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Diabetes Mellitus: An Overview Of Causes, Symptoms And Therapeutic Strategies

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Abstract: Chronic hyperglycemia in synergy with the other metabolic aberration in patients with diabetes mellitus can cause damage to various organ system leading to the development of disability and life treating health complications most prominent of which are microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complication leading to 2-fold 4-fold increased risk of cardiovascular disease. Diabetes one of the 1 disease described with an Egyptian manuscript from 1500 BC. There are two types of diabetes mellitus type 1 rarely found by birth and type 2 is heterogeneous disorder found 90% of people it result in abnormally high glucose level in blood. It cause due to overweight, obesity, genetic factors, insulin resistance, cystic fibrosis hemochromatosis 140 mg/dl is considered healthy human and above 200mg/dl are diabetes patient. To maintain over healthy life we should kept diet, exercise, physical activities and medication like insulin, Biguanides, metformin. Screening and diagnosis still based on world health organization (WHO) and American diabetes association criteria which include both clinical and laboratory parameters. In the present review article, we have made an attempt to explore the pathophysiology of type 2 diabetes mellitus, the conventional treatment approaches in which mono and combination therapy as well as nano-based drug delivery approaches for the treatment of type 2 diabetes mellitus.

Index Terms – Diabetes mellitus, type1 & type2 diabetes, lifestyle modification, complications

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. According to the International Diabetes Federation (IDF), approximately 415 million adults between the ages of 20 to 79 years had diabetes mellitus in 2015. DM is proving to be a global public health burden as this number is expected to rise to another 200 million by 2040. Chronic hyperglycemia in synergy with the other metabolic aberrations in patients with diabetes mellitus can cause damage to various organ systems, leading to the development of disabling and life-threatening health complications,

most prominent of which are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications leading to a 2fold to 4-fold increased risk of cardiovascular diseases. [1]

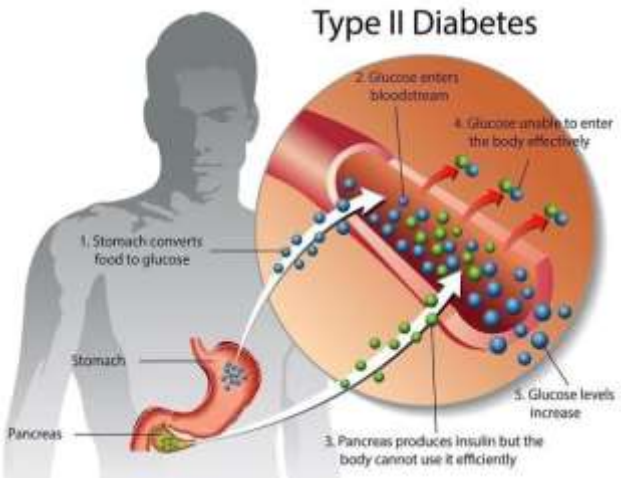

Fig 1: type II diabetes mellitus

HISTORY OF DIABETES MELLITUS

Diabetes mellitus, the ailment often referred to as diabetes today, is believed to have been first mentioned in the Ebers Papyrus, which dates back to approximately 1550 BC. When Ayurvedic doctors discovered that diabetic pee tested sweet, they named the disease madhumeha, or "honey urine" (5th–6th century BC). Demetrius of Apamea is credited with coining the word diabetes in the first century BC. The illness was long known as; "wastingthirst") in traditional Chinese medicine, which also provided treatment for it. Avicenna and other Islamic physicians from the Middle Ages wrote extensively about diabetes. Diabetes was frequently described in earlier accounts as a kidney illness. Thomas Willis proposed in 1674 that blood sickness might be the cause of diabetes. The distinction between diabetes insipidus and diabetes mellitus is attributed to Johann Peter Frank [3]

Diabetes is one of the first diseases described with an Egyptian manuscript from c. 1500 BCE mentioning “too great emptying of the urine.” The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as Mahometh or honey urine noting that the urine would attract ants. The term “diabetes” or “to pass through” was first used in 230 BCE by the Greek Apollonius Memphites. The disease was rare during the time of the Roman empire with Galen commenting that he had only seen two cases during his career. [4]

The first people to treat diabetes were susurrate, Arataeus, and Thomas Willis. Greek doctors advised exercise, ideally while mounted, to reduce frequent urination. Additional treatments for diabetes include alcohol, starvation diets, and overfeeding to make up for fluid loss. Matthew Dobson established in 1776 that the reason diabetics’ urine tastes sweet is because there is an excess of a certain type of sugar in their blood and urine. [5]

The history of diabetes started in approximately 1550BC, long before the mechanics of the disease were understood. Over time diabetes has since become classified as different types and treatments have evolved so people can live for longer and reduce the risk of long-term health complications developing.

Approximately 1550BC

An Egyptian papyrus mentions a rare disease that causes the patient to lose weight rapidly and urinate frequently. This is thought to be the first reference to diabetes.

250 BC

The creation of the term “diabetes” is credited to Apollonius of Memphis, which refers to a disease which drains patients of more fluid than they can consume. [6]

Pathophysiology of diabetes mellitus type 2

Type 2 diabetes mellitus is a heterogeneous disorder with varying prevalence among different ethnic groups. In the United States the populations most affected are native Americans, particularly in the desert Southwest, Hispanic-Americans, and Asian Americans. The pathophysiology of type 2 diabetes mellitus is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining β-cell function, eventually leading to β -cell failure. [7]

Regarding the pathophysiology of the disease, a malfunctioning of the feedback loops between insulin action and insulin secretion results in abnormally high glucose levels in blood . In the case of β-cell dysfunction, insulin secretion is reduced, limiting the body's capacity to maintain physiological glucose levels. On the other hand, IR contributes to increased glucose production in the liver and decreased glucose uptake both in the muscle, liver and adipose tissue. [8]

PATHOPHYSIOLOGY

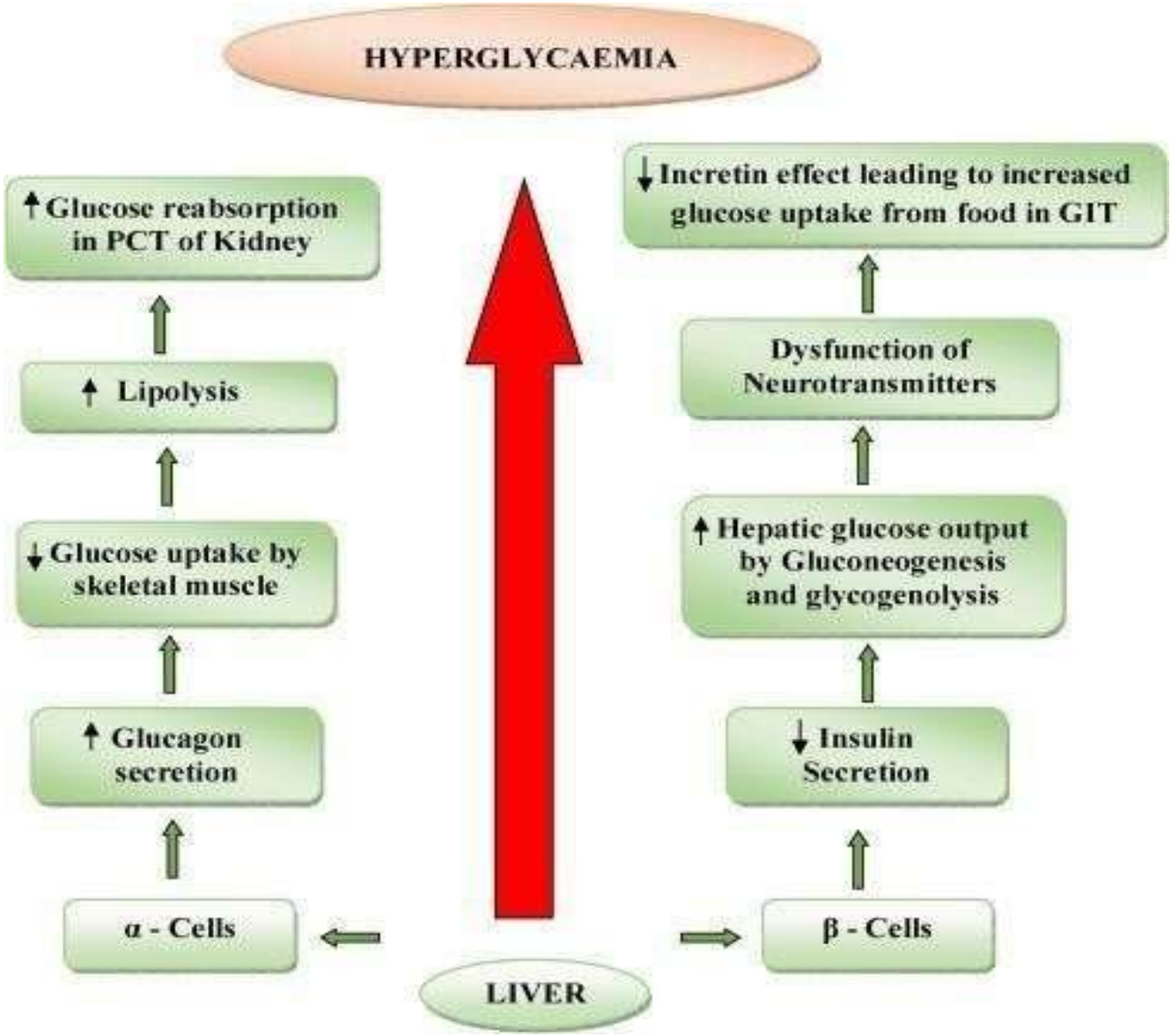

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fig 2: pathophysiology

Type 2 diabetes, the most common type of diabetes, is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes mainly from the food you eat. Insulin, a hormone made by the pancreas, helps glucose get into your cells to be used for energy. In type 2 diabetes, your body doesn't make enough insulin or doesn't use insulin well. Too much glucose then stays in your blood, and not enough reaches your cells. [10]

WHAT ARE THE CAUSES TYPE 2 DIBETES?

Insulin is a hormone made by your pancreas that acts like a key to let blood sugar into the cells in your body for use as energy. If you have type 2 diabetes, cells don't respond normally to insulin; this is called insulin resistance. Your pancreas makes more insulin to try to get cells to respond. Eventually your pancreas can't keep up, and your blood sugar rises, setting the stage for prediabetes and type 2 diabetes.
Type 2 diabetes—the most common form of diabetes—is caused by several factors, including lifestyle factors and genes.

Overweight, obesity, and physical inactivity

You are more likely to develop type 2 diabetes if you are not physically active and are overweight or have obesity. Extra weight sometimes causes insulin resistance and is common in people with type 2 diabetes. The location of body fat also makes a difference. Extra belly fat is linked to insulin resistance, type 2 diabetes, and heart and blood vessel disease. To see if your weight puts you at risk for type 2 diabetes, check out these Body Mass Index (BMI) charts.

Insulin resistance

Type 2 diabetes usually begins with insulin resistance, a condition in which muscle, liver, and fat cells do not use insulin well. As a result, your body needs more insulin to help glucose enter cells. At first, the pancreas makes more insulin to keep up with the added demand. Over time, the pancreas can't make enough insulin, and blood glucose levels rise.

Genes and family history

Having a family history of diabetes makes it more likely that a woman will develop gestational diabetes, which suggests that genes play a role. Genes may also explain why the disorder occurs more often in African Americans, American Indians, Asians, and
Hispanics/Latinas

Genetic mutations

Monogenic diabetes is caused by mutations, or changes, in a single gene. These changes are usually passed through families, but sometimes the gene mutation happens on its own. Most of these gene mutations cause diabetes by making the pancreas less able to make insulin. The most common types of monogenic diabetes are neonatal diabetes and maturity-onset diabetes of the young (MODY). Neonatal diabetes occurs in the first 6 months of life. Doctors usually diagnose MODY during adolescence or early adulthood, but sometimes the disease is not diagnosed until later in life.

Cystic fibrosis

NIH external link produces thick mucus that causes scarring in the pancreas. This scarring can prevent the pancreas from making enough insulin.

Hemochromatosis

Causes the body to store too much iron. If the disease is not treated, iron can build up in and damage the pancreas and other organs.
[11]

MANAGING DIBETES

Unlike many health conditions, diabetes is managed mostly by you, with support from your health care team (including your primary care doctor, foot doctor, dentist, eye doctor, registered dietitian nutritionist, diabetes educator, and pharmacist), family, and other important people in your life. Managing diabetes can be challenging, but everything you do to improve your health is worth it!

You may be able to manage your diabetes with healthy eating and being active, or your doctor may prescribe insulin, other injectable medications, or oral diabetes medicines to help manage your blood sugar and avoid complications. You'll still need to eat healthy and be active if you take insulin or other medicines. It's also important to keep your blood pressure and cholesterol close to the targets your doctor sets for you and get necessary screening tests.

You'll need to check your blood sugar regularly. Ask your doctor how often you should check it and what your target blood sugar levels should be. Keeping your blood sugar levels as close to target as possible will help you prevent or delay diabetes-related complications.

Stress is a part of life, but it can make managing diabetes harder, including managing your blood sugar levels and dealing with daily diabetes care. Regular physical activity, getting enough sleep, and relaxation exercises can help. Talk to your doctor and diabetes educator about these and other ways you can manage stress.

Make regular appointments with your health care team to be sure you're on track with your treatment plan and to get help with new ideas and strategies if needed.

Whether you were just diagnosed with diabetes or have had it for some time, meeting with a diabetes educator is a great way to get support and guidance, including how to:

- Develop a healthy eating and activity plan
- Test your blood sugar and keep a record of the results
- Recognize the signs of high or low blood sugar and what to do about it
- If needed, give yourself insulin by syringe, pen, or pump
- Monitor your feet, skin, and eyes to catch problems early
- Buy diabetes supplies and store them properly
- Manage stress and deal with daily diabetes care

TYPE 2 DIABETES IN CHILDREN

Childhood obesity rates are rising, and so are the rates of type 2 diabetes in youth. More than 75% of children with type 2 diabetes have a close relative who has it, too. But it's not always because family members are related; it can also be because they share certain habits that can increase their risk. Parents can help prevent or delay type 2 diabetes by developing a plan for the whole family:

- Drinking more water and fewer sugary drinks
- Eating more fruits and vegetables 3
- Making favourites foods healthier
- Making physical activity more fun

Healthy changes become habits more easily when everyone makes them together. [12]

PREVENT THE TYPE 2 IN THE KIDS

There's a growing type 2 diabetes problem in our young people. But parents can help turn the tide with healthy changes that are good for the whole family.

Until recently, young children and teens almost never got type 2 diabetes, which is why it used to be called adult-onset diabetes. Now, about one-third of American youth are overweight, a problem closely related to the increase in kids with type 2 diabetes, some as young as 10 years old.

WEIGHT MATTER

People who are overweight—especially if they have excess belly fat—are more likely to have insulin resistance, kids included. Insulin resistance is a major risk factor for type 2 diabetes.
As long as enough insulin is produced, blood sugar levels remain normal. This can go on for several years, but eventually the pancreas can't keep up. Blood sugar starts to rise, first after meals and then all the time. Now the stage is set for type 2 diabetes.

Insulin resistance usually doesn't have any symptoms, though some kids develop patches of thickened, dark, velvety skin called acanthosis nigricans, usually in body creases and folds such as the back of the neck or armpits. They may also have other conditions related to insulin resistance, including:

- High blood pressure
- High cholesterol
- Polycystic ovary syndrome

AGE MATTER

Kids who get type 2 diabetes are usually diagnosed in their early teens. One reason is that hormones present during puberty make it harder for the body use insulin, especially for girls, who are more likely than boys to develop type 2 diabetes. That's an Important reason to help your kids take charge of their health while they're young.

FAMILY STYLE

 Mealtime Makeover

a. Drink more water and fewer sugary drinks.
b. Eat more fruits and vegetables.
c. Make favorite foods healthier.
d. Teach your kids to read food labels to understand which foods are healthiest.
e. Have meals together as a family as often as you can.
f. Serve small portions; let kids ask for seconds.
g. Reward kids with praise instead of food.

 Getting physical

a. Aim for your child to get 60 minutes of physical activity a day, in several 10- or 15-minute sessions or all at once.
b. Keep it positive—focus on progress
c. Take parent and kid fitness classes together
d. Make physical activity more fun; try new things.
e. Ask kids what activities they like best.
f. Encourage kids to join a sports team.
g. Have a "fit kit" available—a jump rope, hand weights, resistance bands
h. Limit screen time to 2 hours a day. [13]

DIAGNOSIS

Type 2 diabetes is usually diagnosed using the glycated hemoglobin (A1C) test. This blood test indicates your average blood sugar level for the past two to three months. Results are interpreted as follows: Below 5.7% is normal.
5.7% to 6.4% is diagnosed as prediabetes.
6.5% or higher on two separate tests indicates diabetes.

If the A1C test isn't available, or if you have certain conditions that interfere with an A1C test, your health care provider may use the following tests to diagnose diabetes: Random blood sugar test.

Blood sugar values are expressed in milligrams of sugar per deciliter (mg/dL) or millimoles of sugar per liter (mmol/L) of blood. Regardless of when you last ate, a level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes, especially if you also have symptoms of diabetes, such as frequent urination and extreme thirst.

Fasting blood sugar test.

A blood sample is taken after you haven't eaten overnight. Results are interpreted as follows: Less than 100 mg/dL (5.6 mmol/L) is considered healthy.
100 to 125 mg/dL (5.6 to 6.9 mmol/L) is diagnosed as prediabetes.
126 mg/dL (7 mmol/L) or higher on two separate tests is diagnosed as diabetes.

Oral glucose tolerance test.

This test is less commonly used than the others, except during pregnancy. You'll need to not eat for a certain amount of time and then drink a sugary liquid at your health care provider's office.
Blood sugar levels then are tested periodically for two hours. Results are interpreted as follows:
Less than 140 mg/dL (7.8 mmol/L) after two hours is considered healthy.
140 to 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) is diagnosed as prediabetes. 200 mg/dL (11.1 mmol/L) or higher after two hours suggests diabetes.

Screening.

The American Diabetes Association recommends routine screening with diagnostic tests for type 2 diabetes in all adults age 35 or older and in the following groups:
People younger than 35 who are overweight or obese and have one or more risk factors associated with diabetes. Women who have had gestational diabetes. People who have been diagnosed with prediabetes. Children who are overweight or obese and who have a family history of type 2 diabetes or other risk factors.

AFTER A DIAGNOSIS

If you're diagnosed with diabetes, your health care provider may do other tests to distinguish between type 1 and type 2 diabetes because the two conditions often require different treatments.
Your health care provider will test A1C levels at least two times a year and when there are any changes in treatment. Target A1C goals vary depending on age and other factors. For most people, the American Diabetes Association recommends an A1C level below 7%. You also receive tests to screen for complications of diabetes and other medical condition. [14]

DIBETES MELLITUS TREATMENT:

Lifestyle choices, including eating a healthy diet, exercising and staying at a healthy weight, are key to managing type 2 diabetes. But you also might need to take medication to keep your blood sugar, also called glucose, at a healthy level.

Sometimes one medication is enough. In other cases, taking several medications works better.
Diabetes treatment: Lowering blood sugar Several classes of type 2 diabetes medicines exist. Each class of medicine works in a different way to lower blood sugar.

A medication may work by:

-Causing the pancreas to make and release more insulin.

-Limiting the liver's ability to make and release sugar.

-Blocking the action of enzymes in the intestines that break down carbohydrates, slowing how quickly cells take in carbohydrates.

-Improving cells' sensitivity to insulin.

-Limiting the kidneys' ability to take in sugar, which increases the amount of sugar that leaves the body in urine. -Slowing how quickly food moves through the stomach.

-Each class of medicine has one or more medications. Some of these medications are taken by mouth, while others must be taken as a shot.

Non pharmacological treatment-

- Exercise

Getting enough exercise is another key part of diabetes self-care and management. The ADA has the following suggestions about physical activity:

Children and adolescents with type 2 diabetes should have at least 60 minutes of moderate intensity or vigorous aerobic activity per day, plus vigorous strengthening activities on at least 3 days per week.

Most adults with type 2 diabetes should do at least 2–3 resistance exercise sessions and at least 150 minutes of moderate-to-vigorous activity per week, while younger and more physically fit people should do at least 75 minutes of vigorous activity or interval training per week.

All adults with type 2 diabetes should spend less time being sedentary and break up long periods of sitting with some activity every 30 minutes.

Older adults with type 2 diabetes should take part in flexibility and balance training 2–3 times per week. [15]

- Wholesome food.

- Blood sugar observation.

- Insulin treatment or diabetes medicine

- Diet

There's no special diet for diabetics. Still, it's crucial to focus your diet on:

- A consistent timetable for meals and wholesome snacks.
- Reduced serving sizes.
- Increased consumption of whole grains, fruits, and non starchy vegetables that are high in fibre.
- Fewer sweets, starchy veggies, and refined grains.
- Modest portions of fish, low-fat meats, and low fat dairy.
- Canola or olive oil are examples of healthy cooking oils.
- Reduced caloric intake. [16]

-Weight loss

Better regulation of blood pressure, triglycerides, cholesterol, and blood sugar is the outcome of weight loss. If you're overweight, even 5% of your body weight loss may start to show improvements in these areas. On the other hand, your health will benefit more the more weight you drop. It may be advised in certain situations to reduce body weight by up to 15%. [17]

PHARMACOLOGICAL TREATMENT

Insulin secretagogues:

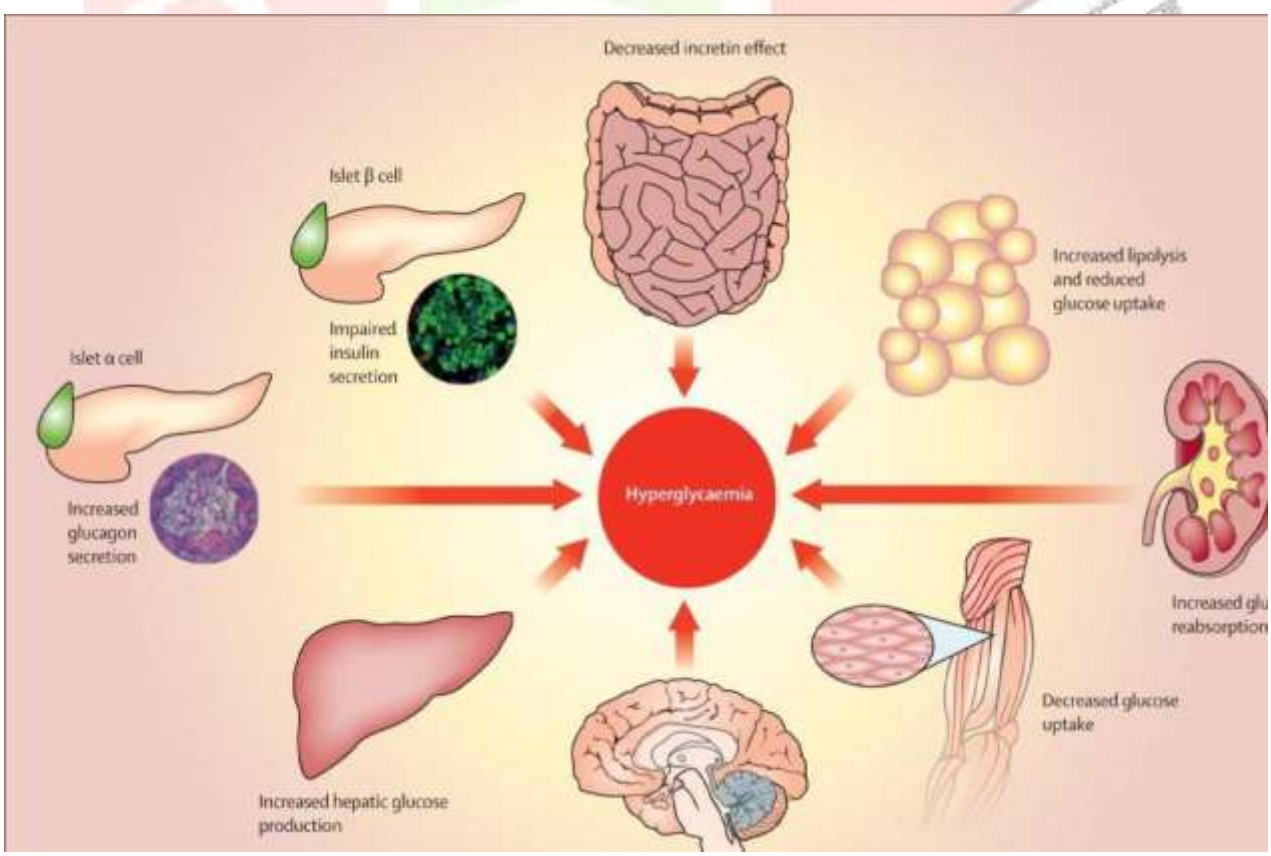
These medications, particularly sulfonylureas and metiglinides, work by attaching to the ATP sensitive potassium channel's sulfonylurea receptor (SUR) on pancreatic β cells to increase the amount of insulin secreted by the pancreas. Glibenclamide, Glipizide, and Glimepiride are examples of second generation sulfonylurea, while Tolbutamide,
Chlorpropamide, Tolazamide, and Acetohexamide are examples of first generation sulfonylurea. [18]

Glucosidase inhibitors alpha

These drugs aid in the breakdown of table sugar and starchy foods by your body. Your blood sugar levels are lowered as a result. These drugs won't result in hypoglycemia (low blood sugar) if taken as directed. However, if you take them along with other diabetes drugs, your risk of hypoglycemia may increase. Alpha-glucosidase inhibitors work best when taken prior to meals. [19] Biguanides:

The sole Biguanides that is currently prescribed in the US is metformin, also known as Glucophage, which is typically used as the first line of treatment for type 2 diabetes mellitus. Metformin enhances

The body's reaction to natural insulin, which lowers the amount of glucose produced by the liver and lessens its absorption from the intestines. [20]



[21]

Fig 3: major organs involved in diabetes mellitus.

Which specialists treat type 2 diabetes?

There are several healthcare specialists that can help treat type 2 diabetes, though many people think of endocrinologists as diabetes doctors. Endocrinologists specialize in disorders of the endocrine system, the network of hormoneproducing glands in your body.
Endocrinologists are qualified to diagnose and treat conditions like diabetes as well as the following:

-Thyroid diseases
-Infertility
-Metabolic disorders
-Osteoporosis
-Some cancers
-Adrenal and pituitary gland disorders

Other specialist doctors that can help treat type 2 diabetes include internal medicine physicians (also known as general physicians), nephrologists, ophthalmologists, cardiologists, and neurologists.

There are many other healthcare practitioners and allied health practitioners that specialize in diabetes care, such as:

-Credentialed diabetes educators
-Clinical nurse practitioners
-Chronic disease nurses
-Physician assistants
-Pharmacists
-Dietitians
-Podiatrists
-Optometrists
-Psychologists
-Physiotherapists

Endocrinologist help with type 2 diabetes

People with type 2 diabetes are usually referred to an endocrinologist if their primary healthcare physician or other healthcare provider feels their expertise is needed.

Some common scenarios in which an endocrinologist might be asked to help include the following:

-current treatment strategies for diet, activity, and medications aren't working as expected

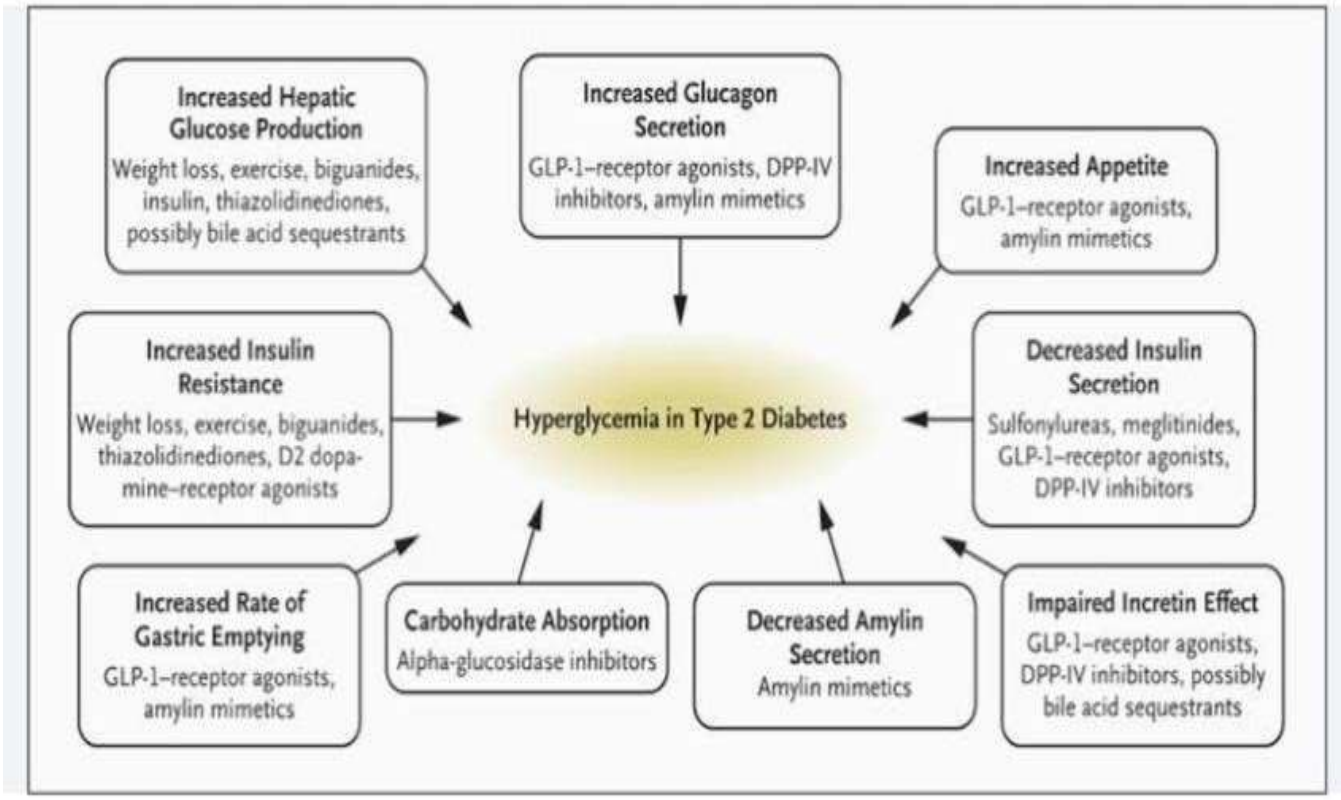
-insulin treatment is being considered, including insulin pump therapy Advice about the likelihood of type 2 diabetes remission

-complications due to type 2 diabetes that require a different approach to treatment

-another endocrine disorder has developed
(e.g., thyroid disease)

-sexual function is decreasing

-concerns about fertility or planning a pregnancy [22]



[23]

Fig. 4: factors involved in development of hyperglycemia in type 2 diabetes.

COMPLICATIONS ASSOCIATED WITH TYPE 2 DIABETES

For many people, type 2 diabetes can be effectively managed. If not properly managed, it can affect virtually all of your organs and lead to serious complications, including:

Skin problems, like bacterial or fungal infections
Nerve damage, or neuropathy, which can cause a loss of sensation or numbness and tingling in your extremities as well as digestive issues, like vomiting, diarrhea, and constipation Poor circulation to the feet, which makes it hard for your feet to heal when you have a cut or an infection and can also lead to gangrene and loss of the foot or leg

Hearing impairment
Retinal damage, or retinopathy, and eye damage, which can cause deteriorating vision, glaucoma, and cataracts Cardiovascular diseases like high blood pressure, narrowing of the arteries, angina, heart attack, and stroke Women with diabetes are more likely to have a heart attack, at a younger age, than women without diabetes Men with diabetes are 3.5 times as likely Trusted
Source to develop erectile dysfunction (ED)

Hypoglycemia
Hypoglycemia can occur when your blood sugar is low. The symptoms can include shakiness, dizziness, and difficulty speaking. You can usually remedy this by having a “quick-fix” food or beverage, like fruit juice, a soft drink, or hard candy.

Hyperglycemia
Hyperglycemia can happen when blood sugar is high. It’s typically characterized by frequent urination and increased thirst. Monitoring your blood glucose carefully, and staying active, can help prevent hyperglycemia.

Complications during and after pregnancy

If you have diabetes while you're pregnant, you'll need to monitor your condition carefully. Diabetes that's poorly controlled may increase the risk of miscarriage, birth defects and other complications for both mother and baby. [24]

CONCLUSION

Diabetes is a serious medical condition that affects millions of people worldwide. It can cause various health complications and should be treated promptly to prevent long-term damage to the body. By understanding the types, causes, symptoms, and treatment options for diabetes, individuals can take steps to manage the condition effectively and lead a healthy life. If you experience any symptoms of diabetes, it is crucial to seek medical attention immediately. [25]

Diabetes mellitus 2 related diseases:

Diabetes nephropathy

Abstract

One of the biggest problems facing healthcare is diabetic nephropathy (DN). It affects up to 50% of people with diabetes, is linked to a markedly higher risk of cardiovascular morbidity and death, and is a primary cause of end stage kidney disease (ESKD), which necessitates dialysis or renal transplantation. Although chronic albuminuria and a progressive deterioration in renal function are the hallmarks of diabetic kidney disease (DN), it is becoming more well acknowledged that the clinical course and presentation of kidney disease in diabetes are diverse. Nowadays, a wide range of diabetic s with albuminuria or decreased renal function are referred to as having diabetic kidney dis ease (DKD).

Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease in developed countries, including the United States. As a microvascular complication, it affects individuals with both type 1 and type 2 diabetes. Significant progress has been made in recent years in understanding the mechanisms of diabetes mellitus, and recent studies have led to updates in treatment guidelines. Staying informed about these latest developments is crucial for providing optimal care to patients with diabetes and kidney disease. The primary pathological features of diabetic kidney disease (DKD) include glomerular hypertrophy, glomerular basement membrane thickening, effacement of podocyte foot processes, and mesangial matrix expansion. Traditional markers of DKD, such as albuminuria and creatinine, are relatively insensitive and have limited utility due to delayed detection. [26]

Histopathology of nephropathy

The study of histopathology with electron microscopy, the more obvious changes are glomerular hypertrophy, modest mesangial expansion (matrix), and thickening of the glomerular capillary walls. The development of nodules in the glomerular tuft is caused by an increase in mesangial cellularity that occurs as the disease progresses. In a single glomerulus, the nodules vary in size and impact the glomeruli in different ways (nodular diabetic glomerulosclerosis). Kimmelstiel-Wilson nodules are the name given to the nod ules. They have a core acellular region, are spherical, eosinophilic, and may have a ring of cells encircling them. [27]

While each of these renal structural abnormalities can be seen separately in other renal illnesses, the constellation of lesions that occur in diabetes is distinct. Although the podocytes, renal tubules, interstitium, and arterioles also experience significant alterations, particularly in the later stages of the disease, the

glomeruli are primarily affected by the morphologic les ions of type 1 diabetes (T1DM), which include thickening of the glomerular basement membrane (GBM) and mesangial expansion. [28]

Abnormal renal pathology is evident even before the onset of microalbuminuria. Characteristic lesions observed on light microscopy include thickened glomerular and tubular basement membranes, diffuse mesangial expansion, and arteriolar hyalinosis.

The pathological classification includes:

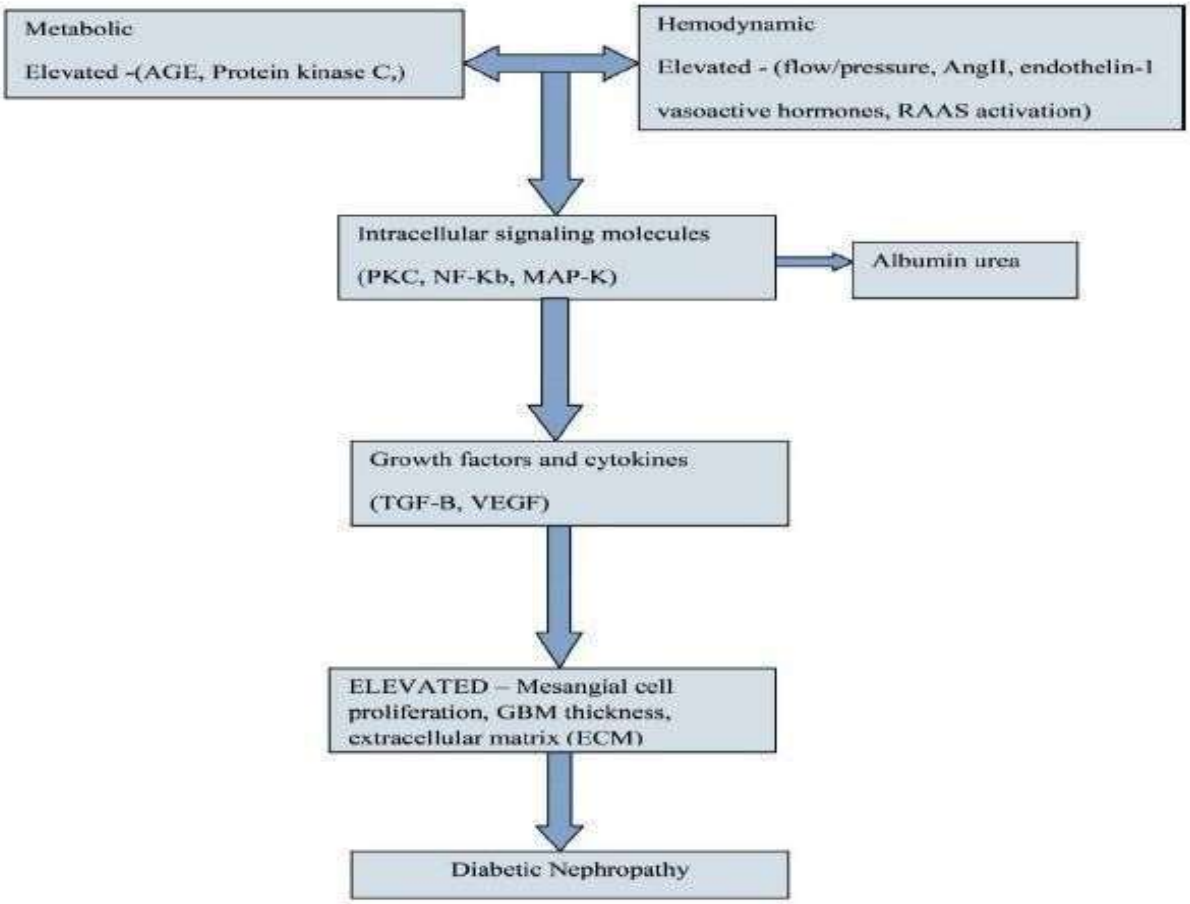
- Class I: GBM thickening
- Class IIa: Mild mesangial expansion
- Class IIb: Severe mesangial expansion
- Class III: Nodular glomerulosclerosis (Kimmelstiel Wilson nodules)
- Class IV: Advanced diabetic nephropathy with over 50% glomerulosclerosis and associated lesions. [29]

Diabetic nephropathy has a pathological background distinguished by the prior clinical period in which hyperglycaemia is followed by an improvement in GFR and microalbuminuria (Urinary albumin excretion of urine samples of up to
20–200 mg /
min). [30]

Pathophysiology of nephropathy

Pathogenesis begins with small vessel disease. Pathophysiology is complex, involving glycosylation of proteins, hormonally influenced cytokine release (e.g., transforming growth factor-beta), deposition of mesangial matrix, and alteration of glomerular hemodynamics. Hyper filtration, an early functional abnormality, only a relative predictor for the development of kidney failure. [31]

Patients with T2D may present with albuminuria at the time of diabetes diagnosis, in contrast to diabetic nephropathy, which usually appears 15– 20 years after T1D onset. Approximately 30% of patients with T1D and 40% of those with T2D develop diabetic nephropathy, primarily because the exact onset of T2D is often unclear. Structural and functional changes occur in the kidney on account of diabetes and result in proteinuria, hypertension, and progressive reduction of kidney function, which are hallmarks of diabetic nephropathy. [32]



[33]

Fig.5: pathogenesis of diabetic nephropathy.

Schema of pathogenesis of diabetic nephropathy. The pathogenesis of diabetic nephropathy is likely to be as a result of metabolic and hemodynamic abnormalities, as seen in diabetes, interacting with each other and with various reactive oxygen species dependent pathways. Both gene regulation and activation of transcription factors are influenced by interactions between metabolic stimuli, hemodynamic factors and reactive oxygen species generation in diabetes. [34]

Causes

Chronic kidney disease occurs when a disease or condition impairs kidney function, causing kidney damage to worsen over several months or years.

Diseases and conditions that cause chronic kidney disease include:

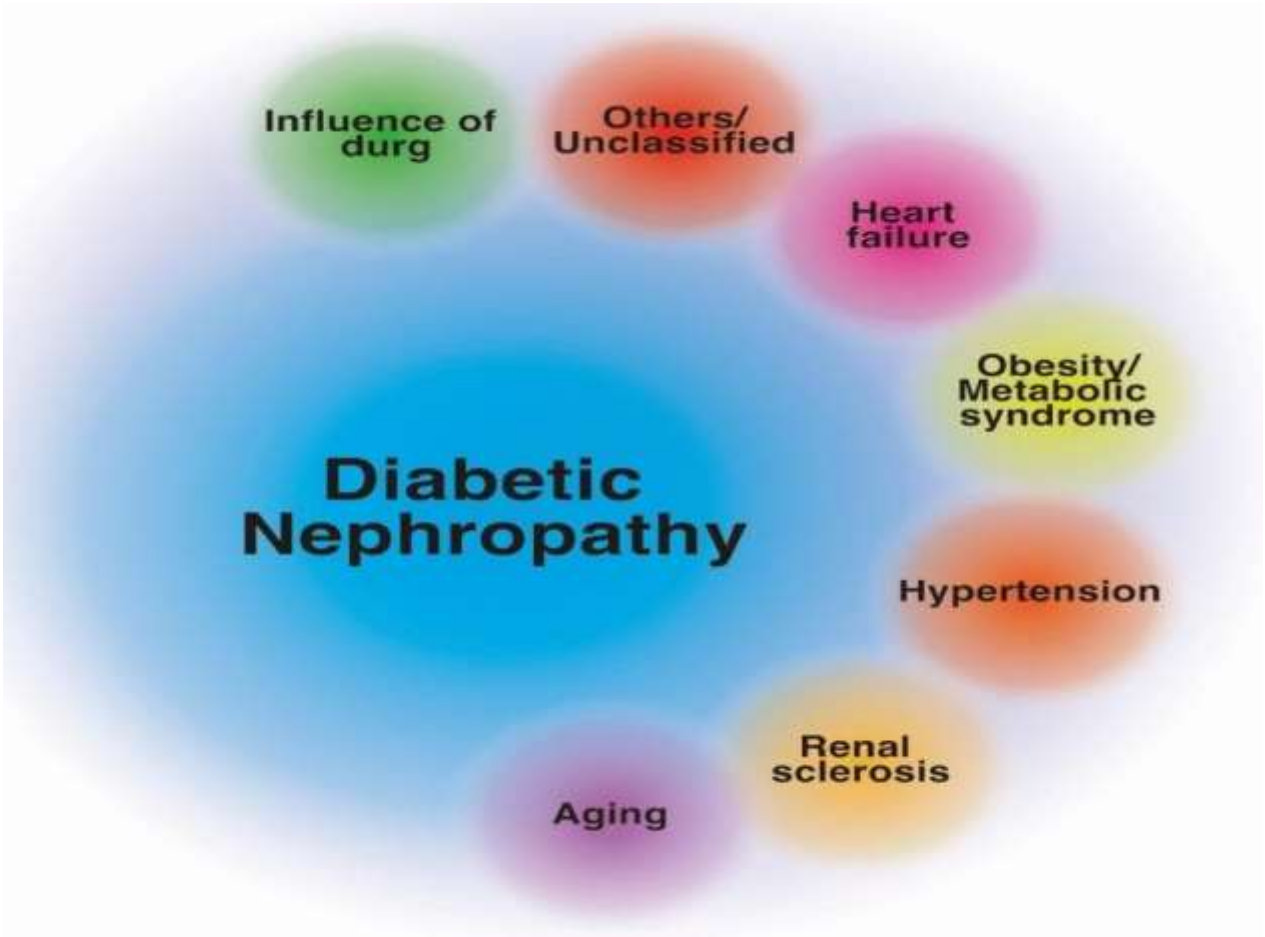
- Type 1 or type 2 diabetes
- High blood pressure
- Glomerulonephritis (gloe-mer-u-low-nuh-FRYtis), an inflammation of the kidney's filtering units (glomeruli)
- Interstitial nephritis (in-tur-STISH-ul nuh-FRYtis), an inflammation of the kidney's tubules and surrounding structures [35]

Damage to the kidneys puts stress on these vital organs and prevents them from working properly.

When this happens:

- the body starts to lose protein through the urine
- the kidneys cannot remove waste products from the blood
- the kidneys cannot maintain healthy fluid levels in the body [36]

Diabetic nephropathy is a complication caused due to diabetes mellitus (type1 and type 2). Long term diabetes can cause damage to the body's tiny blood vessels. Sustained damage to the blood vessels that are present in the kidneys can lead to inadequate blood filtration that can be characterized by ankle swelling and weight gain due to bodily retention of more salt and water. Proteins may also leak into the urine in patients with diabetic nephropathy. [37]



[38] fig.6: risk factors for diabetic nephropathy.

PREVENTION

GLYCEMIC CONTROL: MAINTAINING REASONABLE GLYCEMIC CONTROL IS ESSENTIAL IN PREVENTING DIABETIC NEPHROPATHY.
SEVERAL STUDIES HAVE SHOWN THAT TIGHT GLYCEMIC CONTROL CAN REDUCE THE RISK OF DEVELOPING MICROALBUMINURIA, AN EARLY SIGN OF KIDNEY DAMAGE IN DIABETES. INTENSIVE GLYCEMIC CONTROL CAN ALSO SLOW THE PROGRESSION OF DIABETIC NEPHROPATHY AND REDUCE THE RISK OF END-STAGE RENAL DISEASE. [39]

Eating foods that are low in sodium (salt) and fat can help keep your kidneys healthy.
Here are some tips to eat less sodium (salt):

- Cook with fresh herbs, lemon juice or spices to add flavor instead of adding salt to your food.
- Choose fresh or frozen vegetables instead of canned. If you do use canned vegetables, rinse them with water before eating or cooking to remove extra salt

Being active can keep your kidneys healthy by helping you:

- Stay at a healthy weight.
- Keep a healthy blood sugar level.
- Lower your blood pressure.
- Lower your cholesterol (a waxy, fat-like substance in your blood). [40]

To lower your risk of developing diabetic nephropathy:

See your health care team regularly to manage diabetes. Keep appointments to check on how well you are managing your diabetes and to check for diabetic nephropathy and other complications. Your appointments might be yearly or more often. [41]

For both T1DM and T2DM, serum TNF-α receptor level is the most effective diagnostic tool and forecasts the development of CKD and ESRD. In type II diabetics, besides albuminuria, the levels of TNF-α receptor exhibited as a significant predictive factor. Furthermore, serum uric acid acts as a biomarker and pathogenic [42]

The hallmark of established DN is persistent albuminuria (category A3, severely increased), with co-existing retinopathy and no evidence of alternative kidney disease. In T1DM, this definition is highly specific, that is, if these features are present then the histological picture will almost certainly be that of diabetic glomerulopathy. It is rare for DN to manifest in people with T1DM in the first 10 years following diagnosis, but between 10 and 20 years the incidence of DN is approximately 3% per year. [43]

Diabetic nephropathy is the leading cause of kidney disease in patients starting renal replacement therapy and affects ~40% of type 1 and type 2 diabetic patients. It increases the risk of death, mainly from cardiovascular causes, and is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. Diabetic nephropathy is categorized into stages: microalbuminuria (UAE >20 μg/min and ≤199 μg/min) and macroalbuminuria (UAE ≥200 μg/min). [44]

Treatment

The key treatment choices for DN are maintenance of blood glucose levels, hypertension, hemodynamic control, and other metabolic disorders Concluding and comparing all glucoselowering agents is outside the study's objective, but beyond glucose-lowering, some agents have conceptual advantages, and they are discussed in our study. Some antihypertensive medications have shown benefits in reducing proteinuria or GFR, Lipid lowering and CV risk reduction. [45]

The onset of kidney disease in people with diabetes portends a significant increase in the risk of cardiovascular mortality, and as such aggressive risk factor modification is warranted in all patients. This includes smoking cessation and lipid lowering; the importance of blood pressure lowering is discussed later. There is ongoing debate as to whether lipid lowering therapy has a direct benefit in slowing the progression of DN. [46]
Glycemic Control

Intensive glycemic control is most effective when initiated before the onset of diabetic complications, with reduced efficacy when started later. Therefore, early intensive glycemic control is highly recommended The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that T2D patients who achieved early glycemic control with a hemoglobin A1c (HbA1c) of 7.0% maintained improved microvascular outcomes and lower mortality even after the study ended, despite HbA1c values converging between the 2 groups. [47]

NEWLY DEVELOPED DRUGS THAT PROTECT ORGANS, OTHER THAN VIA GLYCEMIC CONTROL 2.1
SGLT2 inhibitors (SGLT2i)
2.1.1 SGLT2i for glucose control and their effect on the metabolism

SGLT2i competitively binds SGLT2 proteins in the S1 segments of the renal proximal tubules. The subsequent inhibition of co-transporters leads to decreased glucose and sodium reabsorption and increased excretion of glucose/sodium into the urine. The effect of SGLT2i is insulinindependent and there is a lower risk of hypoglycemia.7 SGLT-2 inhibitors reduce HbA1c levels by 0.7%–1.0%, regardless of whether the medication is used alone or in a combination therapy. SGLT-2i has been shown to promote an average weight loss of 2–3 kg over 6 months. The use of SGLT-2i also reduces blood pressure in some studies for up to 5 mmHg in systolic and 2 mmHg in diastolic blood pressure. [48]

A new way to prevent immune cells from attacking insulin-producing beta-cells. Replacing insulin-producing betacells that have been lost in people with type 1 diabetes is a promising strategy to restore control of glucose levels. However, because the autoimmune disease is a continuous process, replacing beta-cells results in another immune attack if immunosorbent drugs are not used, which carry significant side-effects. This year, Dr. Song reported on the potential of an immunotherapy he developed that prevents immune cells from attacking beta-cells and reduces inflammatory processes. This immunotherapy offers several potential benefits, including eliminating the need for immunosuppression, long-lasting effects, and the ability to customize the treatment to each patient. [49]

Complication

Complications of diabetic nephropathy can come on slowly over months or years. They may include:

Body fluid buildup. This could lead to swelling in the arms and legs, high blood pressure, or fluid in the lungs, called pulmonary edema.

A rise in the levels of the mineral potassium in the blood, called hyperkalemia. [50]

CONCLUSION

Our review suggests the early diagnosis of microalbuminuria will help to identify patients with DN at the earliest. Poor blood sugar level control, longer duration of the DM, uncontrolled blood pressure, smoking, and physical inactivity are some of the risk factors for DN mentioned in the literature. Controlled diet, improved glycemic control, protein restriction coupled with sodium and potassium could help to manage the condition. Transplantation, stem cells, novel molecules for therapeutic, and treatments are warranted for DN control and treatments. [51]

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