World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

EFFECT OF DIABETES MELITUS ON NEPHROPATHY: A REVIEW

Prathamesh Jagdale[1], Gurpreet Bawa[2]*, Asish Jain[3], Bittu Gupta[4], Riddhi Ivalekar[5], Mansi Jadhav[6] and Vipul Jadhav[7]

Shri D.D. Vispute College of Pharmacy and Research Centre, New Panvel.

***Corresponding Author: Dr. Gurpreet Bawa**
Shri D.D. Vispute College of Pharmacy and Research Centre, New Panvel.

Article Received on 22/11/2023 **Article Revised on 12/12/2023** **Article Accepted on 01/01/2024**

ABSTRACT
Diabetes is one of the chronic diseases spread worldwide. It is a chronic metabolic disorder characterized by elevated blood glucose levels. It is of three types: type 1, type 2 and type 3 also known as gestational diabetes and it can affect people of any age group. Untreated and undiagnosed diabetes over prolonged period is associated with several complications. One of which is diabetic nephropathy. The nephron is a basic structural and functional unit of the kidney. The kidneys are responsible for various functions in our body. The goal of the study was to analyze diabetic nephropathy, its development, and the present treatment. Hyperglycemia and hypertension play a leading role in the development of diabetic nephropathy. It is a leading cause of end-stage renal disease (ESRD). Glomerular lesions are the main characteristic of diabetic nephropathy. Nonproteinuric diabetes nephropathy does not follow a classical pattern, so its diagnosis and treatment are difficult. The pathogenesis of diabetic nephropathy is still not fully understood. Its main treatments include the management of hyperglycemia and blood pressure. Medications of the oral hypoglycaemic class are beneficial in treatment. Antihypertensive agents decrease blood pressure in the kidneys. Because DN is more common in the elderly, caution should be exercised when selecting a drug. The new potential therapeutic strategy includes the use of mineralocorticoid receptor antagonists and endothelial receptor antagonists. This therapy's main target is a reduction in inflammation in the kidney. Management of diabetic nephropathy is an important topic that is beyond the scope of this review.

KEYWORDS: Diabetes, Diabetic Nephropathy, albuminuria, proteinuria, inflammation.

INTRODUCTION

Diabetes has been diagnosed in large sections of the population. India ranks second on the list of most diabetic cases. According to a report, in India, diabetes presently affects over 74.2 million adults (20–79 years old), and about 25 million people will suffer from prediabetics in 2021. It is estimated that about 53.1%, or around 39.4 million, of current cases of diabetes are undiagnosed. About 1 million Indians die every year due to diabetes.[1] Diabetes is a group of metabolic disorders. The increase in blood glucose level is generally termed diabetes. It is due to a defect in insulin secretion, action, or both. Diabetes happens when insulin is either deficient or not used effectively.[2] The common types of diabetes are: type 1, type 2, and type 3.[3] Type 1 diabetes mellitus is caused by an absolute lack of insulin and has an autoimmune basis. This disorder was previously known as insulin-dependent diabetes mellitus (IDDM) and also as juvenile-onset diabetes mellitus. It results from the autoimmune destruction of the β-cells of the pancreatic islets. It just happens to have nothing to do with diet or lifestyle. In this condition, the body attacks the insulin-producing cells, which are beta cells of the pancreas, so they are unable to produce insulin.[4] India has now estimated the highest number of prevalent type 1 diabetes cases under 20 years of age.[1] About 90% of people with diabetes have type 2 diabetes.[5] Type 2 DM is non-insulin-dependent, the commonest form of diabetes, and accounts for 90–95% of all deaths. It develops primarily due to a defect in insulin resistance. In this condition, the patient's pancreas can't make enough insulin or doesn't use insulin effectively. Cells become insulin resistant and ignore its message to absorb glucose; this is known as insulin resistance. The most noticeable symptoms of this are polyuria and polydipsia.[6] The next type of diabetes is gestational diabetes, which occurs during pregnancy. It is similar to type 2 diabetes; there is an insulin resistance issue, and it occurs during the second or third trimester. It tends to disappear after birth once the baby has left the mother's body. But women who have gestational diabetes about 50% of them will actually go on to develop type 2 diabetes, so they are advised to check their glucose levels for one to three years.[7] As diabetes progresses and is

undiagnosed and untreated, several complications can actually occur. Several complications are associated with chronic hyperglycemia, such as end organ damage, dysfunction, and failure in organs and tissues including the retina, kidney, nerves, heart, and blood vessels. These can be divided into micro-vascular and macro-vascular complications. Macrovascular complications include coronary heart complications, cerebral vascular complications, and peripheral vascular complications. The microvascular complications include retinopathy, neuropathy, and nephropathy.[8] Clinical data also suggest that 30–40% of cases with diabetes will have at least one complication approximately 10 years after the onset of diabetes.[9] Only a few people know about the nephrological complications that can be caused by the sugar level in our body. Diabetic nephropathy, also known as diabetic kidney disease (DKD), It is a chronic, progressive disease that is the most common cause of end-stage renal failure. It is a very common diabetic complication, affecting more than 1/3 of people with type I diabetes and 1/2 of people with type II diabetes. DKD is primarily diagnosed by increased albuminuria and a decreased estimated glomerular filtration rate (eGFR). The temporal relationship between diabetes diagnosis and the onset of kidney disease can help distinguish between diabetes-specific and non-specific DKD. There is no treatment for DKD, but it includes managing blood glucose levels, proteinuria, and progressive kidney damage. In late-stage DKD, dialysis or a kidney transplant is usually necessary for survival. DKD is the most common cause of end-stage kidney disease (ESKD), which itself is associated with increased mortality.[10,11] In the initial stage, there are no symptoms. Symptoms are seen when significant function is already lost. Symptoms of DKD include nocturia, fatigue, loss of appetite, and decreased mental stability. Its pathogenesis includes changes in hemodynamics, hypoxia, oxidative stress, and glomerular hypertension.[12] Chronic blood glucose levels, together with high BP caused by diabetes, damage tiny blood vessels in the kidney and their function. Cellular degradation in the nephron, particularly podocytes of the renal glomeruli, contributes to the impairment of renal function. Poorly managed diabetes is a risk factor for chronic kidney disease and diabetes mellitus. Kidney size and weight increase due to thickening of the glomerular basement membrane and expansion of the mesangium. Diabetic nephropathy results from a multifactorial pathophysiological mechanism and clinically manifests as proteinuria, progressive decline in glomerular filtration rate (GFR), and ultimately progression to end-stage renal disease. Treatment for this includes control over sugar levels, BP, and cholesterol levels with a combination of lifestyle changes and medications. Albuminuria can be reduced by using ACE inhibitors, angiotensin receptor blockers, and RAAS blockers to protect kidney function.[11]

Relationship of kidney with sugar

The kidneys are responsible for various functions in our body, including electrolyte and acid-base balance, excretion of waste products, synthesis of hormones such as erythropoietin, and metabolism of low-molecular-weight proteins. The kidney is composed of two sections. The outer part is the renal cortex, and the inner section is the medulla. Glomerular filtration rate (GFR) is used to measure kidney function. It is the volume of fluid filtered through the glomerular capillaries per unit time. Ultrafiltrates of plasma are transformed into urine at the end of the nephron.[13,14] The nephron is a structural and functional unit of the kidney and is comprised of the glomerulus and complex tubular system. Finally, the nephron drains through the collecting duct via connecting tubules. The glomerulus is formed by a bundle of capillaries surrounded by an impermeable capsule called Bowman's capsule, and it filters a large amount of blood. Podocytes are a visceral epithelium of specialized cells that forms the outermost layer of the filtration barrier and serves to sustain the integrity of the capillary loops. Proximal convoluted tubules (PCT) absorb and transport water, electrolytes, and other particles. The thin descending limb (TDL) of the loop of Henle becomes narrower, and the cells become smaller. Then the tubule turns upward towards the cortex and turns into the thick ascending limb (TAL). The juxtaglomerular apparatus regulates glomerular filtration. Fine-tuning of the urine occurs at the connecting tubule, which is the final part of the nephron. These are made up of the intercalated cells and the connecting tubule (CNT) cells. Collecting tubules form an arcade that drains into a shared collecting duct. This nephron site is also responsible for active solute secretion, hormone production, and renal gluconeogenesis.[15] Traumatic injury to the kidney can affect renal function and may lead to acute kidney injury. Any subtle damage to the structures of the nephron over time can lead to chronic kidney disease (CKD). Under pathophysiological conditions, diabetes induces some pathological changes in the kidney.[13,14]

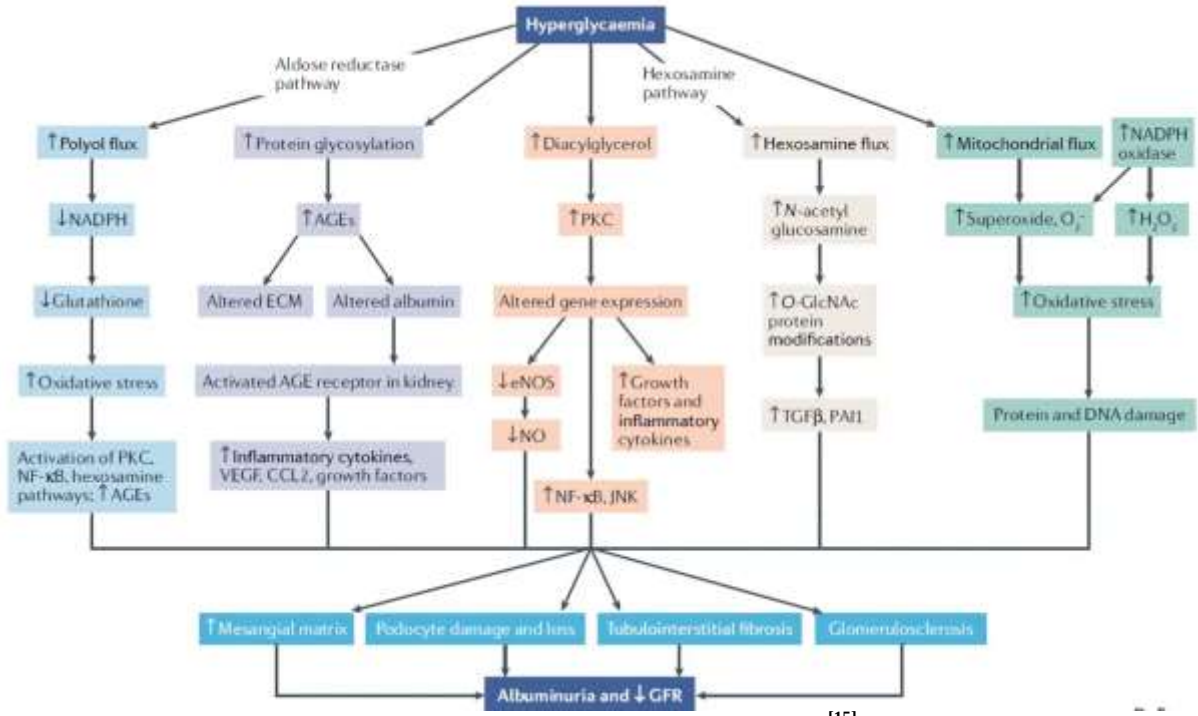

Fig. 1: Effect of hyperglycaemia on kidney.[15]

Pathological Changes in diabetic nephropathy

Glomerular lesions are the most significant change found in DN patients; they include diffuse and nodular mesangial expansion and Glomerular Basement Membrane (GBM) thickening. Diffuse mesangial expansion develops in the early years (5th year since the onset of diabetes), as observed by light microscopy. Albumin excretion rate (AER) and glomerular filtration rate (GFR) are correlated with mesangial fractional volume. In advanced disease conditions, diffuse mesangial expansion progressively develops into nodular accumulations of mesangial matrix. These nodular lesions, also called Kimmelstiel-Wilson nodules, Patients with nodular diabetic glomerulosclerosis suffer from severe renal damage, longer diabetic durations, and a poorer renal prognosis. Thickening of the glomerular basement membrane is an early lesion that can be observed within 2–8 years after the onset of diabetes and observed by electron microscopy (EM). Diabetic glomerular and extraglomerular lesions have been observed for the investigation of DN and the progression of the disease. In the DN condition, hyalinosis occurs in both the afferent and efferent arterioles. The hyalinosis of the efferent arteriole is a typical lesion that works as a marker to differentiate diabetic nephropathy from hypertensive nephropathy. There is increasing recognition of lesions like glomerular endothelial injury, podocyte impairment, and glomerulotubular junction abnormalities in DN.[16,17] The pathogenesis of diabetic nephropathy is still not fully understood, but studies have identified that DKD is associated with genetic factors, obesity, smoking, poor glycaemic control, age, sex, hypertension, and other microvascular complications. A better understanding of the genes and events leading from the onset of diabetes to the deterioration of renal function is urgent, with the aim of identifying at-risk patients and achieving effective prevention. High-glucose concentrations induce specific cellular effects in the kidney that affect several cell types, including endothelial cells, smooth muscle cells, mesangial cells, podocytes, tubular and collecting duct systems, inflammatory cells, and myofibroblasts. Glomerular hyperfiltration leads to abnormalities of preglomerular and glomerular vessels that are associated with changes in the metabolic environment, vasoactive factors, and signal transduction. Albuminuria and proteinuria indicate associated tissue damage in the diabetic kidney and are associated with specific changes in podocyte function, in addition to changes in renal hemodynamics. As the proximal tubule grows, more of the glomerular filtrate is reabsorbed, and less reaches the macula densa (MD) at the end of Henle's loop, which will increase the glomerular filtration rate. Hyperglycemia affects most renal cells, and its effect is specific to individual renal cells. The susceptibility of cells to high glucose-induced injury is determined by their expression of glucose transporters, which mediate cellular uptake of glucose. Persistent hyperglycemia, dyslipidaemia, and oxidative stress all act to hasten the formation of AGEs (advanced glycation end products) and the modification of both long-lived and short-lived proteins. The biochemistry of AGEs is remarkably complex. AGEs induce cell injury and change protein structure and function, such as the formation of cross-links between key molecules of the basement membrane and the extracellular matrix (ECM) proteins. It alters protein structure and function. AGEs also interact with a receptor (RAGE) on the cell surface, thereby altering cellular function.[18]

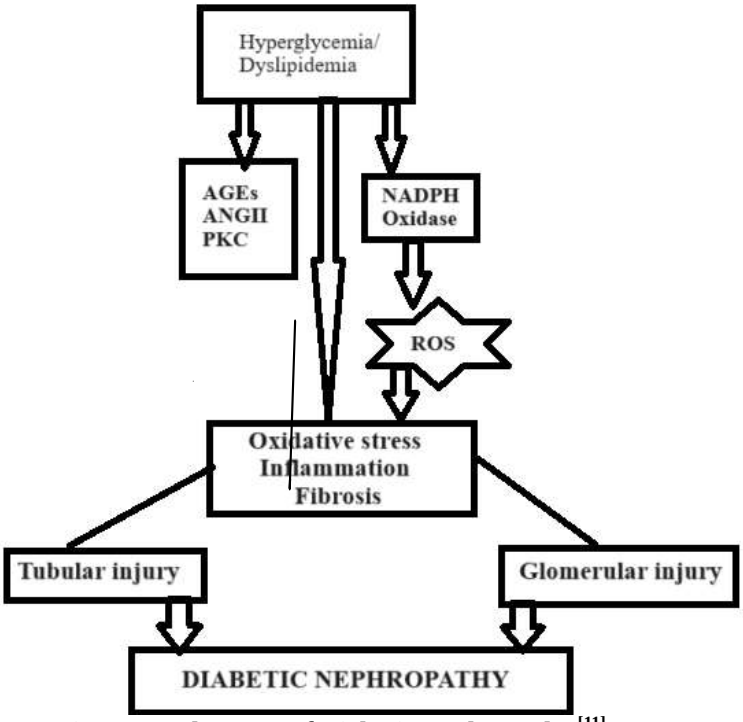

Fig. 2: Development of Diabetic Nephropathy.[11]

Proteinuric and Nonproteinuric Kidney Disease: Divergent Paths in Renal Health

Proteinuria is one of the most important risk factors for the development of kidney disease in diabetic patients. Kidney disease encompasses a spectrum of conditions that can be broadly categorized into proteinuric and nonproteinuric forms. Proteinuric kidney diseases are characterized by the presence of excessive protein in the urine, a condition known as proteinuria. The Urine Albumin-to-Creatinine Ratio (UACR) test quantifies the amount of albumin relative to creatinine in a urine sample, providing insights into the severity of proteinuria. A renal biopsy may be performed to determine the underlying cause of proteinuria and guide specific treatment. Dietary modifications, including protein restriction, may be recommended to alleviate the burden on the kidneys. Nonproteinuric diabetes nephropathy does not follow a classical pattern, so its diagnosis and treatment are difficult. Nonproteinuric kidney diseases are characterized by the absence or minimal presence of protein in the urine. These conditions may still result in significant renal impairment but lack the hallmark feature of proteinuria. Proteinuric and nonproteinuric kidney diseases represent distinct paths in the intricate landscape of renal health.[19]

Diabetic Nephropathy and cellular senescence

One of the critical factors in the process of aging is cellular senescence. In aging kidneys, a wide range of macrostructural changes are seen, such as decreased cortical volume, increased surface roughness, and augmented numbers and sizes of cysts. Cellular senescence in mesangial and tubular cells is induced by hyperglycemia. Sometimes a high glucose level can promote the development of cellular senescence and a low-grade inflammatory state, thus controlling cellular senescence plays a critical role in the therapeutics of DN. It can be accelerated by Inflammation, hyperglycemia, AGEs, and chronic oxidative stress can accelerate telomere shorting, and chromosomal telomere attrition occurs in both type 1 and type 2 diabetes and is associated with the progression of DN. Several studies show that there is a high association between telomere length shortening and the progression of nephropathy. DNA damage due to hyperglycemia triggers premature senescence in cells. Epigenetic modifications include DNA methylation, histone posttranslational modifications (PTMs), and noncoding RNAs. These changes are thought to be important in the development of DN through the induction of oxidative stress. Mitochondrial dysfunction of ROS and mitochondrial reactive oxygen species (mtROS) has been viewed as a cause of the aging process. Wnt/β-catenin signaling is reactivated in a wide range of chronic kidney diseases (CKD), such as diabetic nephropathy. However, in diabetic status, the accumulated intracellular ROS might divert the limited pool of β-catenin from TCF/LEF to forkhead box O- (FOXO-)-mediated transcription that leads to insulin deregulation. Inflammation is also involved in the pathogenesis of diabetes and is an important mediator of aging. Prominent inflammation is observed even in the beginning and ongoing stages of kidney injury. In the early stage of DN, upregulation of systemic and local renal inflammation occurs. In diabetic patients, different conditions like high glucose, AGEs, and oxidative stress induce inflammation. It activates the NF-κB factor, a known transcriptional signature of inflammation. Uremic toxins are endogenous waste

products of metabolism. They are cleared predominantly by the kidneys. The imbalance of the gut microbiome in kidney diseases largely contributes to the formation and retention of uremic toxins, which would create a reciprocal activation loop that accelerates the progression of kidney diseases. The accumulation of uremic toxins would influence cellular senescence.[20]

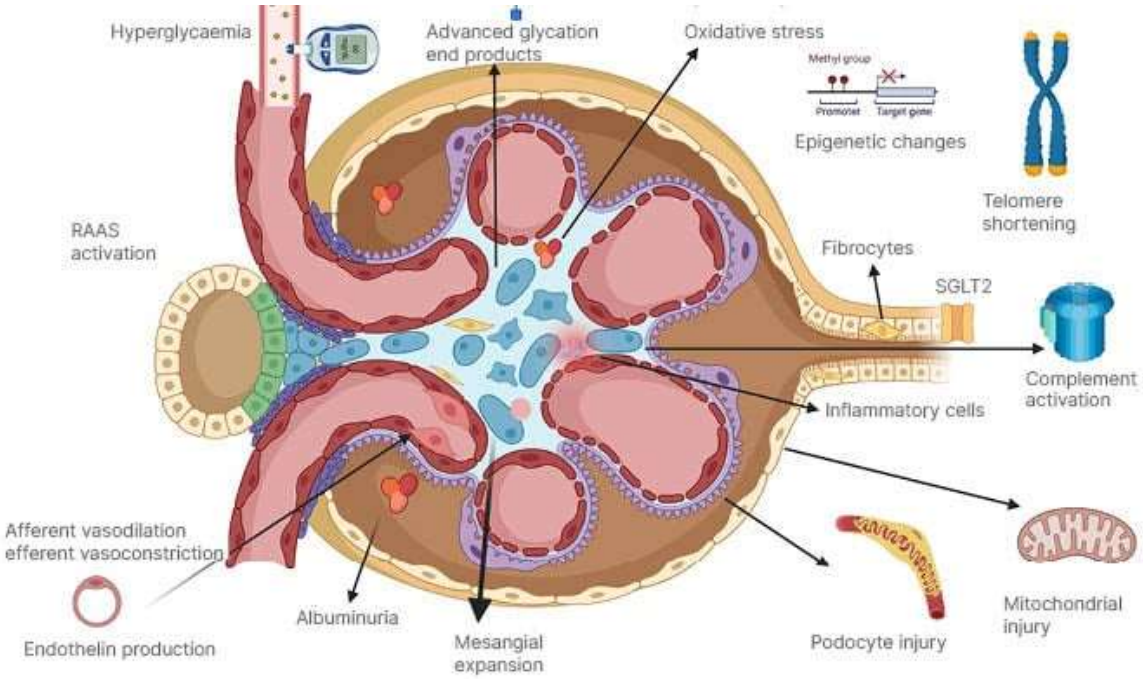

Fig. 3: Pathophysiology of diabetic Nephropathy.[21]

Approaches to Management of diabetic nephropathy

Treatment for diabetic nephropathy centres basically around controlling glucose and pulse levels, determined to end the movement of DN and relapse of albuminuria. It is speculated that decreasing albuminuria in diabetics prompts better renal and CVD results. Yet, it is simply ready to dial back the advancement yet not stop or opposite the sickness, so the generality of DN is as yet expanding. Notwithstanding the above strategies, other vague measures ought to be carried out including weight reduction, protein limitation, lipid decrease and smoking end.[22]

1) Objectives in Blood glucose level management

Convincing glycaemic control is the principal concern in diabetes. The ongoing objective is to keep up with HbA1c levels inside the suggested range. This decreases the chance of difficulties as well as upgrades generally success.[23] Empowering way of life changes stays a focal focus. Objectives incorporate achieving and keeping a comprehensive body weight, taking part in standard actual work, and taking a decent eating regimen wealthy in fibre and low in processed sugars. Way of life changes are perceived as significant in diabetes the executives and anticipation.[24] Supervision lipid levels is another basic objective. People with diabetes are advised to keep a solid lipid profile, with explicit focuses for low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and fatty oils. This moderates the chance of an atherosclerotic cardiovascular infection.[22,23] Occasional health check-ups and screenings are fundamental parts of diabetes the executives. Routine checking of blood glucose, circulatory strain, and lipid levels considers convenient mediation and changes in accordance with the administration plan, guaranteeing that people are on target to meet their wellbeing objectives. A current objective is to empower people with diabetes through instruction. This includes educating a profound comprehension of their condition, treatment choices, and the significance of self-administration.[22-24]

2) Antidiabetic drug therapy

The management of hyperglycaemia in CKD, particularly due to diminished GFR, is a assessment that requires a more definite knowledge, particularly in regards to drug choice.[25] Diabetic nephropathy mostly observe in aged diabetic patient with a longer duration of diabetes. So choice of drug for therapy very important aspect in treatment. Detailed knowledge of drug its interaction and metabolism is essential. Oral antidiabetic drugs are used for management of GFR.[26]

2.1) Biguanides

This class of medications has gained attention for its potential to manage diabetic nephropathy by improving insulin sensitivity and reducing hepatic glucose production. Metformin is a drug in this class and has demonstrated additional beneficial effects on the cardiovascular system, which is crucial in the context of diabetic nephropathy. Metformin exerts its renoprotective effects through multiple pathways.

Inflammation and fibrosis are key players in the progression of diabetic nephropathy. Metformin inhibits various cytokines and signaling pathways associated with inflammation, thus giving it anti-inflammatory action. It has been shown to reduce renal fibrosis, a hallmark of diabetic nephropathy, by improving the expression of fibrotic markers. Hypertension plays a role in the progression of diabetic nephropathy. Metformin helps to lower blood pressure, which may be attributed to its impact on vascular function and endothelial health, thus indirectly contributing to the management of diabetic nephropathy. Metformin also has some antioxidant properties, which neutralize reactive oxygen species and thereby reduce oxidative stress. This antioxidative capacity contributes to the preservation of renal function and structure. Clinical studies show that biguanides, especially metformin, have promising results in diabetic nephropathy. It improves renal function, reduces proteinuria, and slows the progression of nephropathy. Biguanides are cautiously used in patients regarding the potential risk of lactic acidosis, especially in individuals with impaired renal function. Future research should focus on elucidating the specific molecular mechanisms through which biguanides exert their renoprotective effects. Additionally, large-scale clinical trials with longer follow-up periods are warranted to establish the sustained benefits of biguanides in diabetic nephropathy. As our understanding of the intricate interplay between diabetes and renal health evolves, biguanides stand out as promising agents in the comprehensive management of this challenging complication.[27]

2.2) SGLT2 inhibitors

Sodium-glucose cotransporter-2 (SGLT2), initially developed to manage diabetes, belongs to the class of oral antidiabetic agents. They act by blocking glucose reabsorption in the renal tubules and urinary glucose excretion. so used, particularly in diabetic nephropathy. SGLT2 inhibitors also cause a reduction in proteinuria and have a blood pressure-lowering effect, which could potentially impede the progression of diabetic nephropathy. Mechanisms of SGLT2 inhibitors have demonstrated anti-inflammatory effects, mitigating the inflammatory processes that contribute to renal damage. SGLT2 inhibitors reduce glomerular hyperfiltration in the early stages of diabetic nephropathy and help to maintain the structural integrity of the kidneys. Side effects of this include a risk of hypoglycemia and dehydration, particularly in older adults. In recent years, clinical trials and studies have shed light on the renoprotective effects of dapagliflozin, marking a significant advancement in the treatment landscape for patients with CKD. Dapagliflozin belongs to the class of SGLT2 inhibitors, designed to lower blood glucose levels by promoting the excretion of glucose through the urine. Clinical trials, including the DAPA-CKD trial, have shown that dapagliflozin reduces the risk of kidney failure, end-stage renal disease, and cardiovascular events in patients with CKD, even those without diabetes. Dapagliflozin exerts its effects by modulating glomerular hemodynamics. Dapagliflozin has demonstrated anti-inflammatory and anti-fibrotic properties, potentially slowing the structural changes in the kidneys. The integration of dapagliflozin into the therapeutic approach for chronic kidney disease marks a significant milestone in nephrology.[28,29]

2.3) Sulfonylureas

This is a group of medicine stimulate the release of insulin & help in lowering blood pressure glucose level. Drug belong belong to sulfonylureas group are glimepiride, glipizide and glyburide. These drug blocks ATP sensitive potassium Channel in beta cells of pancreas and increase insulin secretion. This helps cells to utilize glucose and regulate blood glucose level in diabetic patient. Impact of sulfonylureas in diabetic kidney disease is a subject of debate because different studies get mixed result and there is complex relationship between sulfonylureas & diabetic kidney disease. Sulfonylureas indirectly contribute to the prevention on delay in progression of diabetic kidney disease. But this medication may induce hypoglycaemia and there is concern about its I long term safety mainly in individuals with pre-existing kidney issues.[30]

2.4) Glucagon – like peptide-1 receptor agonist's

This agent acts as incretin -mimetics. Exenatide is first approved drug of this class. Other drugs belong to this class are liraglutide, albiglutide dulaglutide, semaglutide. These medication binds to glucagon-like peptide -I receptor pancreas, increase the insulin secretion and supress the secretion of glucagon. GLP-1RA slower gastric emptying & also act on central nervous system and supress apatite causes weight loss and improve metabolic control. This medications are safe and effective and promote renal protection as it decrease glomerular act atherosclerosis, reduce oxidative stress, fibrosis & inflammation. They are not prescribed in individuals with T2DM and CKD. GLP1RA are indicated to be used with metformin and with other oral glucose lowering agents. Side effect associated with medication are generally mild but caused cautiously in people with pancreatis & diabetic retinopathy.[31]

2.5) Dipeptidyl Peptidase-4 (DPP4) inhibitors

DPP 4 is cell surface aminopeptidase, member of serine peptidase/ prolyl oligopeptide gene family. DPP-4 rapidly inactivates the GLP-1 which reduce function of incretins. Inhibition of DDP 4 results in increased GLP-1 accumulation which increase insulin secretion and maintain blood glucose level. Some of approved DPP-4 inhibitors are sitagliptin, Saxagliptin, Vildagliptin, linagliptin, anagliptin. Efficiency of these medication to in reducing glycaemia it is weaker than that of sulfonylureas but are better tolerated & do not produce weight gain. Many studies found that DPP4, Inhibitors prevent kidney Fibrosis of has nephroprotective action.[32]

2.6) Renin-Angiotensin- Aldosterone System (RAAS)

It is dual therapy involves combination of angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEis), direct renin inhibitors (DRIs). These are shown to reduce progressive kidney disease in several trials. AGE receptor (RAGE) is member of the immunoglobulin superfamily of the receptor initiates the intracellular signalling mechanisms which involved in inflammatory response in the kidney. ACE is and ARBs could decrease proteinuria & improve outcomes in patient with DKD. Inhibition of RAAS with decrease aldosterone production and reduce aldosterone secretion. Inhibition of RAAS helps in regulation of kidney function and decrease eGFR. According to recent clinical guidelines for DKD it shows that combination of ACEi/ ARB cause volume depletion & reduce kidney perfusion so not tube used in treatment nowadays.[33]

3) Management of blood pressure

Reduction of systolic blood pressure about 10mmHg shows reduction in diabetic microvascular complications, including nephropathy. It helps in slowing the progression diabetic nephropathy. Recommended blood pressure level is less than 130/80 mmHg for diabetic patient. RAAS inhibitor used for blood pressure management. These drugs also have protective effect on kidney but monotherapy is more effective as compared to combination. Sodium balance plays supportive in the hypertension seen in diabetics with renal disease.[34]

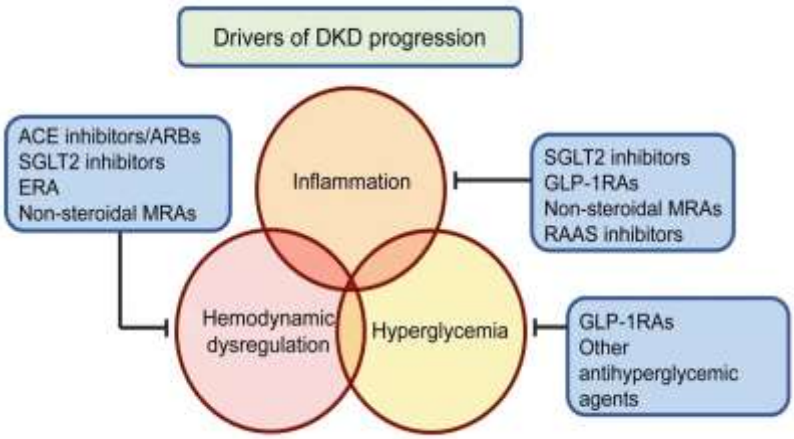

Fig. 4: Diabetic Nephropathy Progression.[35]

4) New strategies in diabetic nephropathy management

Management of blood glucose level and blood pressure can only helpful in slow down rate of progression. So discovery new drugs effective against oxidative stress and inflammation is a major focus in in diabetic nephropathy treatment. Mineralocorticoid receptor antagonist decrease the inflammation and fibrosis. This drug has shown some renoprotective action over RAAS therapy.[36] Mineralocorticoid receptor antagonists (MRA), spironolactone and eplerenone associated with risk of hyperkalaemia, especially in patients with diabetes and CKD.[37] Endothelial receptor antagonist, avocentan decreased albuminuria and renal fibrosis in phase III clinical trials. Endothelin-1 (ET-1) associated with the progression of DKD. It is involved in hemodynamic changes, inflammation, decrease GFR, increase albuminuria and proteinuria and ultimately leading to glomerulosclerosis and renal failure.[38] But during clinical trials some other effect of avocentan are examined such as congestive heart failure, edema and fluid retention so trials are terminated.[39] Ruboxistaurin is selective PKC-β enzyme inhibitor. Its clinical trials showed reduced albuminuria, hyperfiltration, macrophage accumulation and reducing mesangial expansion.[40]

CONCLUSION

It is a very common diabetic complication, affecting many people with type I and type 2 diabetes. Its progression causes end-stage renal failure. Hyperglycemia and hypertension contribute to the morphological changes in the kidney. Hyperfiltration and hyperperfusion of the glomerulus cause albuminuria. Initially, it does not show any symptoms; it appears when there is a loss of significant function. are the main reason for the development of diabetic nephropathy. The untreated condition leads to renal failure. There is no single treatment for its progression. It should include control over blood glucose levels and management of hypertension. The development of specific drugs that specifically target inflammation is under clinical study.

REFERENCE

1. IDF diabetes atlas 2021, 10th edition 37,39,44,55. https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf
2. Harreiter J, Roden M.Diabetes mellitus-Definition, classification, diagnosis, screening and prevention (Update 2019)]. Wien Klin Wochenschr, May, 2019; 131(1): 6-15. German. doi: 10.1007/s00508-019-1450-4. PMID: 30980151 [PubMed].

3. Schwerin DL, Svancarek B. EMS Diabetic Protocols For Treat and Release. 2023 Jul 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, Jan. 2023. PMID: 32809447 [PubMed].
4. Primavera M, Giannini C, Chiarelli F. Prediction and Prevention of Type 1 Diabetes. Front Endocrinol (Lausanne), Jun. 2, 2020; 11: 248. doi: 10.3389/fendo.2020.00248. PMID: 32670194; PMCID: PMC7326081 [PubMed].
5. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol, Nov. 2021; 69(11): 2932-2938. doi: 10.4103/ijo.IJO_1627_21. PMID: 34708726; PMCID: PMC8725109 [PMC free articles].
6. Damanik J, Yunir E. Type 2 Diabetes Mellitus and Cognitive Impairment. Acta Med Indones, Apr. 2021; 53(2): 213-220. PMID: 34251351 [PubMed].
7. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev., Sep 26, 2022; 43(5): 763-793. doi: 10.1210/endrev/bnac003. PMID: 35041752; PMCID: PMC9512153 [PubMed].
8. Schiborn C, Schulze MB. Precision prognostics for the development of complications in diabetes. Diabetologia, Nov. 2022; 65(11): 1867-1882. doi: 10.1007/s00125-022-05731-4. Epub 2022 Jun 21. PMID: 35727346; PMCID: PMC9522742 [PubMed].
9. Huang DD, Shi G, Jiang Y, Yao C, Zhu C. A review on the of Resveratrol in prevention and therapy of diabetes and diabetic complications. Biomed Pharmacother, May, 2020; 125: 109767. doi: 10.1016/j.biopha.2019.109767. Epub 2020 Feb 12. PMID: 32058210. [PubMed].
10. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol, Jul. 2020; 16(7): 377-390. doi: 10.1038/s41581-020-0278-5. Epub 2020 May 12. PMID: 32398868; PMCID: PMC9639302 [PMC free articles].
11. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, Rossing P, Groop PH, Cooper ME. Diabetic kidney disease. Nat Rev Dis Primers, Jul. 30, 2015; 1: 15018. doi: 10.1038/nrdp.2015.18. PMID: 27188921; PMCID: PMC7724636 [PMC free articles].
12. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature, Dec. 13, 2001; 414(6865): 813-20. doi: 10.1038/414813a. PMID: 11742414 [PubMed].
13. Hu R, Layton A. A Computational Model of Kidney Function in a Patient with Diabetes. Int J Mol Sci., May. 29, 2021; 22(11): 5819. doi: 10.3390/ijms22115819. PMID: 34072329; PMCID: PMC8198657 [PMC free articles].
14. Wang X, Garrett MR. Nephron number, hypertension, and CKD: physiological and genetic insight from humans and animal models. Physiol Genomics, Mar. 1, 2017; 49(3): 180-192. doi: 10.1152/physiolgenomics.00098.2016. Epub 2017 Jan 27. PMID: 28130427; PMCID: PMC5374451 [PMC free articles].
15. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nature reviews. Nephrology, May, 2021; 17(5): 319-334. DOI: 10.1038/s41581-021-00393-8. PMID: 33547417. [europepmcarticle].
16. Madrazo-Ibarra A, Vaitla P. Histology, Nephron. [Updated 2023 Feb 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2023 Jan. Available from: [gov/books].
17. Qi C, Mao X, Zhang Z, Wu H. Classification and Differential Diagnosis of Diabetic Nephropathy. J Diabetes Res., 2017; 2017: 8637138. doi: 10.1155/2017/8637138. Epub 2017 Feb 20. PMID: 28316995; PMCID: PMC5337846 [PMC free articles].
18. Vallon V, Komers R. Pathophysiology of the diabetic kidney. Compr Physiol, Jul. 2011; 1(3): 1175-232. doi: 10.1002/cphy.c100049. PMID: 23733640; PMCID: PMC6029262 [PMC free articles].
19. Yamanouchi M, Furuichi K, Hoshino J, Ubara Y, Wada T. Nonproteinuric diabetic kidney disease. Clin Exp Nephrol, Jul., 2020; 24(7): 573-581. doi: 10.1007/s10157-020-01881-0. Epub 2020 Mar 31. PMID: 32236782; PMCID: PMC7271053 [PMC free articles].
20. Xiong Y, Zhou L. The Signaling of Cellular Senescence in Diabetic Nephropathy. Oxid Med Cell Longev, Oct. 3, 2019; 2019: 7495629. doi: 10.1155/2019/7495629. PMID: 31687085; PMCID: PMC6794967 [PMC free articles].
21. EMJ Nephrol, 2022; 10(1): 102-113. DOI/10.33590/emjneohrol/22-0006. Google image: https://doi.org/10.33590/emjnephrol/22-00060.
22. Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. Biomed Res Int, Jul. 8, 2021; 2021: 1497449. doi: 10.1155/2021/1497449. PMID: 34307650; PMCID: PMC8285185 [PMC free articles].
23. Stratton I. M., Adler A. I., Neil H. A., et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.*, 2000; 321(7258): 405–412. doi: 10.1136/bmj.321.7258.405 [PMC free article].
24. Koenigsberg MR, Bartlett D, Cramer JS. Facilitating treatment adherence with lifestyle changes in diabetes. Am Fam Physician, Jan. 15, 2004; 69(2): 309-16. PMID: 14765768 [PubMed].
25. Pugliese G, Penno G, Natali A, Barutta F, Di Paolo S, Reboldi G, Gesualdo L, De Nicola L; Italian Society of Nephrology on "The natural history of diabetic kidney disease and treatment of hyperglycemia in patients with type 2 diabetes and impaired renal function". J Nephrol., Feb., 2020; 33(1): 9-35. doi: 10.1007/s40620-019-00650-x. PMID: 31576500; PMCID: PMC7007429. [PMC free article]
26. Palmer K. J., Brogden R. N. Gliclazide. An update of its pharmacological properties and therapeutic

efficacy in non-insulin-dependent diabetes mellitus. *Drugs*, 1993; 46: 92–125. doi: 10.2165/00003495-199346010-00007. [PubMed]

27. Kawanami D, Takashi Y, Tanabe M. Significance of Metformin Use in Diabetic Kidney Disease. Int J Mol Sci., Jun, 14, 2020; 21(12): 4239. doi: 10.3390/ijms21124239. PMID: 32545901; PMCID: PMC7352798. [PMC free articles].
28. Bae JH, Park EG, Kim S, Kim SG, Hahn S, Kim NH. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Sci Rep., Sep. 10, 2019; 9(1): 13009. doi: 10.1038/s41598-019-49525-y. PMID: 31506585; PMCID: PMC6736944 [PMC free articles] .
29. Clemmer JS, Yen TE, Obi Y. Modeling the renoprotective mechanisms of SGLT2 inhibition in chronic kidney disease. Physiol Rep., Nov., 2023; 11(21): e15836. doi: 10.14814/phy2.15836. PMID: 37957121; PMCID: PMC10643202 [PMC free articles].
30. Boddepalli CS, Gutlapalli SD, Lavu VK, Abdelwahab Mohamed Abdelwahab R, Huang R, Potla S, Bhalla S, AlQabandi Y, Nandula SA, Khan S. The Effectiveness and Safety of Metformin Compared to Sulfonylureas in Diabetic Nephropathy: A Systematic Review. Cureus, Dec. 7, 2022; 14(12): e32286. doi: 10.7759/cureus.32286. PMID: 36628027; PMCID: PMC9822529 [PubMed].
31. Górriz JL, Romera I, Cobo A, O'Brien PD, Merino-Torres JF. Glucagon-Like Peptide-1 Receptor Agonist Use in People Living with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Narrative Review of the Key Evidence with Practical Considerations. Diabetes Ther., Mar, 2022; 13(3): 389-421. doi: 10.1007/s13300-021-01198-5. Epub 2022 Feb 17. PMID: 35175551; PMCID: PMC8934828 [PMC free articles].
32. Shi S, Koya D, Kanasaki K. Dipeptidyl peptidase-4 and kidney fibrosis in diabetes. Fibrogenesis Tissue Repair, Feb. 13, 2016; 9: 1. doi: 10.1186/s13069-016-0038-0. PMID: 26877767; PMCID: PMC4752740 [PMC free articles]
33. Ames MK, Atkins CE, Pitt B. The renin-angiotensin-aldosterone system and its suppression. J Vet Intern Med. Mar., 2019; 33(2): 363-382. doi: 10.1111/jvim.15454. Epub 2019 Feb 26. Erratum in: J Vet Intern Med., Sep., 2019; 33(5): 2551. PMID: 30806496; PMCID: PMC6430926 [PMC free articles].
34. Sawicki PT, Mühlhauser I, Didjurgeit U, Berger M. Effects of intensification of antihypertensive care in diabetic nephropathy. J Diabetes Complications, Oct-Dec, 1995; 9(4): 315-7. doi: 10.1016/1056-8727(95)80030-i. PMID: 8573755 [PubMed].
35. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, St Peter WL, Warfield C, Powe NR. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. Am J Kidney Dis., Feb., 2022; 79(2): 268-288.e1. doi: 10.1053/j.ajkd.2021.08.003. Epub 2021 Sep 23. PMID: 34563581[PubMed].
36. Zac-Varghese S., Winocour P. Managing diabetic kidney disease. *British Medical Bulletin*, 2018; 125: 55–66. doi: 10.1093/bmb/ldx047. [PubMed]
37. Van Buren PN, Toto R. Hypertension in diabetic nephropathy: epidemiology, mechanisms, and management. Adv Chronic Kidney Dis., Jan., 2011; 18(1): 28-41. doi: 10.1053/j.ackd.2010.10.003. PMID: 21224028; PMCID: PMC3221014 [PMC free articles].
38. Zhang S, Li X, Liu S, Zhang W, Li M, Qiao C. Research progress on the role of ET-1 in diabetic kidney disease. J Cell Physiol, Jun., 2023; 238(6): 1183-1192. doi: 10.1002/jcp.31023. Epub 2023 Apr 17. PMID: 37063089 [PubMed]
39. Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, Viberti G; ASCEND Study Group. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol, Mar., 2010; 21(3): 527-35. doi: 10.1681/ASN.2009060593. Epub 2010 Feb 18. PMID: 20167702; PMCID: PMC2831858. [PMC free article]
40. Koya D, Haneda M, Nakagawa H, Isshiki K, Sato H, Maeda S, Sugimoto T, Yasuda H, Kashiwagi A, Ways DK, King GL, Kikkawa R. Amelioration of accelerated diabetic mesangial expansion by treatment with a PKC beta inhibitor in diabetic db/db mice, a rodent model for type 2 diabetes. FASEB J., Mar., 2000; 14(3): 439-47. doi: 10.1096/fasebj.14.3.439. PMID: 10698958. [PubMed]