes (5%), which is an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes is form of2 diabetes that occurs in pregnancy, and other forms of diabetes are very rare and are caused by single gene mutation (Rama Rao and Tejomurtula, 2024; Chaudhary and Tyagi, 2018).

Type 1 diabetes (T1D) is an autoimmune disease characterized by the T cell-mediated destruction of insulin producing pancreatic beta cells, resulting in insufcient insulin production and hyperglycemia. T1D represents 5–10% of all diagnosed diabetes cases and most often develops in children and adolescents, but can occur at any age. Tere are signifcant ethnic diferences in T1D incidence, Type 1 diabetes is often referred to as insulin-dependent (IDDM) or juvenile-onset diabetes (Addissouky et al., 2024; Chaudhary and Tyagi, 2018).

Type 2 diabetes occurs when the body becomes resistant to insulin or fails to use it properly, leading to elevated blood glucose levels. It typically appears in middle-aged or older adults but is increasingly seen in youth due to rising obesity and inactivity. Causes include insulin resistance from oxidative stress, fewer insulin receptors, or their downregulation. This resistance leads to compensatory hyperinsulinemia, contributing to Syndrome X and cardiovascular diseases. Also known as adult-onset diabetes, type 2 DM affects 5–7% of the global population. It is often managed through diet, exercise, and hypoglycemic drugs. Risk factors include family history, age, obesity, and physical inactivity. (Chaudhary and Tyagi, 2018)**.**

Gestational DM is the development of glucose intolerance during pregnancy with associated insulin resistance and hyperinsulinemia. The global prevalence of gestational DM as of 2021 is 14 % when standardized to 25–30 years of age. This form of diabetes is associated with increases in the risk of complications during pregnancy as well as ischemic heart disease, hypertension, and the potential development of type 2 diabetes. Risk factors associated with this type of diabetes, according to epidemiological studies, include, but are not limited to, maternal age, family history of type 2 diabetes, obesity, cigarette smoking, physical inactivity, and genetic factors. According to the International Association of Diabetes and Pregnancy Groups, a diagnosis of gestational DM is made if there is at least one abnormal value after an OGTT. Fasting, one-hour, and two-hour plasma glucose concentrations greater than 92, 180, and 153 mg/dl, respectively, are abnormal. Frequent monitoring of HbA1c may not be necessary in pregnant women with low HbA1c values but may be helpful in those with overt diabetes (HbA1c > 6.5 %). Suggested treatment modalities include MNT, daily self-monitoring of blood glucose, insulin, exercise, dietary interventions, my-inositol, and oral antihyperglycemic agents such as glibenclamide and metformin (Dilworth et al., 2024; Touami and Tifrani, 2022).

Other forms of diabetes include MODY, neonatal diabetes, type 3c DM, LADA, cystic fibrosis-related diabetes, and steroid-induced diabetes. MODY is a genetic condition causing early-onset hyperglycemia due to impaired insulin secretion. Neonatal diabetes appears in infants under one year, with severe insulin deficiency. Type 3c DM results from exocrine pancreatic diseases like chronic pancreatitis, leading to insulin deficiency. LADA resembles type 2 diabetes but has autoimmune markers similar to type 1; it is treated with insulin and other therapies. Cystic fibrosis-related diabetes shows traits of both type 1 and 2 and is more common in severe cystic fibrosis genotypes, treated mainly with insulin. Steroid-induced diabetes occurs in patients on glucocorticoid therapy due to β-cell dysfunction and insulin resistance and is managed through insulin therapy and lifestyle changes (Dilworth et al., 2024).

I.1.2. Pathophysiology and molecular mechanism

A healthy person’s body keeps blood glucose levels in a normal range through several complex mechanisms. Insulin and glucagon, two hormones made in the pancreas, help regulate blood glucose levels.

- Insulin, made by beta cells, lowers elevated blood glucose levels.
- Glucagon, made by alpha cells, raises low blood glucose levels. When blood glucose levels rise after a meal, the pancreas releases insulin into the blood.
- Insulin helps muscle, fat, and liver cells absorb glucose from the bloodstream, lowering blood glucose levels.
- Insulin stimulates the liver and muscle tissue to store excess glucose. The stored form of glucose is called glycogen.
- Insulin also lowers blood glucose levels by reducing glucose production in the liver. When blood glucose levels drop overnight or due to a skipped meal or heavy exercise, the pancreas releases glucagon into the blood.
- Glucagon signals the liver and muscle tissue to break down glycogen into glucose, which enters the bloodstream and raises blood glucose levels.
- If the body needs more glucose, glucagon stimulates the liver to make glucose from amino acids. (NIH, 2014)

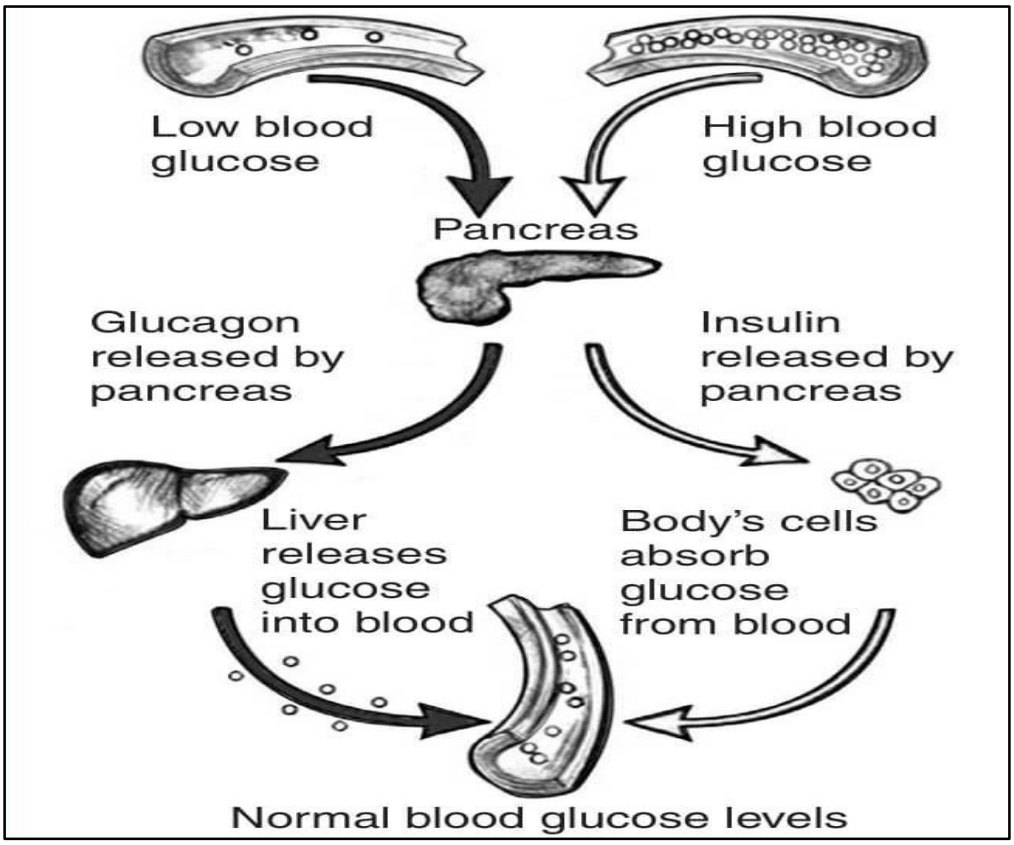

Figure 1: Insulin and glucagon help regulate blood glucose levels (NIH, 2014)

The pathophysiology of type 2 diabetes is characterized by variable degrees of insulin resistance and impaired insulin secretion. Insulin resistance is a state in which the target tissues, such as skeletal muscle, adipose tissue, and the liver, fail to respond adequately to insulin. This results in decreased glucose utilization in muscle and fat and increased gluconeogenesis in the liver. Multiple genetic and environmental factors, and the complex interplay thereof, contribute to both insulin resistance and impaired insulin secretion. Understanding the relative contribution of insulin resistance and impaired insulin secretion to the pathogenesis of type 2 diabetes is important for deciphering the clinical presentation of each patient, establishing preventive measures, and determining the optimal treatment approach (Garcia et al., 2020; Kwak and Park, 2018).

Resistance to insulin is the primary anomaly of people who develop type 2 diabetes and it is observed that the majority of patients with this type of diabetes. Insulin resistance is defined as the decreased effectiveness of insulin on major target tissues, such as muscle, liver, and adipose tissue. This resistance impairs the functions of these tissues, which are involved in various metabolic processes. As a result, the pancreas compensates by increasing insulin secretion, leading to hyperinsulinemia. This condition is exacerbated by abnormal responses in insulin-sensitive tissues. Muscle and liver cells often exhibit insulin resistance, leading to disruption of many cellular functions, especially in adipose tissue (Laissaoui, 2018).

When ß cells stop secreting insulin in a normal, periodic pattern, continuous exposure to insulin causes receptor downregulation or internalization, reducing insulin signaling and responsiveness. A study found that 20 hours of constant insulin exposure in healthy individuals reduced insulin sensitivity and response. Hyperinsulinemia, or elevated insulin, is relative to normal trough levels . Fasting insulin may appear normal, making dysfunction hard to detect with standard tests. Thus, insulin impairment can go unnoticed for long periods (Lwis et al., 2023; Laissaoui, 2018).

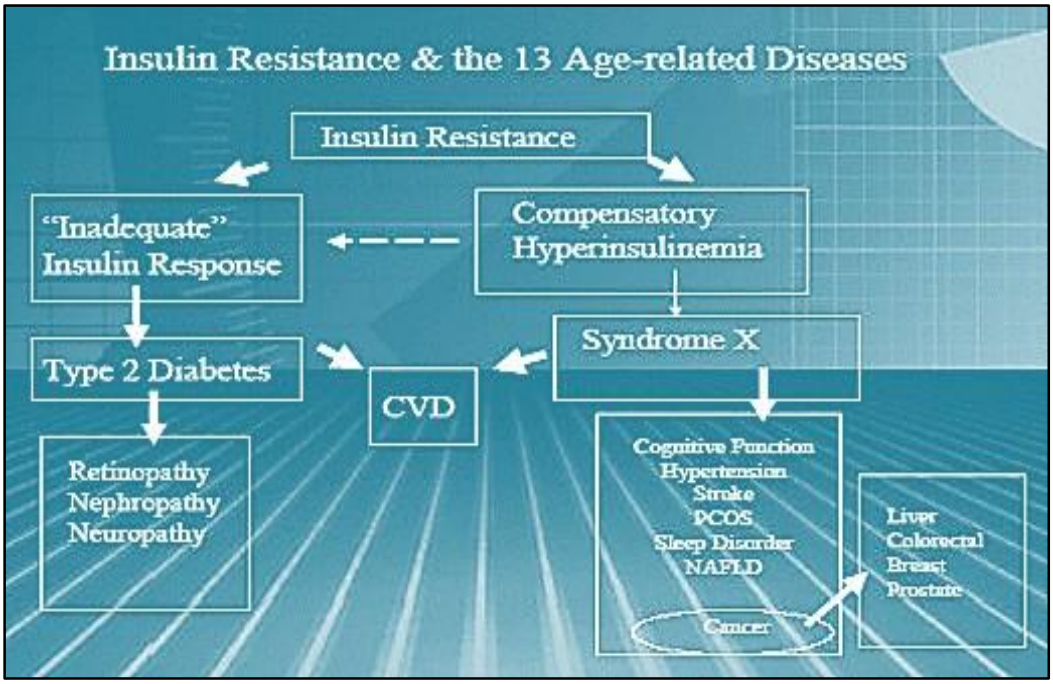

Figure 2: Pathophysiology of type 2 DM (Paul and Paul, 2012)

I.1.3. Factors Influencing the Physiology of Type 2 Diabetes

The majority of cases of type 2 diabetes are multifactorial, with the interaction of environmental and genetic factors. The genetic contribution is largely unknown. However, it is evident that several geneses are involved. Moreover, obesity is a major risk factor for type 2 diabetes due to its role in causing insulin resistance. When the body becomes resistant to insulin and cannot produce enough to compensate, diabetes may occur. Studies show that people who maintain insulin production despite weight gain avoid diabetes. Abdominal fat increases this risk, as it promotes insulin resistance. Fat tissue also releases substances like TNF-alpha, IL-6, and adiponectin, which affect insulin sensitivity. In obesity, harmful substances increase while beneficial ones like adiponectin decrease. Obesity also raises free fatty acids and oxidative stress, both of which further reduce the body's ability to use glucose effectively. Over nutrition, particularly in combination with obesity and under activity, is associated with the development of type 2 diabetes. Obesity likely acts as a diabetogenic factor. Adipocytes secrete several biological products (lepton, tumor necrosis factor-α, and free fatty acids) that modulate processes such as insulin secretion. Insulin action and body weight may contribute to insulin resistance (Pavithra et al., 2025; Laissaoui, 2018).

In addition, age is physiologically accompanied by a progressive reduction in insulin secretion and glucose-using lean mass, and possibly a decrease in insulin sensitivity, which promotes disease

expression. The late onset also reflects the diagnostic delay linked to its insidious nature, and its progressive nature is long preceded by a pre-diabetic phase. Similarly, during pregnancy, insulin sensitivity is reduced by the action of placental hormones, and this affects permanent hyperglycemia. Repeated pregnancies can increase the risk of developing permanent diabetes, particularly in obese women. Furthermore, it is proposed that malnutrition in utero and in the newborn may impair β-cell development at a critical period, predisposing to the development of type 2 diabetes later in life. Moreover, smoking contributes to major chronic diseases like diabetes, which cause over half of all deaths. It raises plasma triglycerides, lowers HDL cholesterol, and worsens glucose tolerance. Diabetic smokers face double the mortality risk of non-smoking diabetics. Those smoking over 15 cigarettes daily have a 2.68 times higher MI risk (95% CI: 2.07–3.48). Complications are 14 times more likely in diabetic smokers than in others (Laissaoui, 2018).

I.1.4. Causes of type 2 diabetes

Type 2 diabetes generally appears in people over the age of 40. Overweight, obesity, and a lack of physical activity are the primary causes of type 2 diabetes. In type 2 diabetes, formerly known as non-insulin-dependent diabetes, the process is different from that of type 1 diabetes. Two abnormalities are responsible for hyperglycemia, either the pancreas still produces insulin, but not enough, relative to blood sugar levels, or this insulin works poorly, which is called insulin resistance. Insulin can no longer regulate blood sugar levels, and this resistance gradually exhausts the pancreas, which eventually stops producing sufficient insulin. These two mechanisms prevent glucose from entering the body's cells and remain in the bloodstream. Blood glucose levels are not regulated by insulin (Touami and Tifrani, 2022).

I.1.5. Symptoms and diagnosis

Diagnosis is often incidental or because of the presence of diabetic complications. Symptoms of T2DM are generally mild and have a gradual onset, albeit some patients experience the classic symptoms, which include:

- **Polydipsia** symptom of many conditions that are characterized by an extreme thirst or a need to take in fluids
- **Polyuria** the passage of excessive volumes of urine with an increased frequency of urination
- **Polyphagia** a medical term that is used to describe excessive hunger or increased appetite

- **Weight loss** Conversely, some patients may experience blurred vision (retinopathy), parenthesis of the lower extremities (neuropathy), nephropathy, and opportunistic yeast infections. The clinical characteristics of T2DM (Labuschagne et al., 2017).

The diagnosis of DM is based on plasma glucose (fasting and postprandial) levels, a 75-gram oral glucose tolerance test (OGTT), and HbA1c. If there are no severe symptoms of diabetes, the diagnosis should be confirmed at a later date, preferably with the same method. Impaired fasting glucose (IFG) is defined as fasting plasma glucose (FPG) between 100 and 125 mg/dl, and impaired glucose intolerance (IGT) is defined as 2nd-hour plasma glucose between 140 and 199 mg/dl after the oral glucose tolerance test (OGTT). DM is diagnosed if FPG is ≥126 mg/dl, 2nd hour glucose on OGTT is ≥200 mg/dl, or plasma glucose value in randomly drawn blood is ≥200 mg/dl with polyuria, polydipsia, ketonuria, and weight loss (Erdin and Cifci, 2023; Touami and Tifrani, 2022).

I.1.6. Complications of diabetes

Below is a list of possible complications that can be caused by badly controlled diabetes:

- **Eye complications** glaucoma, cataracts, diabetic retinopathy, and some others.
- **Foot complications** neuropathy, ulcers, and sometimes gangrene, which may require that the foot be amputated.
- **Skin complications** people with diabetes are more susceptible to skin infections and skin disorders.
- **Heart problems,** such as ischemic heart disease, when the blood supply to the heart muscle is diminished.
- **Hypertension** common in people with diabetes, which can raise the risk of kidney disease, eye problems, heart attack, and stroke
- **Mental health** Uncontrolled diabetes raises the risk of suffering from depression, anxiety, and some other mental disorders.
- **Hearing loss** diabetes patients have a higher risk of developing hearing problems.
- **Gum disease** there is a much higher prevalence of gum disease among diabetes patients.
- **Gastroparesis** the muscles of the stomach stop working properly.
- **Ketoacidosis** a combination of ketosis and acidosis; accumulation of ketone bodies and acidity in the blood.

- **Neuropathy** Diabetic neuropathy is a type of nerve damage that can lead to several different problems.
- **HHNS (Hyperosmolar Hyperglycemic Nonketotic Syndrome)** blood glucose levels shoot up too high, and there are no ketones present in the blood or urine. It is an emergency condition.
- **Nephropathy** Uncontrolled blood pressure can lead to kidney disease.
- **PAD (peripheral arterial disease)** symptoms may include pain in the leg, tingling, and sometimes problems walking properly.
- **Stroke** If blood pressure, cholesterol levels, and blood glucose levels are not controlled, the risk of stroke increases significantly.
- **Erectile dysfunction** male impotence.
- **Infections** people with badly controlled diabetes are much more susceptible to infections.
- **Healing of wounds** cuts and lesions take much longer to heal (Suresh Lal, 2016).

I.1.7. Treatment of patients with type 2 diabetes

The treatment of type 2 diabetes depends on a number of factors:

1. Body weight
2. Current eating habits
3. Current level of physical activity
4. Severity of symptoms
5. Blood glucose levels
6. Time period of diabetes

The treatments include diet, exercise, medication, and insulin therapy:

- Self-care It includes physical exercise, quitting smoking, weight loss, nutritional counseling, diabetic diet, and dietary fiber.
- Medications Anti-diabetic medication, blood thinners, statins, and insulin
- Preventative influenza vaccine and pneumococcal vaccine.

The pharmacological treatments for diabetes includes:

- **Oral anti-diabetic drugs** blood glucose levels are mainly determined by absorption of glucose from the gut, uptake of glucose by peripheral tissues, hepatic glucose output, and the insulin secretion from the pancreas.
- **Sulfonylureas** Sulfonylureas were the first widely used oral hypoglycemic medications. The Sulfonylureas bind to specific sulfonylurea receptors on pancreatic β cells and increase insulin secretion. They are preferably given 15 to 30 minutes before meals.
- **Meglitinide analogues** Meglitinide analogues (repaglinide and netaglinide) are non-sulfonylurea insulin secretagogues. They are benzoic acid derivatives, which act on separate non-sulphonylurea receptor binding sites on β-cells and enhance insulin secretion.
- **Biguanides** Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Metformin has become the most commonly used agent for type 2 diabetes in children and teenagers, e.g., metformin, phenformin, and buformin. Metformin is the preferred biguanide**.**
- **Alpha-glycosidase inhibitors** Alpha-glycosidase inhibitors such as acarbose act bycompetitively inhibiting alpha-glycosidase, the enzyme in the small intestine brush border, which breaks down oligosaccharides and disaccharides into monosaccharides. The starting dosage is 25-50mg once daily, which is increased to 50mg two to three times in a day. It must be ingested with the first bite of food.
- **Thiazolidinediones (Glitazone)** These agents act by improving insulin sensitivity in adipose tissue and skeletal muscle. It also inhibits hepatic glucose output. Pioglitazone has partial PPAR-alpha agonist activity. The dosage of rosiglitazone is 2-8mg in one to two divided doses, while that of pioglitazone is 15 to 45mg once a day. The onset action of these drugs starts from 2-4 weeks of therapy, and the maximum effect is observed after 8-12 weeks (Chaudhary and Tyagi, 2018).

I.2. Diabetes nephropathy

I.2.1. Definition

Diabetes nephropathy is a kidney disease. In normal conditions the function of kidneys helps to regulate fluid and salt balance in the body, which is vital for controlling blood pressure (BP) and

protecting cardiovascular condition. In diabetic conditions, blood sugar levels are high. If these sugar levels increase over a long period of time, then these high glucose levels can damage various regions of the body, including the cardiac system and kidneys. Damage to the kidney that results from this condition is termed diabetes nephropathy (Savant et al., 2022).

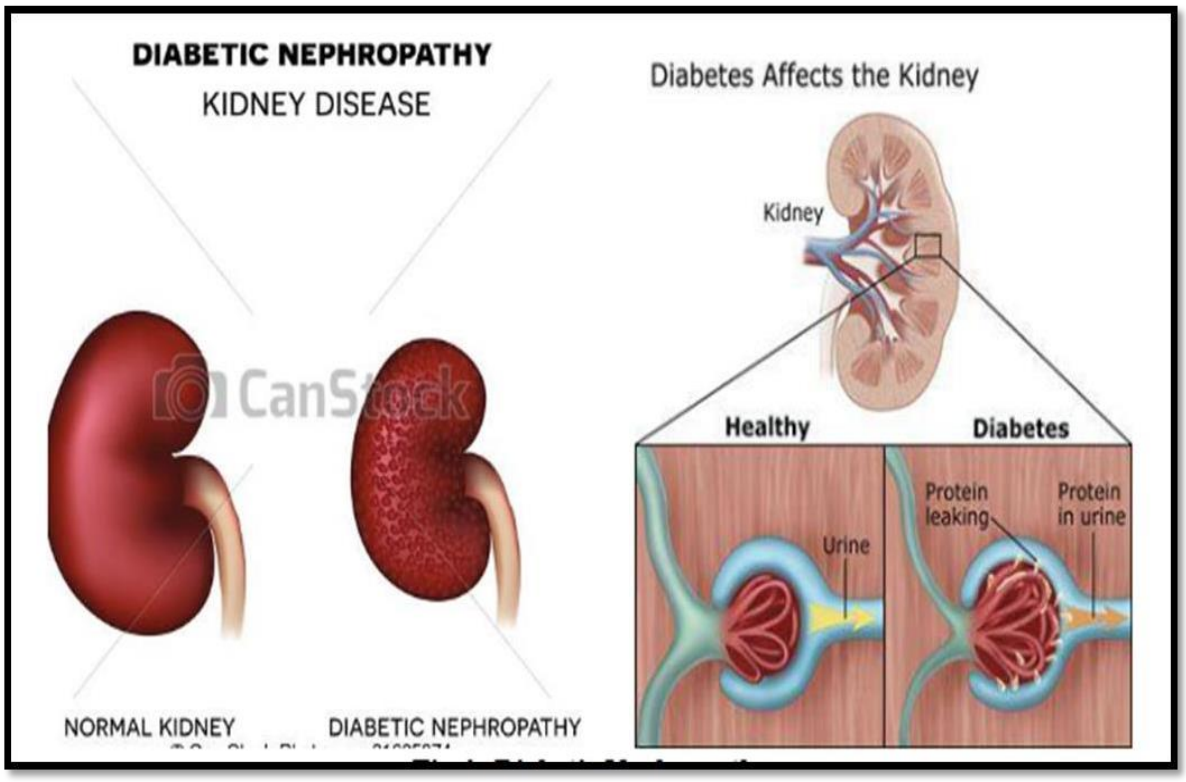

Figure 3: Diabetic Nephropathy (Bansal and Dhiman, 2022)

"Diabetic nephropathy" is a diagnosis that refers to specific pathologic structural and functional changes seen in the kidneys of patients with DM (both type 1 and type 2 diabetes mellitus [T1/T2DM]) that result from the effects of DM on the kidney. Clinically it is characterized by persistent albuminuria and a progressive decline in renal function, and the term infers the presence of a typical pattern of glomerular disease. "Diabetic kidney disease" (DKD) is a clinical diagnosis based upon the presence of proteinuria, decreased estimated glomerular filtration rate (eGFR), or both in diabetes. It does not indicate a specific pathological type. It can be from many diverse causes, including hypertensive nephrosclerosis and unresolved acute kidney failure. The likelihood that "diabetic nephropathy" is the cause of diabetic kidney disease varies widely depending upon the clinical circumstances. It is highly likely that diabetic nephropathy is the cause of diabetic kidney disease in type 1 diabetes of five or more years' duration with albuminuria, but the frequency can range widely in type 2 diabetes (Suneja, 2021).

Anatomically, the histological lesions of diabetic nephropathy visible on biopsy are:

- Renal hypertrophy due to local production of growth factors, particularly IGF1, induced by glycemic imbalance.
- Hyaline arteriolar infiltrates in the subendothelial spaces of the afferent and efferent arteries.
- Thickening of the glomerular basement membrane.
- Expansion of the mesangium, which corresponds to cellular and matrix hypertrophy. This will lead to an increase in the total glomerular filtration surface area.
- Beyond a 37% increase, there is a reduction in the functional capacity of the kidney. Glomerular lesions will result in glomerulosclerosis, which can be diffuse or nodular. These are referred to as "Kimmelstiel-Wilson nodular lesions," characteristic of diabetic nephropathy (Copol, 2017).

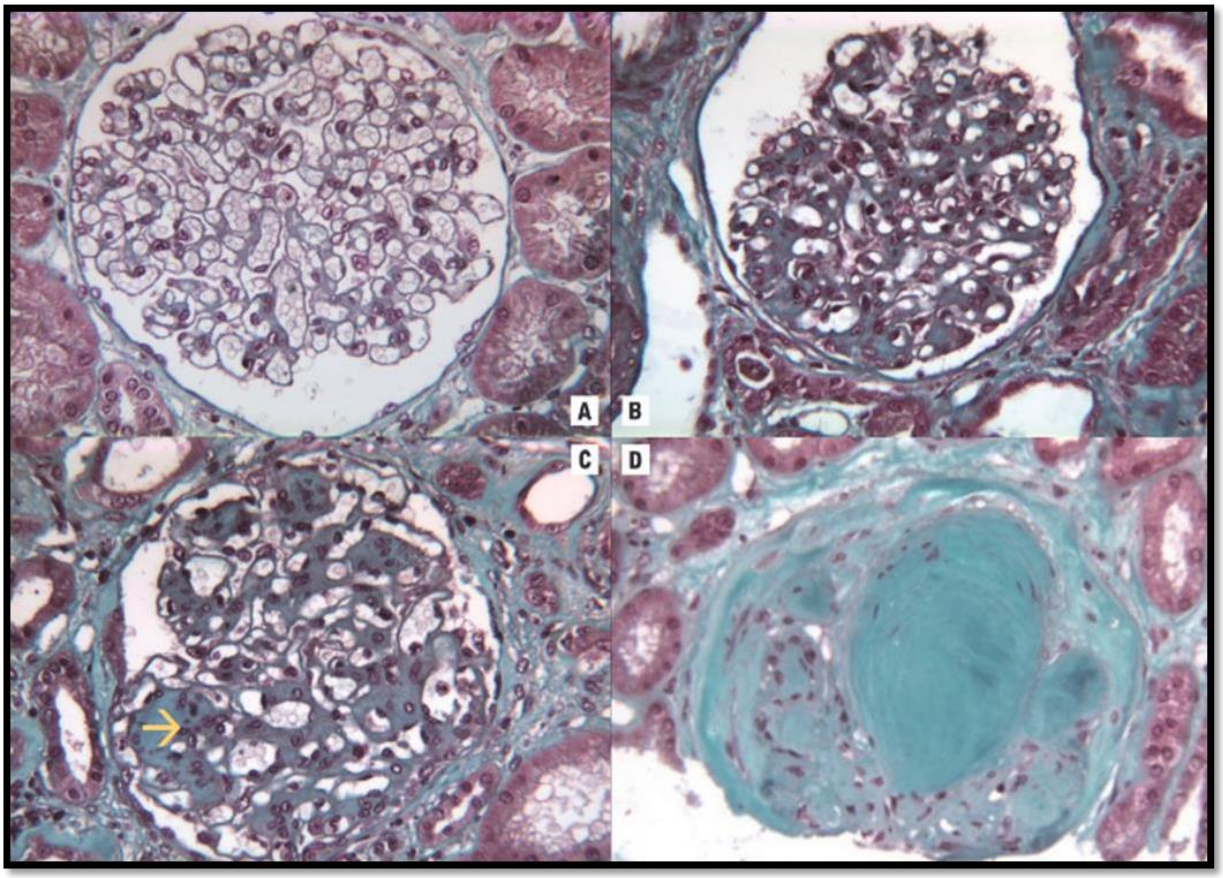

Figure 4: Histology and stage of progression of diabetic nephropathy (Copol, 2017)

A.Normal glomerulus; B. Mesangial expansion without nodules (stage II); C. Nodular sclerosis (Kimmelstiel-Wilson nodule) in at least one glomerulus (stage III); D. Global glomerulosclerosis (> 50% glomeruli) (stage IV).

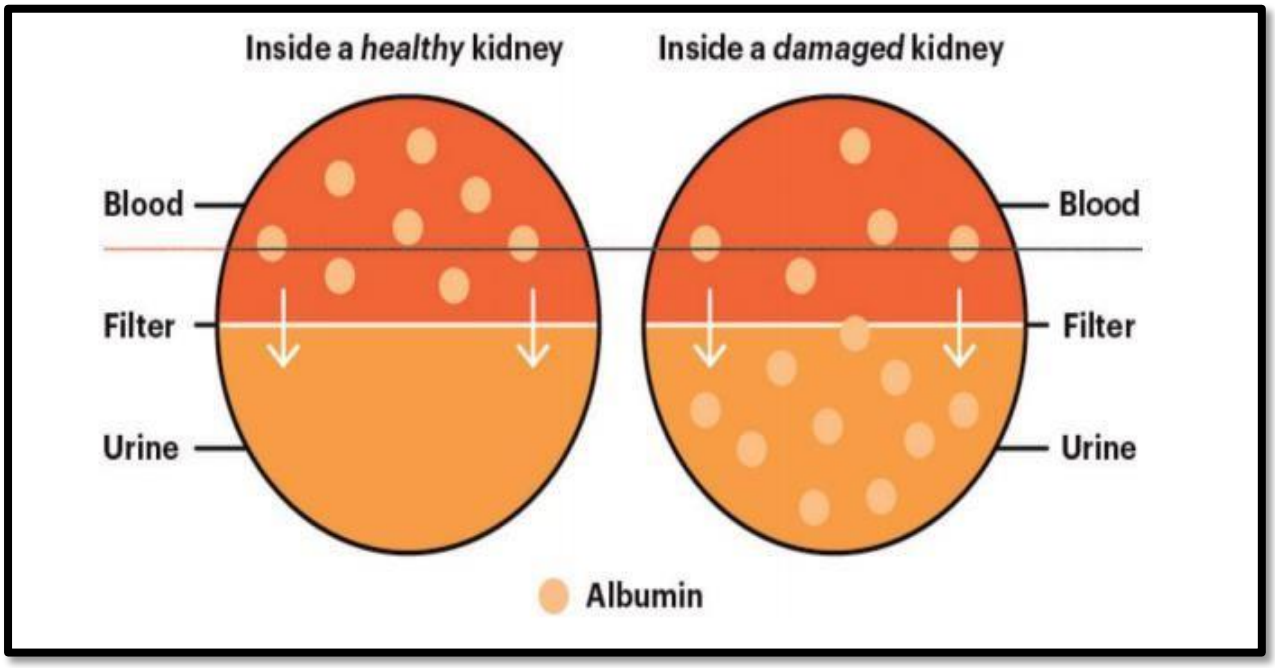

Figure 5: Albuminuria in kidney disease (Mishra and Watson, 2023)

I.2.2. Stages in Diabetic Nephropathy

Diabetes-related nephropathy stages can be categorized based on the estimated glomerular filtration rate (eGFR). The eGFR is a measure of kidney function, with a normal value being around 100. At the lowest end of the spectrum, an eGFR of 0 indicates complete loss of kidney function. This information helps in understanding the severity of kidney damage in individuals with diabetes.

The stages of any kidney disease, including diabetes-related nephropathy, include (Faruk et al., 2016) There are 5 stages in DN

Stage 1 Renal or kidney functions are changed in this stage. The kidney increases in size, and it is accompanied by high filtration and priming rates.

Stage 2 The structure of the kidney is changed for the worse, and patients pass protein in their urine after intense physical activity.

Stage 3 This stage comes after patients have suffered from diabetes for 5 to 15 years and their renal functions begin to decline.

Stage 4 This stage is known as clinical diabetic nephropathy, whose characteristic is a large amount of proteinuria, more than 3.5 grams daily, along with edema and high blood pressure.

Stage 5 It is called uremia, and the patient's condition is critical. They need to undergo dialysis and a kidney transplant to sustain their life. Other therapies are dialysis and osmotherapy (Sulaiman, 2024; Bansal and Dhiman, 2022).

Table 1: Stages of diabetes-related nephropathy (Faruk et al., 2016)

Stage I	Your glomerular filtration rate (GFR) is 90 or higher. At this stage, your kidneys have mild damage but still function normally.
Stage II	Your glomerular filtration rate (GFR) may be as low as 60 or as high as 89. You have more damage to your kidneys than in stage I, but they still function well.
Stage III	Your glomerular filtration rate (GFR) may be as low as 30 or as high as 59. You may have mild or severe loss of kidney function.
Stage IV	Your glomerular filtration rate (GFR) may be as low as 15 or as high as 29. You have severe loss of kidney function
Stage V	Your glomerular filtration rate (GFR) is below 15. Your kidneys are nearing or at complete failure.

I.2.3. Pathophysiology and molecular mechanisms

DN is a progressive kidney disease caused by longstanding DM. It is marked by a gradual decline in the GFR, persistent albuminuria (the presence of albumin in the urine), and hypertension. The pathophysiology of DN is multifactorial, involving several interconnected mechanisms that lead to kidney damage.

A. Protein Glycosylation Chronic hyperglycemia leads to the no enzymatic glycosylation of proteins, resulting in the formation of advanced glycation end products (AGEs). AGEs contribute to the pathogenesis of DN by promoting inflammation, oxidative stress, and the cross-linking of collagen

fibers in the kidney's extracellular matrix (ECM), thereby impairing normal kidney function (Wang et al., 2024).

B. Mesangial Matrix Deposition The mesangial cells within the glomeruli produce excessive amounts of ECM components, such as fibronectin and type IV collagen, in response to hyperglycemia and AGEs. This leads to mesangial expansion, which compromises the glomerular structure and function, contributing to glomerulosclerosis.

C. Glomerular Hemodynamic Alterations Hyperglycemia induces changes in glomerular hemodynamics, including increased glomerular capillary pressure (hyper filtration). This is partly mediated by the dilation of the afferent arterioles and the constriction of efferent arterioles, leading to increased intraglomerular pressure. Over time, this hyperfiltration damages the glomerular filtration barrier, exacerbating proteinuria and kidney injury.

D. Cytokine Release and Hormonal Influences High blood glucose levels stimulate the release of various cytokines and growth factors, such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor. These molecules promote fibrosis and inflammation, further contributing to kidney damage. Hormonal factors, including insulin and angiotensin II, also play roles in modulating the inflammatory and fibrotic responses in the kidneys.

E. Extracellular matrix accumulation and basement membrane thickening The excessive production and deposition of ECM components lead to the thickening of the glomerular and tubular basement membranes. This structural alteration impairs the normal filtration function of the kidneys and promotes the development of glomerulosclerosis and tubulointerstitial fibrosis.

F. Hemodynamic factors and RAAS activation Hemodynamic factors such as systemic Hypertension and increased intraglomerular pressure contribute significantly to DN. The renin-angiotensin-aldosterone system (RAAS) is often overactivated in DM, leading to vasoconstriction, sodium retention, and increased blood pressure. Angiotensin II, a key effector of RAAS, exacerbates glomerular hypertension and promotes inflammation and fibrosis within the kidneys (Habli, 2024).

Diabetic nephropathy is a syndrome marked by persistent albuminuria (confirmed twice over 3–6 months), declining glomerular filtration rate (GFR), and high blood pressure. A key feature is thickening of the glomerular basement membrane (GBM), leading to changes in mesangial and

vascular cells. This involves the formation of AGEs, polyol accumulation, and protein kinase C activation, triggering inflammation and GBM damage. Both types of diabetes show similar renal hemodynamic changes, starting with glomerular hyperfiltration and progressing to microalbuminuria the earliest clinical sign of diabetic nephropathy.

The exact pattern observed in the pathophysiology of diabetic nephropathy is:

- Hyperglycemia
- Thickening of GBM
- Glomerular hyperfiltration
- Impaired endothelial integrity
- Onset of Microalbuminuria
- Impairment of nitric oxide transport
- Loss of afferent/efferent autoregulatory control
- Continued loss of glomerular filtration capabilities

Diabetic nephropathy often begins silently, progressing from microalbuminuria (30–300 mg/day) to overt albuminuria (>300 mg/day). Once established, kidney function declines significantly (GFR drops ~220 ml/min/year), influenced by diabetes type, genetics, blood sugar control, and especially blood pressure hypertension being the main driver of progression and intervention. Later stages may involve noticeable albuminuria, edema, nephrotic syndrome, and eventually, renal failure. This pattern occurs similarly in both types of diabetes. Moreover, DKD results from diabetes-induced hyperglycemia, which activates multiple harmful pathwayshemodynamic, metabolic, inflammatory, and oxidative that affect all kidney parts. This leads to structural and functional damage, including glomerulosclerosis, basement membrane thickening, albuminuria, and reduced kidney function (Siva Rami Reddy, 2019).

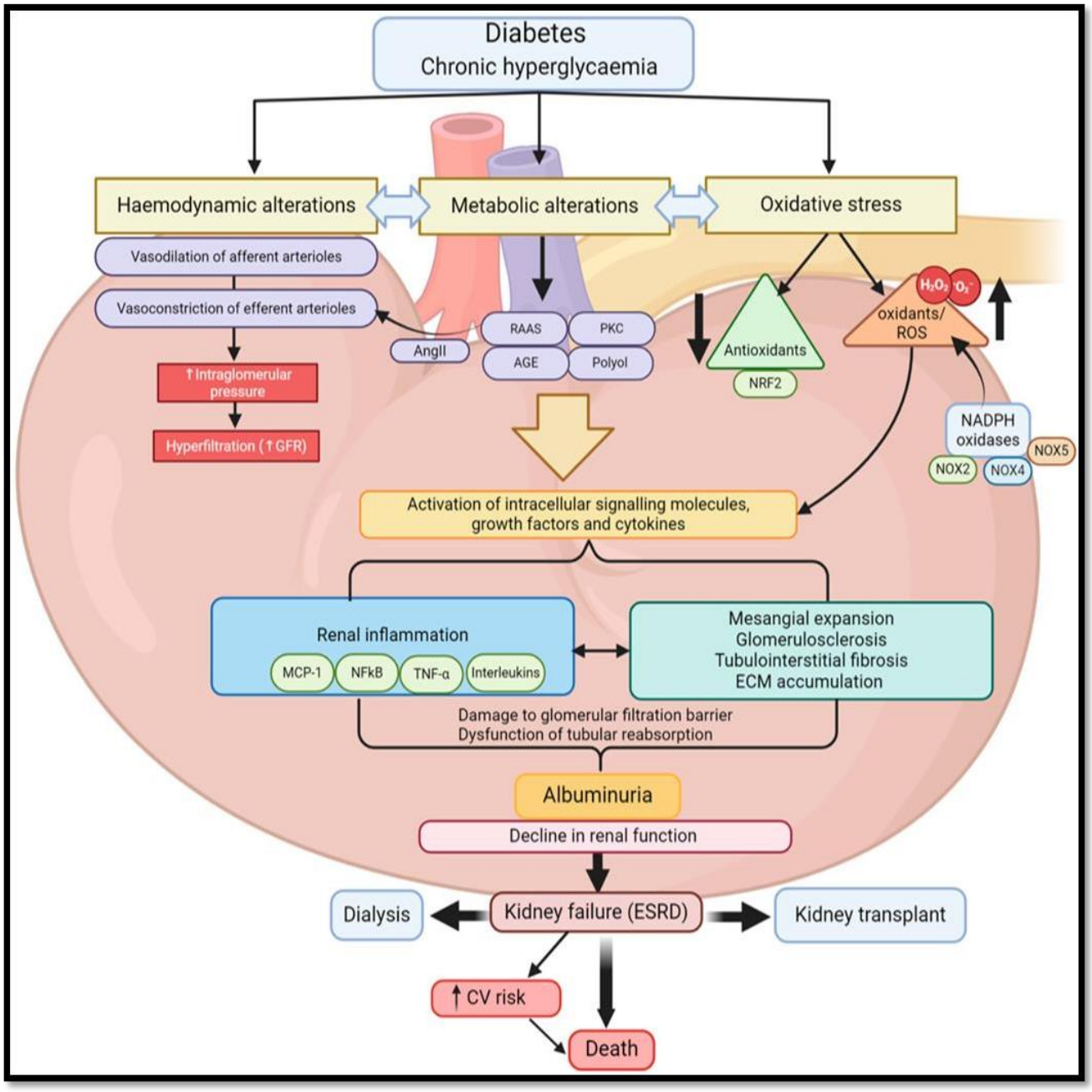

Figure 6: Schematic outlining the major pathways involved in the pathogenesis of DKD (Jha et al., 2024)

a. Hemodynamic Changes

Chronic hyperglycemia in diabetes increases glomerular capillary osmolarity, causing afferent arteriole dilation and elevated glomerular pressure, leading to hyperfiltration and increased glomerular filtration rate (GFR). These changes activate various intrarenal systems like the renin-angiotensin-aldosterone system (RAAS), protein kinase C, the polyol and AGE pathways, and NADPH oxidases. Elevated

angiotensin II, a key RAAS component, constricts the efferent arteriole, further raising intraglomerular pressure and promoting injury. It also triggers inflammatory and fibrotic responses through direct effects and barotrauma. Normally, kidneys reabsorb most filtered glucose via SGLT2 in the proximal tubules. In diabetes, increased glucose filtration boosts SGLT2 expression, worsening hyperglycemia. Enhanced sodium reabsorption reduces delivery to the macula densa, lowering adenosine levels and causing afferent arteriole dilation, further amplifying hyperfiltration (Ratan et al., 2025; Leon-Jiménez et al., 2025 ; Wang et al., 2024; Jha et al., 2024).

B. Metabolic Pathways and Oxidative Stress Oxidative stress is a key factor in the onset and progression of diabetic kidney disease (DKD). Chronic hyperglycemia increases reactive oxygen species (ROS) production and reduces antioxidant defenses, disrupting redox balance and leading to kidney damage. Excess ROS, especially from NADPH oxidases (NOXs), plays a central role in metabolic and structural kidney changes in DKD. Altered pathways such as protein kinase C, polyol, hexosamine, and advanced glycation end products (AGEs) further enhance ROS generation. NOX4 and NOX5 are major ROS sources, particularly in renal cells like podocytes and endothelial cells, where their up regulation under high glucose conditions coincides with decreased antioxidant enzymes like glutathione peroxidase. This results in hydrogen peroxide accumulation and promotes inflammation, fibrosis, et albuminuria. While mitochondrial ROS also contribute, NOXs are considered the primary ROS source in chronic DKD. Additionally, NRF2, a transcription factor regulating antioxidant responses, is suppressed in DKD due to increased Keap1, weakening antioxidant defenses and exacerbating oxidative damage (Gao et al., 2025; Chen et al., 2025 ; Wang et al., 2024; Jha et al., 2024 ; Sakashita et al., 2021).

c. Renal Inflammation In diabetic kidney disease (DKD), inflammation plays a key role, driven by oxidative stress and activation of pathways like JAK/STAT and NF-κB, which increase pro-inflammatory cytokine production. Normally, reactive oxygen species (ROS) support immune defense, but under diabetic conditions, excessive ROS promotes inflammatory cytokine release and immune cell recruitment. NF-κB activated via JAK/STAT and enhanced by PKC and ROS in high glucose, increases cytokine, chemokine, and adhesion molecule expression. Elevated NF-κB and MCP-1 levels, particularly in mesangial cells, contribute to renal inflammation. Cytokines such as IL-1, IL-6, IL-18, and TNF-α, produced by immune and kidney cells, are up regulated in DKD. MCP-1 recruits monocytes and macrophages, amplifying inflammation and fibrosis. TNF-α promotes inflammation, apoptosis, and vascular permeability. IL-1 increases prostaglandin E and phospholipase A2, enhancing

glomerular hyper perfusion. IL-6 contributes to immune cell infiltration and glomerular damage, while IL-18 induces apoptosis and promotes INF-γ release (Bhatia and Srivastava, 2025; Zheng et al., 2024 ; Wang et al., 2024; Jha et al., 2024).

d. Renal Fibrosis Renal fibrosis is a key feature in DKD progression, marked by extracellular matrix (ECM) accumulation and structural kidney damage. High glucose levels activate profibrotic growth factors like CTGF and TGF-β, which stimulate epithelial and endothelial cells to undergo EMT and EndoMT, forming myofibroblasts that secrete ECM proteins (collagen I, III, IV, and fibronectin), leading to fibrosis and glomerulosclerosis. Hyperglycemia also activates fibroblasts and pericytes, worsening injury. Fibrosis is characterized by ECM buildup, renal hypertrophy, thickened glomerular basement membrane, mesangial expansion, podocyte damage, and tubulointerstitial fibrosis. Mesangial cells contribute to ECM deposition (e.g., collagen IV, fibronectin) through TGF-β1 and protein kinase B activation triggered by oxidative stress. Angiotensin II and endothelin further boost TGF-β expression. Elevated ROS levels drive these fibrotic pathways, causing irreversible kidney damage and accelerating diabetic renal disease (Wang et al., 2025 ; Zhang et al., 2024; Wang et al., 2024; Jha et al., 2024).

E. Glomerular Filtration Barrier Alteration et albuminuria Albuminuria is an early marker of DKD progression. Various pathological factors—oxidative stress, inflammation, fibrosis, and hemodynamic changes—damage the glomerular filtration barrier. Early injury to podocytes, essential for barrier integrity, includes foot process effacement and detachment, leading to endothelial dysfunction. This damage causes protein leakage into urine, resulting in albuminuria and proteinuria. As DKD advances, microalbuminuria (30–299 mg/g creatinine) may progress to macro albuminuria (≥300 mg/g), a key feature of DKD (Zhang et al., 2024; Wang et al., 2024; Jha et al., 2024; KI, 2024).

f. Role of Renal Biopsy in DKD Renal biopsy is crucial for diagnosing and managing Diabetic Kidney Disease (DKD). It helps differentiate kidney damage caused by diabetes from other kidney conditions and assesses its severity, guiding treatment and prognosis. The biopsy identifies key pathological features of DKD, such as glomerular basement membrane thickening and nodular glomerulosclerosis, which help in understanding the damage mechanisms. It also informs treatment planning for slowing DKD progression and managing complications. However, renal biopsy has limitations. It samples only a small portion of kidney tissue, which may not fully represent the extent of damage. The procedure carries risks like bleeding, infection, and injury, especially in diabetic patients with comorbidities.

Interpretation can be challenging due to overlapping features with other diseases. In some cases, biopsy findings may not influence treatment decisions. Despite these challenges, renal biopsy is an important tool in managing DKD, particularly when the diagnosis is unclear or additional information is needed, but it should be used cautiously, weighing risks against benefits (Zoccali, 2024 ; Gesualdo et al., 2024; Wang et al., 2024; Jha et al., 2024).

II.2.4. Risk Factors and Pathogenesis

Diabetic nephropathy develops in, at most, 40% of patients with diabetes, even when high glucose levels are maintained for long periods of time. This observation raised the concept that a subset of patients has an increased susceptibility to diabetic nephropathy (Sulaiman, 2024).

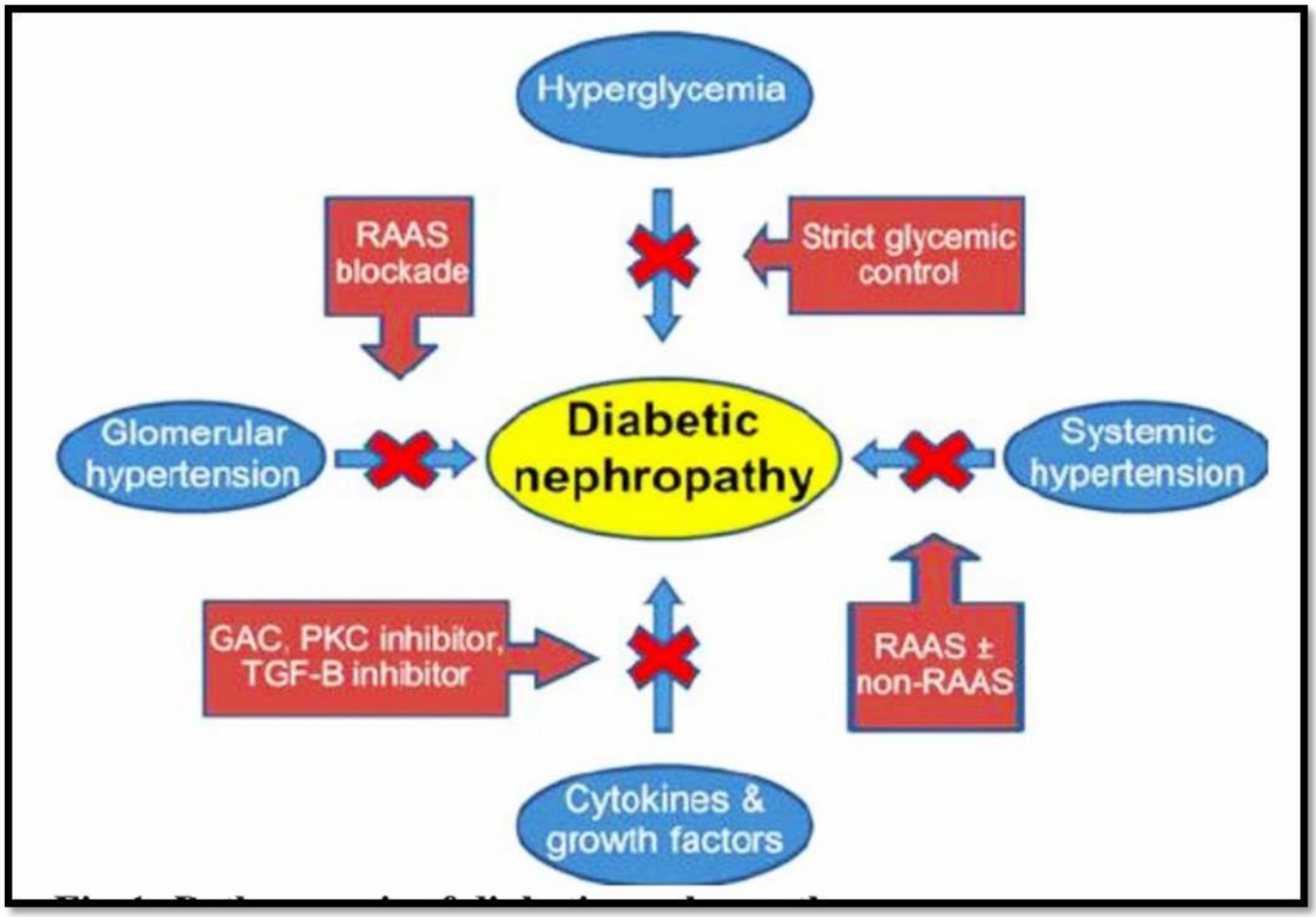

Figure 7: Pathogenesis of diabetic nephropathy (Savant et al., 2022)

Furthermore, epidemiological and familial studies have demonstrated that genetic susceptibility contributes to the development of diabetic nephropathy in patients with both type 1 and type 2 diabetes.

The main potentially modifiable diabetic nephropathy initiation and progression factors in susceptible individuals are sustained hyperglycemia and hypertension. Other putative risk factors are glomerular hyperfiltration, smoking, dyslipidemia, proteinuria levels, and dietary factors, such as the amount and source of protein and fat in the diet (Savant et al., 2022).

The precise reason is unknown; however, a few reasons are poor management of blood sugar and the idea of causing kidney harm. If there's additionally excessive blood pressure, kidney harm is even more likely; in a few instances own circle of relatives' records may additionally play a role. Not everybody with diabetes develops this kidney problem. People with diabetes who smoke and people with type 1 diabetes additionally have a greater threat of kidney problems (Bansal and Dhimani, 2022).

I.2.5. Symptoms

The early stages of diabetic nephropathy may not exhibit any symptoms, posing a challenge in its identification. However, as the disease advances, a range of signs may become apparent, including uncontrolled hypertension, swelling in the limbs, frothy urine, cognitive decline, breathing difficulties, reduced appetite, queasiness, skin irritation, tiredness, and muscle weakness. If diabetes remains unregulated over an extended period, it can lead to the breakdown of the blood vessels in the kidneys that are responsible for eliminating toxins from the blood. This impairment can result in diminished kidney function and the onset of high blood pressure. The heightened stress on the kidney's filtration mechanism due to hypertension can worsen kidney damage, establishing a harmful cycle of deteriorating renal health. Effective management of diabetes is essential to either prevent or decelerate the progression of diabetic nephropathy and its associated complications. By controlling blood sugar levels, individuals can reduce the risk of kidney damage and maintain optimal kidney function. Regular monitoring, lifestyle modifications, and adherence to prescribed medications are crucial components of diabetes management to safeguard against the detrimental effects of diabetic nephropathy (Faruk et al., 2016).

I.2.6. Complications

Complications of diabetic nephropathy may develop gradually over months or years. They may include:

- Fluid retention, which could lead to swelling in your arms and legs, high blood pressure, or fluid in your lungs (pulmonary edema)

- A rise in potassium levels in your blood (hyperkalemia)
- Heart and blood vessel disease (cardiovascular disease), possibly leading to stroke
- Damage to the blood vessels of the retina (diabetic retinopathy)
- Anemia
- Foot sores, erectile dysfunction, diarrhea, and other problems related to damaged nerves and blood vessels
- Pregnancy complications that carry risks for the mother and the developing fetus
- Irreversible damage to your kidneys (end-stage kidney disease), eventually needing either dialysis or a kidney transplant for survival (Savant et al., 2022).

I.2.7. Laboratory tests in detecting and monitoring diabetic nephropathy

Laboratory tests are crucial in detecting and monitoring DN, a serious complication of DM that affects the kidneys. Key tests include:

a. Urine albumin-to-creatinine ratio Measures albumin in urine, with elevated levels indicating kidney damage;

b. Serum Creatinine and Estimated Glomerular Filtration Rate Assess kidney function, with decreased eGFR suggesting impaired kidney performance;

c. Blood Urea Nitrogen Higher levels can indicate reduced kidney function;

d. Blood Pressure Monitoring Hypertension often accompanies nephropathy and can worsen kidney damage;

e. Serum Electrolytes Imbalances can signal kidney dysfunction. Regular monitoring of these parameters helps in early detection and effective management of DN, potentially slowing its progression and preventing complications (Habli, 2024).

I.2.8. Therapy of diabetic nephropathy

The glycemic control of diabetes A common statement of guidelines is that the intention to reach normoglycemia can delay development of abnormal albuminuria in both type 1 diabetic and type 2 diabetic patients. It seems that in an established nephropathy, glycemic control may not be as

effective to slow down the progression. While attempting euglycemia, we should not forget that an ideal HbA1c range can be set up for mortality, as mortality increases both above and underneath this range. We have to try to reach values in the lower part of this range in order to decrease the risk of diabetic nephropathy. The use of oral antidiabetic medications should be tailored individually to the GFR, while we know that gliquidone, pioglitazone, gliptins, and insulin can be given at any stage of renal disease (Habas et al., 2025; Matarid, 2023; Boer et al., 2022 ; Istvan et al., 2020).

Inhibition of the renin-angiotensin-aldosterone system (RAAS) According to guidelines, diabetic patients with albuminuria (in females, excluding time of pregnancy), an ACEI or ARB is recommended. In the case of patients with type 1 diabetes mellitus, ACE may be preferred, while in patients with type 2 diabetes, hypertension, and abnormal albuminuria, ACEI and ARB may be equally good. If these patients also exhibit a decline in GFR, ARB therapy is preferred. In case of intolerance to ACEI or ARB, an agent from the other class should be chosen. After starting ACEI and ARB therapy, serum creatinine and potassium measurements are eligible. Normalization of proteinuria is an important consideration in the therapy of a diabetic patient. The RAAS-inhibitor therapy should not be discontinued when the renal function becomes impaired, as it is further needed to prevent cardiovascular damage in these diabetic patients (Zoja et al., 2024).

Order of use of antihypertensive drugs in diabetic nephropathy The following order may be set up between antihypertensive drugs in diabetic nephropathy (numbers indicate order of choice)

1. RAAS inhibitors
2. Diuretics and/or calcium channel blockers
3. Beta-blockers (cardio selective, metabolically neutral, neutral to peripheral arterial disease; if myocardial infarction or heart failure is found in the past medical history, then use with RAAS inhibitors in the first line)
4. Central nervous system-acting or alpha1-blocker
5. Direct vasodilator (Tong et al., 2023 ; Colbert et al., 2023 ; Istvan et al., 2020).

Lipid-lowering therapy Statins (except for rosuvastatin) may decrease albuminuria and proteinuria; some studies even described a beneficial effect in GFR decline. Fenofibrate may significantly decrease albuminuria both in micro- and macroalbuminuria; this effect is most evident among patients with hypertriglyceridemia, and fenofibrate also leads to a slowing down of the

progression of albuminuria. Moreover, it seems favorable concerning GFR loss (Xiao et al., 2024; Varghese et al., 2021; Istvan et al., 2020).

The role of diet In CKD stages 1-4, sodium intake should be below 2.3 g/day, total fat intake less than 30% of the total energy intake, saturated fatty acids less than 10% of total calorie intake, cholesterol intake should be below 200 mg/day, and carbohydrate intake should cover 50-60% of total energy intake. Protein intake in CKD stages 1-4 should be 0.8 g/day (Cai et al., 2024; Zhou et al., 2024; Ria et al., 2022 ; Istvan et al., 2020).

The role of weight loss Weight loss could lead to a decrease in proteinuria in obese diabetic and non-diabetic patients, meanwhile the GFR decreased (if they were hyperfiltering) or remained constant (Gong et al., 2024; Wan et al., 2024; Istvan et al., 2020).

Cessation of smoking Although no randomized, controlled study was carried out because of ethical reasons, the available data suggest that cessation of smoking may provide significant benefit in regard to the development and progression of diabetic nephropathy (Walicka et al., 2024; Walika et al., 2022; Istvan et al., 2020).

New treatment modalities verified as effective by human studies From vitamin D and its analogues, paricalcitol proved to decrease the rate of albuminuria and does not cause significant adverse effects. In a meta-analysis, glitazones have been shown to decrease albuminuria. In randomized, controlled trials, pentoxifylline led to a significant decrease in albuminuria in patients with abnormal albuminuria (>300 mg/day) (9 studies) but proved inefficient in cases of slighter (30-300 mg/day) albuminuria (4 studies). Aldose reductase inhibitors have been known and studied for 40 years; however, their effect on albuminuria was only studied in one clinical study in patients with type 1 diabetes and abnormal albuminuria. There, a significant improvement was observed. Endothelin inhibitors, given on top of RAAS inhibitors, are able to decrease proteinuria; unfortunately, they increase the chance of edema formation, and one of them may lead to a higher rate of heart failure. Further studies are required to weigh risks and benefits (Istvan et al., 2020).

The prevention measures of diabetic nephropathy may include:

- Keep blood sugar under control.
- Maintain blood pressure in a normal range.

- Consume less salt, less meat, and less saturated fats. Set a dietary plan and follow it.
- Exercise regularly.
- Maintain a healthy weight.
- Avoid smoking.
- Avoid alcohol or limit alcohol intake (Bansal and Dhimani, 2022).

I.2.9. Future directions and promising research areas

Emerging evidence supports novel therapeutic agents for DKD. Investigational drugs targeting inflammatory pathways, such as endothelin receptor antagonists and cannabinoid-1 receptor inverse agonists, hold potential for future DKD management. These agents aim to reduce inflammation and fibrosis, key contributors to DKD progression. Furthermore, new classes of medications like aldosterone synthase inhibitors and RNA interference therapies targeting hepatic angiotensin synthesis are being explored for their renal and cardiovascular protective effects. Research into personalized medicine, leveraging genetic and biomarker profiling, also offers the promise of tailored treatments that optimize individual patient outcomes. Collectively, these advancements herald a new era in DKD management, focusing on comprehensive and targeted therapeutic approaches (Habli, 2024).

CHAPTER II

Work methodology

This chapter presents the methodology used to conduct this study on the impact of type 2 diabetes and its complications on the kidneys and the use of laboratory test results as a tool for data collection.

II.1. Study principle

Diabetes mellitus is a serious, chronic metabolic disorders that characterized by high sugar level either when the pancreas does not produce enough insulin, or when the body cannot effectively use insulin. Complications of diabetes mellitus are progressive and almost resulting by chronic exposure to high blood levels of glucose caused by impairments in insulin metabolism and biological macromolecules. When blood sugar levels rise sharply and for long periods, Type 2 diabetes can be identified by a diabetes diagnosis (for example, an HbA1c ≥ 6.5%), or the presence of signs suggesting type 2 diabetes, such as age over 40 (but possibly younger), being overweight or obese, no sudden acute symptoms, no need for insulin immediately after diagnosis, or a family history of type 2 diabetes. Type 2 diabetes can often be confirmed if C-peptide is normal or elevated, and antibody tests (such as GAD) are negative, the kidneys lose the ability to regulate the balance of fluids and salts in the body, which leads to kidney damage. Nephropathy is a chronic complication characterized by increased urinary albumin excretion (proteinuria) or reduced kidney glomerular filtration rate in both forms of diabetic mellitus, type 1 diabetes mellitus and type 2 diabetes mellitus. Diabetic nephropathy is a major cause of end stage renal disease. It is detected and diagnosed by a group of laboratory biological tests, including blood levels of sugar it is the concentration of glucose in the bloodstream at the moment of taking the sample (normal value: 70-99 mg/dl), glycated hemoglobin it is the percentage of glucose bound to hemoglobin in red blood cells and an assessment of the average blood sugar over 3 months (normal value: less than 5.7%), urea it is an end product of protein breakdown, excreted through the kidneys (normal value: (15-45 mg/dl), and creatinine it is a product of muscle breakdown and excreted through the kidneys, and reflects the efficiency of blood filtration (normal value: in men 0.6-1.2 mg/dl, in women 0.5-1.1 mg/dl), and Microalbuminuria is an early detection of microalbuminuria, which is kidney damage in diabetic patients. Normal value: (30-300 mg/24 h) (Helin, 2024; Bereda, 2022).

Therefore, the aim of the present study is to determine the prevalence of kidneys pathology induced by diabetes (diabetic nephropathy) from the metabolic indicators of medical tests.

II.2. Work methodology

The study methodology includes the source, the nature, and the presentation of the data collected.

II.2.1. Data source

The data collection was carried out from 400 medical test reports of patients from different age groups and both sexes, who underwent tests related to diabetes and kidney disease from Al Medjed Laboratory (Wilaya of El Oued). The obtained medical test reports, chosen randomly, contained the data sought over a period extending from 2017 to 2025.

Figure 8 : Al Medjed Laboratory (Wilaya of El Oued)

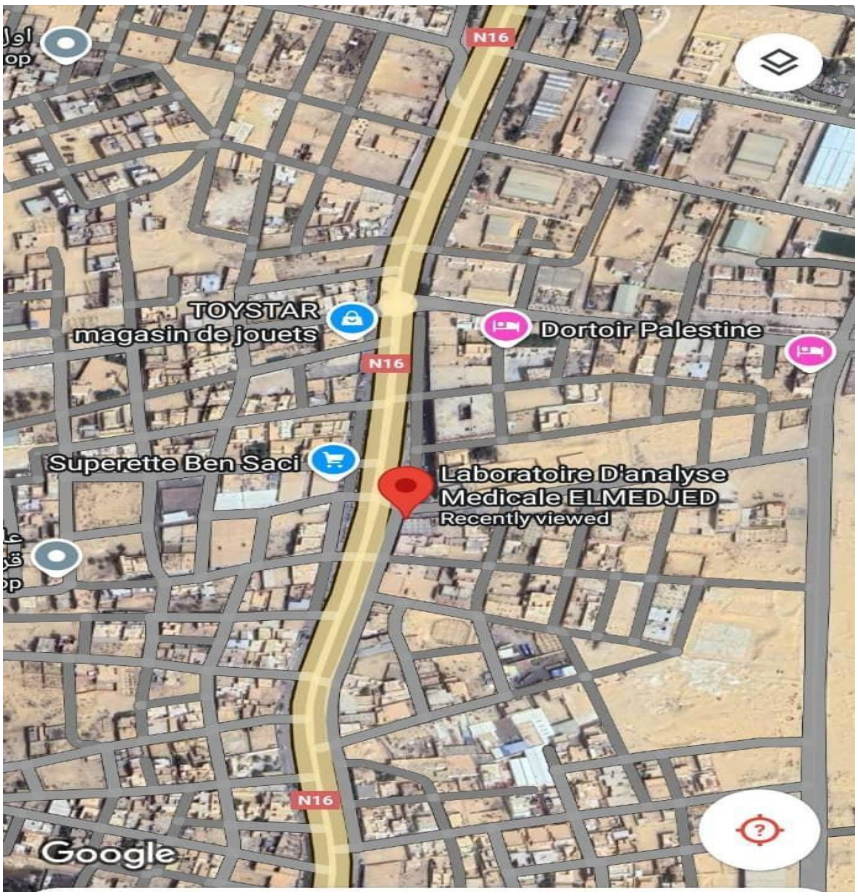

Figure 9 : Site of Al Medjed Laboratory (Wilaya of El Oued)

II.2.2. Data collection

The data were chosen according to the results of laboratory tests that may indicate diabetic nephropathy, via the abnormal level of glycated hemoglobin. General information about the patients were noted such as gender and age. The medical tests selected were blood levels of sugar (BS), glycated hemoglobin (HbA1c), urea, and creatinine (crea), along with microalbuminuria (µAlb). The collected data were then analyzed to determine the extent to which type 2 diabetes affects the kidneys and their functions in the study group.

II.2.3. Data presentation

After data entry, the results are expressed as percentages by relativistic circles, and as values by histograms. A statistical study of the data is carried out using Excel-stat (version.2016.02.28451), by principal component analysis (PCA), in order to determine the different correlations existing between the variables studied (medical tests specific to diabetic nephropathy).

CHAPTER III

Results and discussion

This chapter present the main results obtained from the collected data, followed by a discussion of the noted findings.

III.1. Results

The selected medical test reports (400 cases) had a number of 125 report of diabetic individuals, determined based on the high blood level of glycated hemoglobin, and considered as the study sample.

III.1.1. Distribution of the studied sample according to sex

This section provides information by gender, which is most likely to develop type 2 diabetes. It is noted that the number of Women, estimated at 70 Women (56%), is more than the number of Men, estimated at 55 Men (44%).

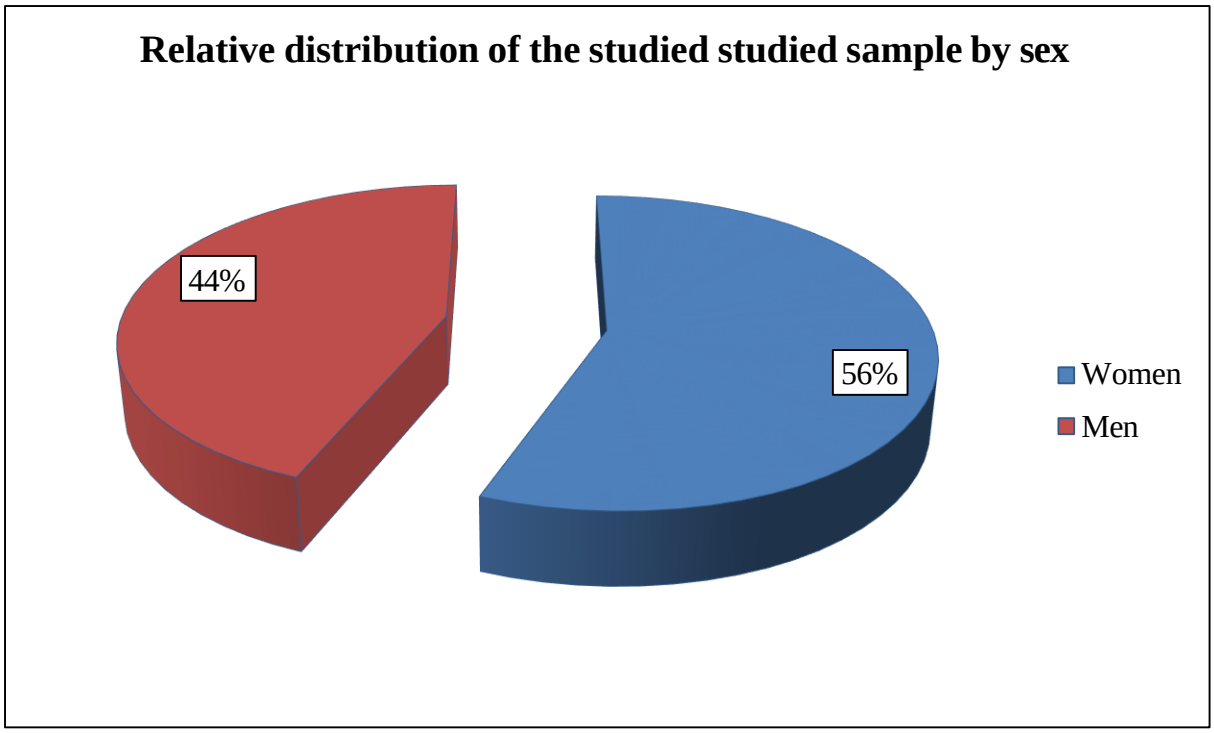

Figure 10: Relative distribution of the studied sample according to sex

III.1.2. Distribution of the studied sample according to age groups

According to the ages of diabetics, the group most presented by type 2 diabetes is [62; 72[, with 33 individuals (22%), followed by the age group [52; 62[with 19% (24 individuals), the age group [72; 82[with 18% (22 individuals), the age group [42; 52[with 15% (19 individuals). The age groups less

presented by type 2 diabetes are [32; 42[with 8% (10 individuals), [82; 92[with 6% (8 individuals), [22; 32[with 6% (7 individuals), and [12; 22[, with 2 individuals (2%).

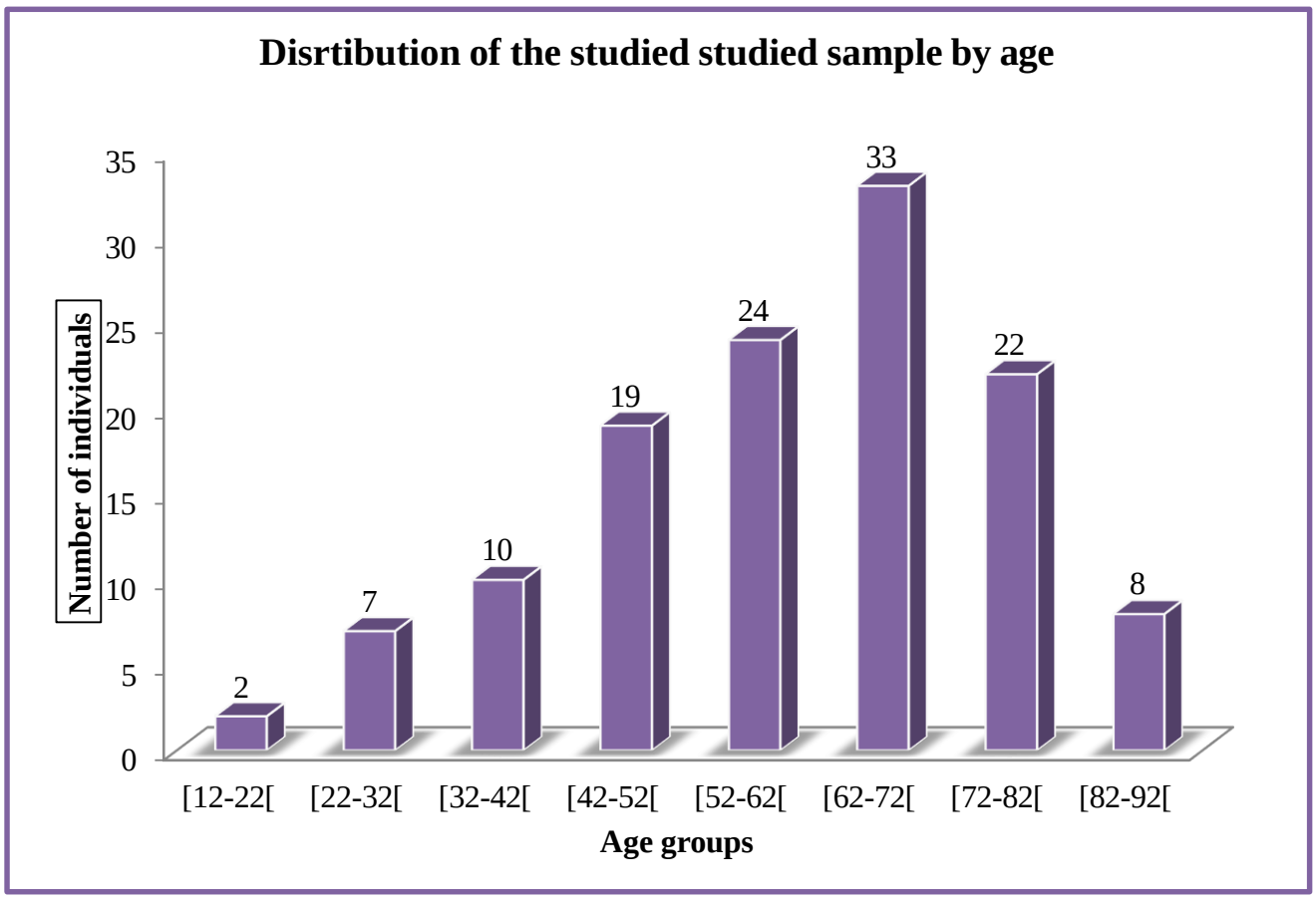

Figure 11: Distribution of the studied sample according to age

III.1.3. Distribution of the studied sample according to blood urea

The studied sample's condition is diagnosed according to the blood urea levels, where we note that the abnormal levels of urea, estimated at 68 individuals at a rate of 54%, is superior to the normal levels, estimated at 57 individuals at a rate of 46%.

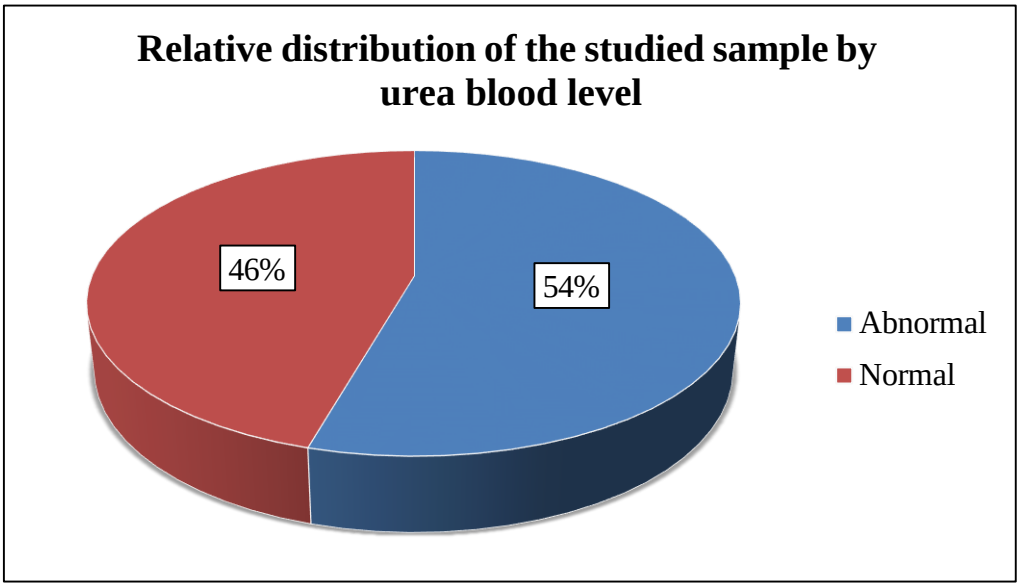

Figure 12: Relative distribution of the studied sample according to the level of blood urea

III.1.4. Distribution of the studied sample according to blood creatinine

The number of normal and abnormal levels of creatinine is determined according to gender because the normal standards for women are different from those for men. Therefore, it is marked that the number of abnormal levels of creatinine, assessed at 33 cases for men, is 60% more than the number of normal levels, estimated at 22 individuals (40%). In addition, it is noted that the number of abnormal levels of creatinine, estimated at 38 cases for women, is 54% more than the number of normal levels, estimated at 32 individuals (46%).

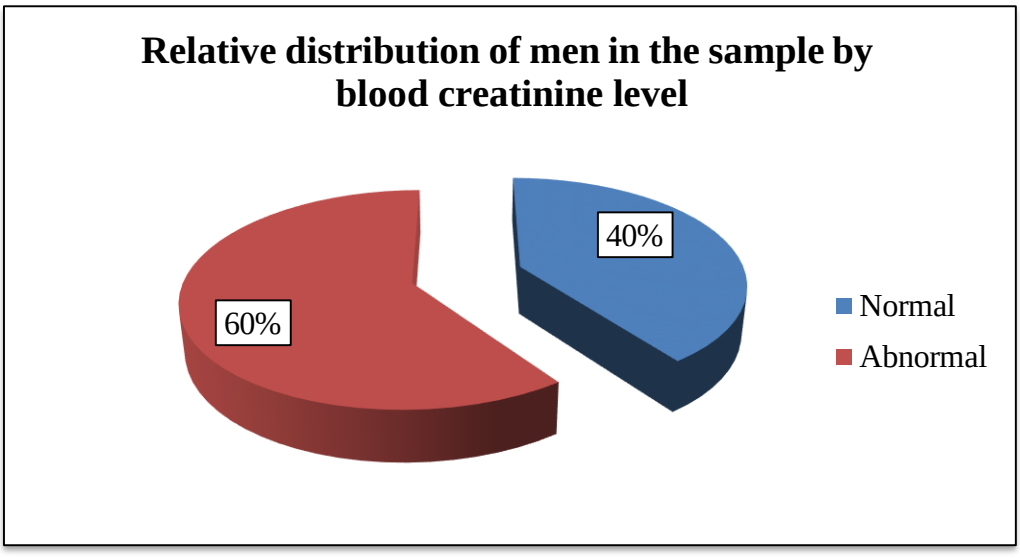

Figure 13: Relative distribution of men in the studied sample according to the level of blood creatinine

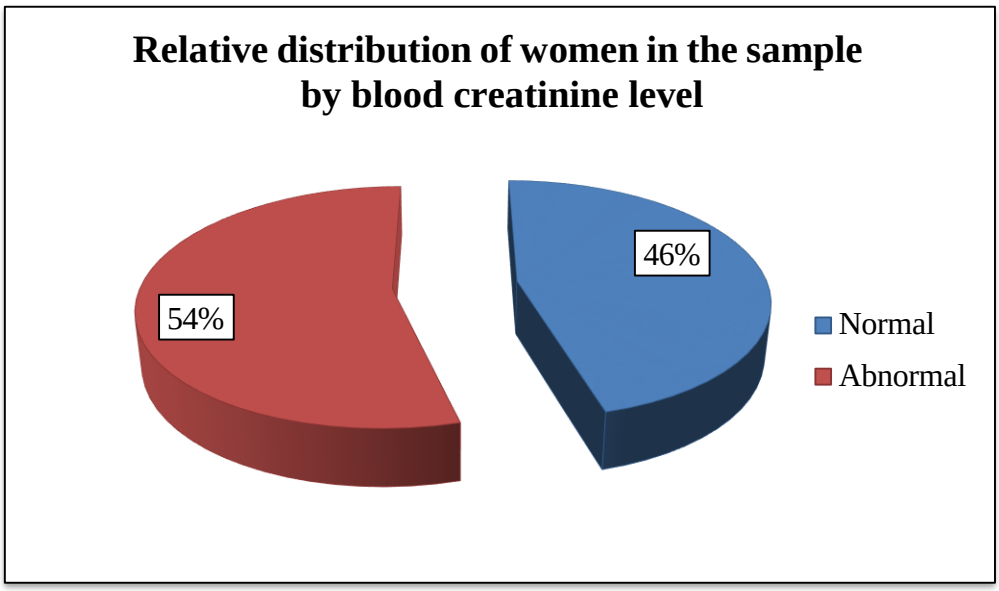

Figure 14: Relative distribution of women in the studied sample according to the level of blood creatinine

III.1.5. Distribution of the studied sample according to according to kidney damage

The presence or absence of kidney damage is determined based on the level of albumin protein in the urine. It is noted that the incidence of kidney damage, estimated at 80 cases at rate of 64%, is higher than the incidence of no kidney damage, estimated at 45 cases at a rate of 36% of the 125 cases studied.

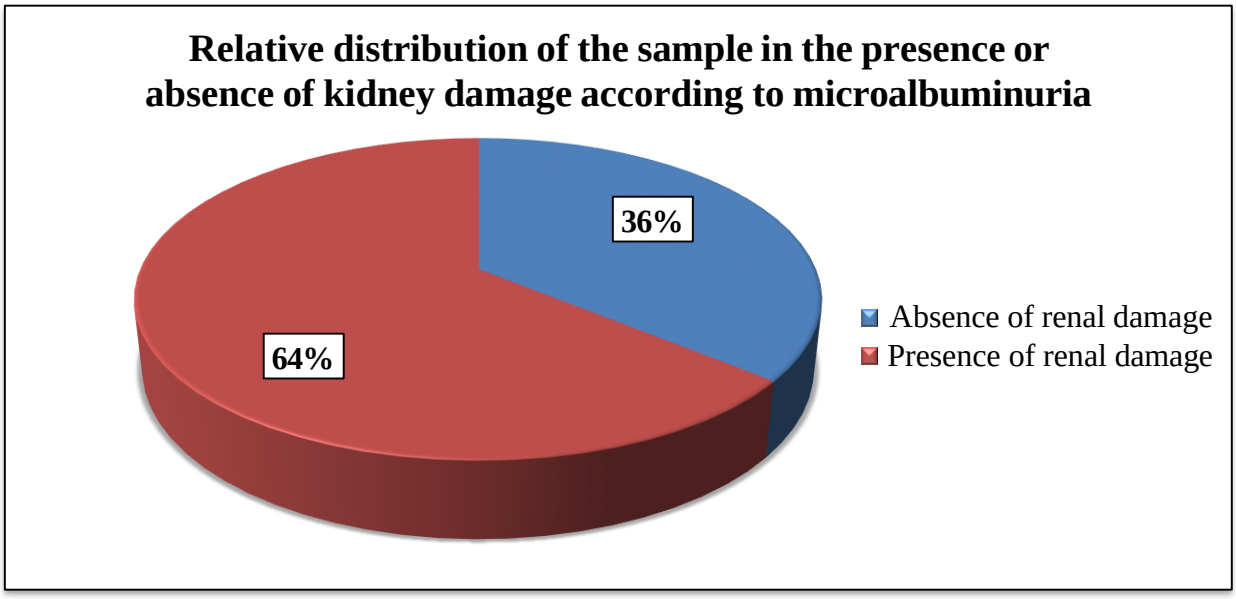

Figure 15: Relative distribution of the studied sample in the presence or absence of kidney damage according to microalbuminuria

The level of kidney damage is determined based on the level of albumin in the urine and the level of creatinine in the blood. The results indicate that the level of advanced kidney damage, estimated at 71 patients (89%), is higher than the level of early kidney damage, estimated at 9 patients (11%).

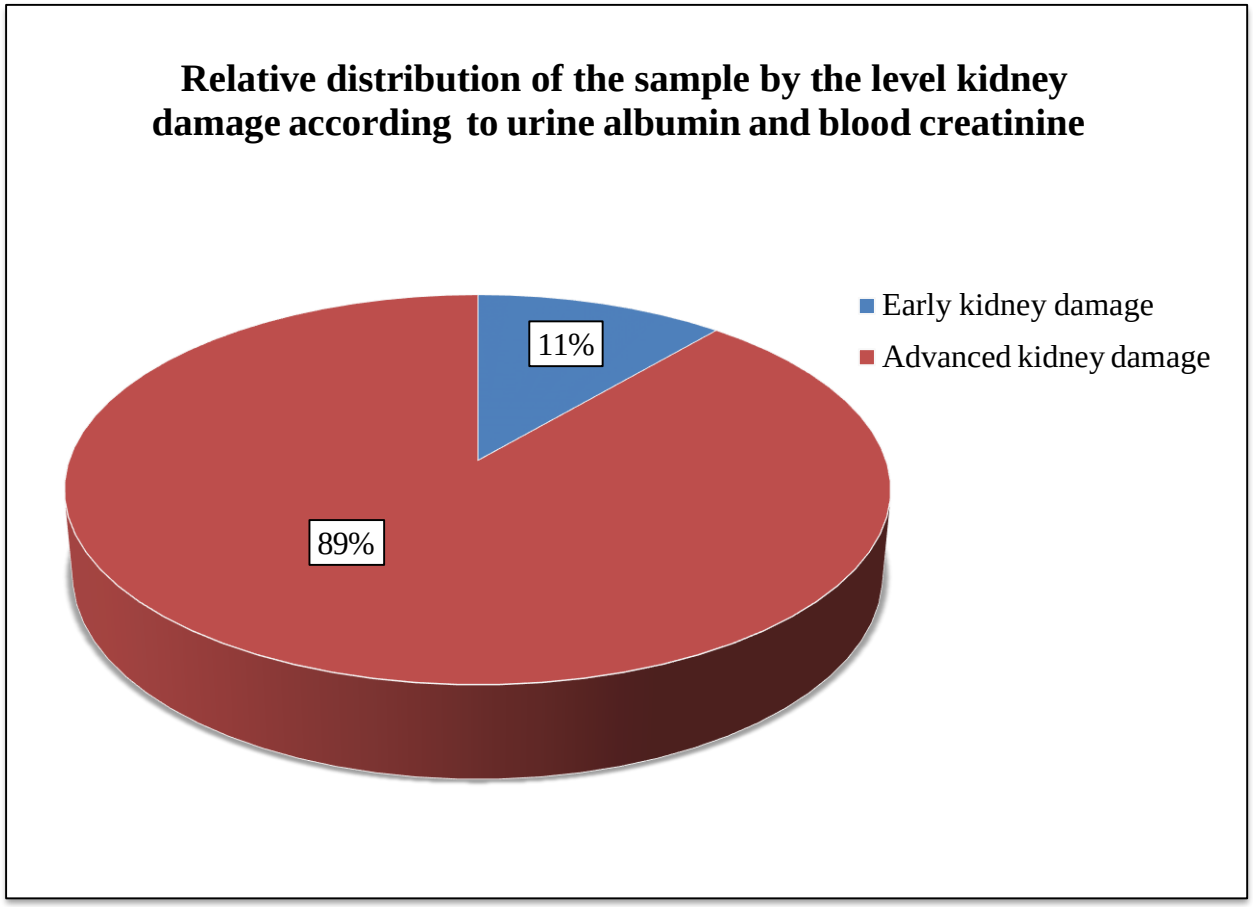

Figure 16: Relative distribution of the studied sample according to the level of kidney damage

III.1.6. Principal component analysis (PCA) of the studied variables of diabetic patients

Based on the PCA, the correlation rate of medical test results is determined at 63.06%, indicating the consequence of type 2 diabetes on kidney function. The results show a strong positive correlation between blood levels of sugar (BSL), and glycated hemoglobin (HbA1c). In addition, the variables of age, blood level of creatinine (crea), and microalbuminuria (µAlb) note a strong positive correlation. Moreover, blood levels of urea is positively correlated with BLS, HbA1c, µAlb, crea, and age. Therefore, high levels of urea are associated with high BLS, high HbA1c, increased microalbumin and creatinine, and older age which reinforce its role as biomarker of systematic dysfunction, particularly kidney function and diabetes-related complications.

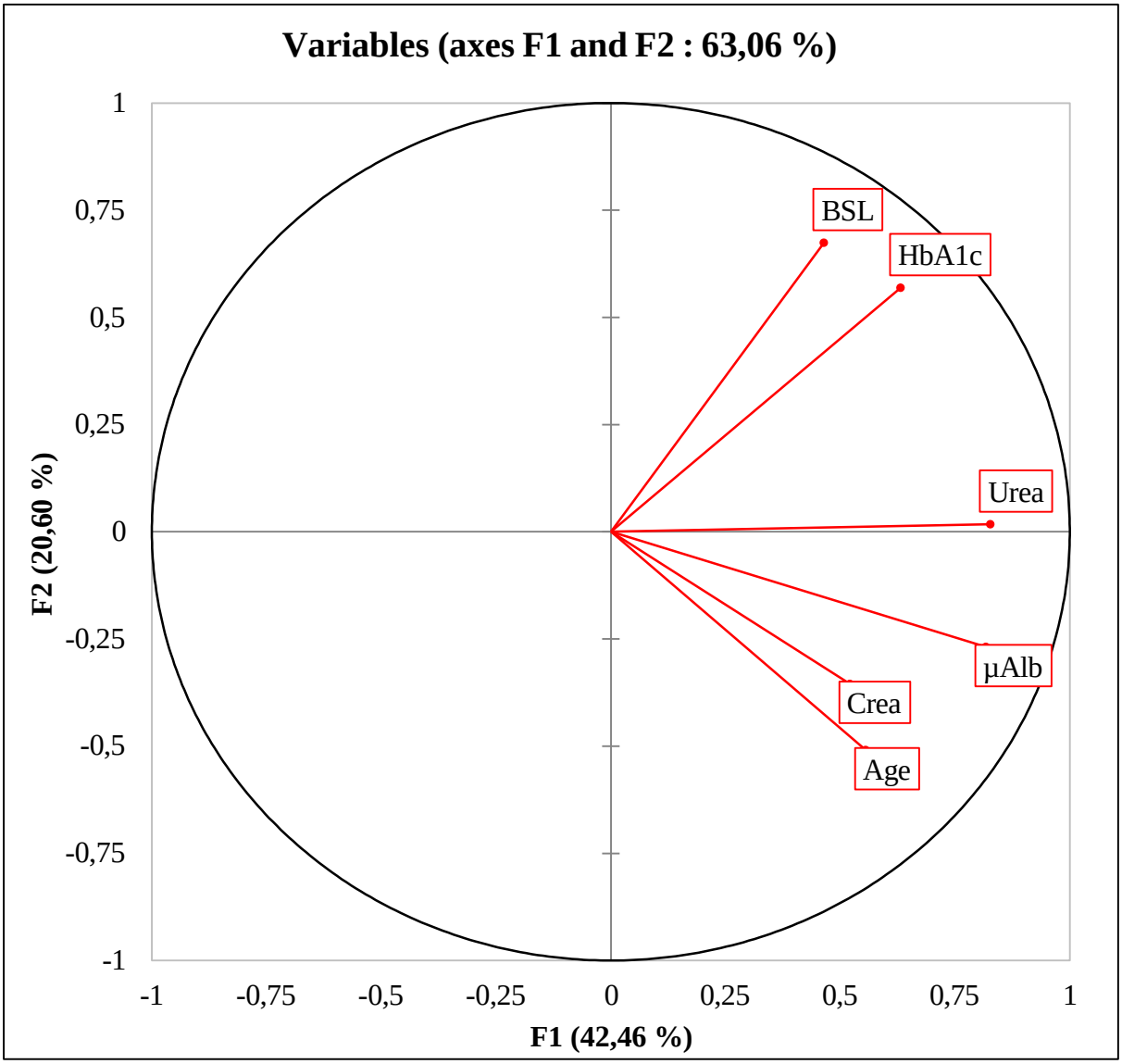

Figure 17: Principal component analysis of the study variables

III.2. Discussion

This study identified the levels of impact of type 2 diabetes on kidney function and the most important metabolic markers that indicate the risk of developing diabetic nephropathy, which is a progressive kidney disease resulting from long-term high blood sugar levels (from 5 to 15 years). It is characterized by a gradual decrease in the glomerular filtration rate and persistent albuminuria (the presence of albumin in the urine).

According to the results obtained from the set of medical laboratory test reports of the selected studied sample represented by 125 individuals with diabetes, it is noted found the relative distribution

of the studied sample is that women are more affected by diabetes by 56% than men, estimated at 44%. This is due to hormonal changes, especially during pregnancy (gestational diabetes) and menopause, in addition to weight gain, obesity and fat distribution, such as visceral fat around the abdomen, which women tend to have, especially after pregnancy or with age, increasing insulin resistance. Visceral fat around the abdomen secretes inflammatory compounds that negatively affect the function of insulin receptors in cells. This is also due to a lack of physical activity, which increases the risk of developing insulin resistance. In women, low levels of physical activity contribute to reduced glucose uptake by muscles, leading to its accumulation in the blood (IDF, 2025; Kautzky-Willer et al., 2023).

Furthermore, the age group with the highest risk of developing type 2 diabetes is 62 to 72 years old representing 26%. This is due to physiological changes with age as the body's efficiency in using insulin decreases, which increases the risk of developing diabetes. This age group is also known for a change in weight and dietary pattern. People tend to be overweight and obese in conjunction with physical inactivity and lack of physical activity (ADA, 2025; Yelverton et al., 2019; Rasineni et al., 2017).

With regard to the clinical and laboratory results related to diabetes and diabetic nephropathy, it was found that the number of cases of diabetic patients with elevated blood urea level, estimated at 54%, is more than the number of cases without elevated levels of blood urea, estimated at 46%. This can be explained by the relationship between diabetes and kidney function diseases (Minz et al., 2023; Ali et al., 2023; Simbolon et al., 2020). High blood levels of urea and creatinine confirms the diagnosis of type 2 diabetes patients suffering from kidney damage. This increase reflects a decline in kidney function, indicating an accumulation of nitrogenous waste in the blood due to the kidneys' inability to filter it out. In patients with type 2 diabetes, the kidneys are at risk of gradual damage caused by chronically elevated blood sugar levels, which leads to the deterioration of the tiny blood vessels in the renal glomeruli (Butt et al., 2024; Ullah et al., 2023; Bamanikar et al., 2016).

As for the level of kidney damage according to urine levels of microalbumin, it is indicated that the rate of advanced kidney damage (89%) exceeded the level of early kidney damage (11%). This is due to the duration of type 2 diabetes, as people who suffer from it for a long time are more likely to develop advanced renal damage. Creatinine analysis is a direct indicator of kidney function. The higher its level in the blood, the more it indicates a decrease in the glomerular filtration rate (GFR). This means that the percentage of patients with elevated creatinine levels suggests that diabetic nephropathy

is very common among these patients. In addition, microalbuminuria is an early marker of kidney damage, indicating the leakage of proteins from the kidneys before any noticeable impairment in kidney function occurs. The higher the amount of albumin in the urine, the more advanced the stage of diabetic nephropathy. The fact that more patients are in advanced stages than in the early stages means that many patients are not diagnosed in the early stages due to the absence of symptoms, or that there is a delay in regular screening or poor adherence to treatment. Moreover, poor control of blood sugar and blood pressure accelerates the progression of kidney damage (Mandel and Sylvia, 2025; Chen et al., 2025; Shahidur Rahman et al., 2024; Mishra et al., 2024).

BSL and HbA1c represent blood sugar control. An elevated HbA1c level indicates chronic hyperglycemia, which is a major factor in the development of diabetes complications, particularly diabetic nephropathy. Blood levels of urea and creatinine are indicators of kidney function. Their elevation reflects a deterioration in the kidney's filtering ability, which may result from damage caused by chronic diabetes. The presence of small amounts of albumin in the urine (microalbuminuria) is the first sign of diabetic nephropathy. It is considered as an early indicator of glomerular damage. Most of the changes in these five variables are interrelated and reflect a common situation, most likely the impact of type 2 diabetes on kidney function. The clustering of these variables in one or more principal components demonstrates that they vary together, supporting the hypothesis that deterioration in blood sugar control (HbA1c) is associated with impaired kidney function (elevated urea, creatinine, and the presence of microalbumin in urine). (Minz et al., 2023; Ali et al., 2023).

The correlation rate of 63.06% indicate that the component(s) extracted in PCA (Principal Component Analysis) provide a strong explanation of the relationship between these variables. This supports their use as a set of biomarkers for early diagnosis or monitoring the progression of diabetic nephropathy.

The analysis reveals a strong positive correlation cluster in the top right of the plot, consisting of BSL (Blood Sugar Level) and HbA1c (Glycated Hemoglobin). These two variables are positioned very close to each other and point in the same direction, indicating a very strong positive correlation. This is biologically and medically expected, as sustained high blood sugar levels over time result in elevated HbA1c, which reflects average glucose levels over the past 2–3 months. In the bottom right quadrant, there is another cluster showing positive correlations among Urea, µAlb (Microalbuminuria), Crea (Creatinine), and Age. Urea and Crea are located near each other, signifying a strong positive correlation due to their shared role as indicators of kidney function. µAlb is also close to Urea and Crea, indicating a

positive relationship, as microalbuminuria often rises alongside these markers in cases of kidney damage. Age, positioned near Crea and µAlb, shows a positive correlation with these renal indicators, aligning with the fact that kidney function tends to decline with age. When examining the relationship between the two groups—BSL and HbA1c on one hand, and Urea, µAlb, Crea, and Age on the other—it is evident that although both are situated in the right quadrants (indicating a positive correlation with the F1 axis), the angle between them is not sharply defined, suggesting a moderate to weak positive correlation. Despite this, it is clinically significant, as diabetes (indicated by high BSL and HbA1c) is a well-established risk factor for kidney disease (represented by elevated Urea, Crea, and µAlb). Notably, all variables are positioned close to the circle, meaning they are well represented on the F1 and F2 axes and contribute meaningfully to the variance explained. In summary, there is a very strong correlation between the diabetes indicators (BSL and HbA1c), a strong positive correlation among kidney function markers and age (Urea, Crea, µAlb, Age), and a moderate, though clinically important, correlation between diabetes and kidney function indicators.

CONCLUSION, PERSPECTIVES AND RECOMMENDATIONS

Conclusion

This study aims to assess the impact of type 2 diabetes on the kidneys as a result of high blood glucose levels and decreased kidney function (diabetic nephropathy), accompanied by advanced kidney damage.

Based on the randomly chosen sample of 400 medical test reports, the results indicate a total of 125 individuals with diabetes type 2 and considered as the study sample. It was found that the rate of women estimated 56% is the most vulnerable to diabetes, as the percentage of men is estimated at 44%. The age group between 62 to 72 years is the most susceptible to diabetes by 26%. It was also found that the percentage of kidney damage is also the most, as estimated at 64%, according to the analysis of blood urea, which helped determine the level of renal damage.

Moreover, it was found that the high levels of sugar in the blood in a chronic way leads to the damage of the microscopic blood vessels in the kidneys (renal glut). This damage weakens the kidney's ability to filter the blood. This is evident through the presence of protein (especially albumin) in the urine, that is, an early sign of diabetic nephropathy. In addition to the chronic inflammatory condition, it affects the renal tissues and leads to fibrosis and a gradual function.

Perspectives

Further studies are needed to answer the various questions highlighted in the findings presented in this study:

- Finding new treatments for diabetes patients, particularly those with diabetic nephropathy.
- Developing new and more accurate techniques for monitoring blood sugar levels.
- Developing accurate techniques for identifying the level of kidneys damage for an early prevention.
- Study the genetic diversity of patients with type 2 diabetes and its impact on the development of diabetic nephropathy.
- Developing dedicated therapeutic plans based on the genetic and biological print of each patient.
- Explore the use of stem cells to stimulate the regeneration of diabetic kidney cells.

Recommendations

To prevent kidney complications, especially diabetes nephropathy, type 2 diabetes patients must follow strict medical recommendations, namely:

1. Strict control of blood sugar levels;
   - Keep the HbA1c less than 7% (or according to the doctor's recommendation).
   - Sugar monitoring regularly (before and after eating).
   - Use medications or insulin regularly according to the prescription.
2. Blood pressure control and the use of medications such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers that protect the kidneys if needed.
3. Regular follow -up of kidney function;
   - Testing the album levels by the albumin/creatinine ratio, annually.
   - Creatinine examination and estimation of the Kabbi nomination rate (EGFR).
4. Follow a healthy diet for kidney;
   - Reducing animal protein if the doctor advises it.

- Reducing sodium (salt) to reduce the burden on the kidneys.
- Avoid treated foods rich in phosphorus or potassium (depending on the stage of illness)

5. Quit smoking that speeds up kidney damage, and increases the risk of heart disease.
6. Blood fat control;
   - Reducing harmful cholesterol (LDL) and triglycerides.
   - Use statins if recommended by the doctor.
7. Practicing regular physical activity at least 150 minutes per week of moderate activity.
8. Avoid harmful medications such as non-steroidal anti-inflammatory drugs.
9. Raise awareness with education campaigns about diabetic nephropathy and symptoms of kidney deterioration (swelling of the feet, fatigue, changes in quantity or aspect of urine)
10. The use of smart technology and early detection programs;
11. Early detection of slight changes in kidney function and alerting the patient and doctor before the deterioration occurred.
12. Aiming towards biological treatments (such as probiotics or diet modification) as part of prevention or treatment strategies.
13. Directing health policies to improve care in the vulnerable groups like type 2 diabetes and diabetic nephropathy.

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