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A THERAPEUTIC APPROACH TO THE PREVALENCE, CLINICAL MANIFESTATIONS AND TREATMENT OF DIABETIC NEPHROPATHY

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ABSTRACT

Background: The most common cause of diabetic nephropathy isend- stage renal disease (ESRD). The prevalence of DKD remains high despite rigorous treatments such as hyperglycemic management, blood pressure control, and the use of renin-angiotensin system blockades. Recent research reveals that the DKD spectrum has shifted, and that much progress has been made in developing new DKD treatments. As a result, it's past time to conduct a systemic evaluation of recent DKD advances**.**

The aim of this review paper was to investigate the knowledge regarding the diabetic nephropathy. This disease condition involves the management and prevention of diabetes kidney disease.

Result: Selection of data has been done by studying a combination of research and review paper from different data bases like pub med, NCBI, science direct, and web of science from 1991-2017 by using keywords like “Diabetic kidney disease”, “microalbuminuria”, “proteinuria”, “antihypertensive treatment”, “glomerular filtration rate”, “glycemic control”, “End stage renal disease”.

Conclusions: The variety of DKD's clinical presentation and progress has crucial implications for its diagnosis, prognosis, and possibly treatment. Patients with type 2 diabetes with compromised renal function now have a wider range of treatment alternatives, allowing for better management of these patients**.**

Keywords: renal failure, proteinuria, glycaemic control, type 1 diabetes mellitus, antihypertensive treatment, blood pressure control, glomerular filtration rate, diabetic nephropathy

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Background

Diabetic nephropathy is a long term complication of diabetes mellitus which affect approximately 30% of the patient with type 1 diabetes and 40% of those with type 2 Diabetes [1]. Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) [2]. Persistent albuminuria is a symptoms of diabetic nephropathy, which is clinical condition elevated arterial blood pressure, a rapid decrease in glomerular filtration and high risk of cardiovascular morbidity and mortality [3].Recent epidemiological studies have highlighted the unique variability of natural history of these issues, causing the term diabetic kidney disease to be used to refer to all type of renal injury that occur in diabetic patient[4].DN is defined as persistently elevated albuminuria of more than 300mg/24hr or an albumen/creatinine ratio > 300 mg/g creatinine, confirmed in at least two out of three samples with concurrent presence of diabetes retinopathy and absence of other signs of renal disease in both type 1 and type 2 diabetes[5].

Pathology of diabetic nephropathy

DN is characterized by structural and functional changes. Mesangial enlargement, basement membrane thickening, and nodular glomerulosclerosis are all symptoms of glomrulosclerosis. Tubular hypertrophy is seen in early DN, although intestinal fibrosis with tubular atropy,as well as arteriolarhyalinosis,develops later. There is a macrophage and T-lymphocyte infiltration in advanced instances. There is a decrease of podocytes and reduction in endothelial cell fenestration on an ultrastructural level [6]. There is early glomerular hyperfilteration and increased albumin excretion, as well as growing proteinuria and falling GFR as the nephropathy progresses. Functional and cellular pathology described below. (Figure:1)

Hemodynamic factors

Increased glomerular hydrostatic pressure and hyperfilteration come from an imbalance in afferent and efferent arteriolar resistance. The renin–angiotensin system (RAS) elevates angiotensin II levels, which causes efferent arteriolar vasoconstriction and the synthesis of pro-inflammatory and profibrotic substances via numerous processes.

In diabetics, high levels of angiotensin converting enzyme (ACE) are linked to increased albuminuria and nephropathy in humans and mice [7]. Vasoconstriction is further aided by increased levels of endothelin-1 and urotensin II. DN has been linked to a variety of nitric oxide and nitric oxide synthase dysregulations. Endothelial nitric oxide synthase produces nitric oxide from L-arginine, which mediates endothelium-dependent vasodilation [8].

Metabolic factors

Oxidative stress and the production of reactive oxygen species (ROS) cause DNA and protein damage, as well as acting as signaling amplifiers for cellular stress pathways like PKC, MAPK, and NF-ќB[9].Activation of the polyol pathway, which involves aldose reductase converting excess glucose to sorbitol and then sorbitol dehydrogenase converting it to fructose, contributes

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to oxidative stress by increasing the NADH/Fructose ratio[10].Non-enzymatic binding of glucose to proteins, lipids, and nucleic acids results in the development of advanced glycation end-products (AGE), which can cause changes in protein structure and function, oxidative stress, and the release of proinflammatory cytokines and growth factors[11].

Cell signaling and transcription factors

Increased PKC- gene transcription in the kidneys was found to have a strong link to glycemic control [12]. PKC activation has a variety of consequences, including increased angiotensin II actions, nitric oxide dysregulation, endothelial dysfunction, and MAPK and NF-ќB activation [13]. MAPKs are intracellular kinases that help cells respond to signals from outside the cell. A number of nuclear transcription factors are activated by MAPKs.NF-B is one of them, and it regulates gene expression. Cytokines, chemokines, and adhesion molecules, to name a few. Renal inflammation and DN are significantly linked to the activation of the p38 iso-form of the p38 MAPK pathway [14]. Finally, transcription factors bind to gene promoter regions and regulate messenger RNA transcription. In DN, NF-ќB has received the most attention.

NF-ќB activation in human peripheral blood mononuclear cells and kidney biopsies is linked to proteinuria severity and glycemic control [15].

Inflammation

In DN, innate immune cells are recruited and activated, and proinflammatory cytokines are produced [16]. In early diabetic glomeruli, macrophages and T lymphocytes are prevalent, but an interstitial infiltrate emerges later. DN is mediated by macrophages, as evidenced by strategies that inhibit renal leukocytes migration, proliferation ,or activation [17]. The main proinflammatory cytokines implicated in DN are TNF-α, MCP-1, ICAM-1, IL-1, IL-6, and IL-18.

Management of DN:

In diabetic individuals with micro-albumineria, the risk of cardiovascular death is 7-40 times that of an age-matched general population in normo-albuminuric diabetes. The management of the patient with diabetic nephropathy must pay the attention to all cardiovascular risk factor, as well as steps to slow the advancement of renal disease.

Hypertension

Because of the well-established benefits of decreasing blood pressure on both the course of renal disease and total cardiovascular mortality, blood pressure monitoring and control has become an important part of diabetic therapy.

Antihypertensive therapy's effectiveness in preserving renal function was first revealed in limited investigations of type 1 diabetic patients. Mogensen lowered the mean blood pressure of a group of type 1 diabetes patients with overt nephropathy from 163/103 to 144/95mmHg, and the monthly decline in GFR was reduced from 1.23 to 0.49ml/min[18]. Blood pressure lowering reduces or stabilizes AER in both type 1 and type 2 diabetic individuals with micro-albuminemia ,slowing the progression to overt nephropathy[19].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

Blood pressure target

Although the exact level of blood pressure below which further benefits is not seen has yet to be determined, the British hypertension society recommends starting therapy in diabetic patients with a blood pressure of >140/90mmHg and a target blood pressure of <140/80mmHg, or <125/75mmHg in type 1 diabetic patients with >1g/day of proteinuria [20]. The US joint national committee on the detection, evaluation, and treatment of high blood pressure has suggested that diabetes individual's blood pressure be kept below 130/85mmHg [21]. Blood pressure should be monitored in all diabetic patients for at least 6 months and when micro albuminuria develops for at least 6 months.

ACE Inhibitors

Although blood pressure reduction with any of the traditional antihypertensive drugs is beneficial, in some cases, ACE inhibitors have Reno-protective effect in addition to their antihypertensive properties. A combined analysis of two large studies comparing captopril to placebo in micro-albuminuria type 1 diabetes with controlled hypertension found a 63 % reduction in progression to over proteinuria over two years, as well as a decrease in albumin excretion rate [22]. In both type 1 and type 2 diabetes, ACE inhibitors should now be used as first line antihypertensive agent. In non- hypertensive type 1 and type 2 diabetic patients with micro- albuminuria or overt nephropathy, ACE inhibition is also indicated, with the dose gradually increasing until AER returns to normal or hypotension develops [23].

Angiotensin Ⅱ receptors blockers are a possible alternative to ACE inhibitors. They are effective antihypertensive medications, but they have not been validated in large outcomes studies and should be reserved for patient who do not tolerate ACE inhibition. Other antihypertensive medication may be added in accordance with standard protocols [24].

Glycemic control

Although there is no clear evidence that it affects the progression of nephropathy in diabetes complicated by micro-albuminuria, good glycemic management reduces the incidences of micro-albuminuria and overt renal disease [25]. In view of this, and the potential benefits in both renal and cardiovascular illness, the British and US recommendations are to establish and maintain tight blood glucose control, with a HbA1c target of≤ 7% [26, 27].

Low-protein diet

Dietary protein has been proven to slow the progression of diabetic nephropathy in people with type 1 diabetes in two meta-analyses [28, 29].

It's still unknown what level of protein restriction should be employed, how patient acceptable it will be, and how this would affect therapy adherence in ordinary general care . To investigate these concerns in both type 1and type 2 diabetes, long term prospective studies are required.

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

Lipid control

In primary renal disease, dyslipidemia is a risk factor for the development and progression of renal impairment [30]. Lipid reduction has demonstrated to be beneficial in diabetic people with established coronary heart disease. diabetic subgroup was studied in two large secondary prevention studies, the Scandinavian simvastatin survival study and the cholesterol and recurrent events trial, and the efficacy of statins in lowering coronary events was equivalent to, if not larger, than the whole group [31].

Prevention and treatment

Prevention; normo- albuminuric patients

The treatment of known risk factors for diabetic nephropathy, such as hypertension, hyperglycemia, smoking and dyslipidemia, serves as the foundation for prevention. These are also risk factors for cardiovascular disease and should be vigorously treated.

Intensive blood glucose control:

Clinical trials have consistently shown that A1c level of <7% are associated with a lower risk of clinical and structural manifestations of diabetic nephropathy in type 1 and type 2 diabetic patients. The diabetes control and complication trial found that intensive diabetes treatment reduced the incidence of micro-albuminuria by 39% [32]. It is worth nothing that patients randomized to strict glycemic control had a 40% reduction in the risk of developing diabetes 7-8% years after the end of the diabetes control and complications trial [33].

Intensive blood pressure control:

Treatment of hypertension significantly reduces the risk of cardiovascular and micro- vascular events in diabetic patients. even in diabetic patients who do not have renal involvement, hypertension is common. Blood pressure levels of > 140/90mmHg are found in approximately 40% of type 1 diabetic patients and 70% of type 2 diabetic patients with normo-albuminuric [34].

Patients with diabetes have lower blood pressure targets of 130/80mmHg than those without diabetes [35]. A reduction in diastolic blood pressure from85 to 81mmHg resulted in 50% reduction in the risk of cardiovascular events in diabetic but not non-diabetic patients in the hypertension optimal treatment study [36].

Renin – angiotensin system blockade:

The role of ACE inhibitors in preventing diabetic nephropathy in type 1 diabetes patients has yet to be determined. The treatment of perindopril in normotensive normo- albuminuric type 1 diabetes individuals for three year slowed the progression of albuminuria [37]. As shown in (Figure 2)

Treatment: micro and macro-albuminuric patients

The goal of treatment is to avoid the progression of micro-albuminuria to 09macroalbuminuria, as well as the deterioration of renal function in micro-albuminuria patients and the incidence of cardiovascular events. The strategies and goals are described in TABLE 1.

Intensive blood glucose control:

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

The impact of strict glycemic management on the development of micro-albuminuria to normo-albuminuria, as well as the rate of renal function detoriation in macro-albuminuric patients, is still debated. Glycemic management did not slow the transition of micro-albuminuria to micro-albuminuria in individuals with type 1 diabetes who were microalbumiuric at the starting of the study in the DCCT [38]. Few studies have looked at the effect of blood glucose control in the evaluation of diabetic nephropathy in people with type 2 diabetes. With extensive treatment, a reduction in the conversion from micro to macro-albuminuria was noted in the kumamotostudy [39]. Oralanti hyperglycemic drugs appear to be beneficial. Rosiglitazone has been demonstrated to reduce UAE in type 2 diabetic patients as compared to glyburide. This suggests that it may help reduces type 2 diabetes related kidney problems [40].

Challenges and opportunities in developing new therapies for DKD:

Better hyperglycemic control, RAS blockers, and other management options for DKD include lipid-lowering medication, and so on. RAS inhibition has been shown to be the most effective therapy for reducing the course of DN in humans [41]. The combination therapy with an angiotensin-converting enzyme inhibitor with an angiotensin II receptor blocker does not prevent renal disease progression or death, and it raises the risk of significant side effects like AKI, hyperkalemia, and hypotension in diabetes nephropathy [42].

Newly approved drug for DKD treatment

For nephrologists, the recent success of SGLT2 inhibitors as a new therapy for DKD patients is exciting and encouraging news. SGLT2 is responsible for around 90% of glucose reabsorption in the renal proximal tubule and its inhibitors are used to treat hyperglycemia in type 2 diabetes by increasing glucose excretion in the urine[43].Through enhanced urinary excretion of glucose and salt, osmotic diuresis, and improved tubule-glomerular feedback mechanism, SGLT2 inhibitors have been demonstrated to lower body weight, blood pressure, serum uric acid, and glomerular hyperfilteration[44].When empagliflozin is added to standard therapy in individuals with type 2 diabetes and high cardiovascular risk, it is related with a slower progression of kidney disease and a lower rate of clinically meaningful renal events than placebo when added to standard care[45,46].

Promising Drugs in Phase III Clinical Trials for DKD Treatment

One of the incretins secreted from the intestine in response to food consumption is glucagon-like peptide-1 (GLP-1), which can promote insulin secretion. Its level has been reduced, and analogues (such as liraglutide) have been utilized to treat type 2 diabetes. According to Liraglutide Effect and Action in Diabetes: Cardiovascular Outcomes Evaluation, Liraglutide demonstrated a lower rate of new onset of persistent macro-albuminuria and progression of DKD than placebo in a double-blind trial involving 9,340 individuals with type 2 DM and high cardiovascular risk[47].Endothelin-1 receptor agonist, avosentan Although an antagonist can lower urine albumin excretion, the research was cut short due to a high number of cardiovascular events during the treatment period due to fluid overload[48].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

After three months of treatment, rosiglitazone, a peroxisome proliferator activated receptor agonist, can significantly lower urine albumin to creatinine ratio in type 2 diabetic patients [49].

Potential Drugs Required Further Validations

The production of advanced glycation end products (AGE) in response to hyperglycemia, as well as the engagement of the AGE receptor with its ligands, can cause oxidative stress and renal inflammation. Pyridoxamine, a vitamin B6 family member, can neutralize free radicals and carbonyl compounds while also preventing the formation of AGEs. Pyridoxamine did not give significant renal protection in DKD patients in clinical investigations [50], although it did have a significant protective effect in a subgroup of DKD patients.

Both NF-kB and the Janus kinase (JAK)/signal transducer and activator of transcription pathway are extensively engaged in the etiology of DKD, according to a system biology approach. JAK-signal transducer and activator of transcription is important not only in immune cells, but also in renal cells including mesangial cells, podocytes, and tubular epithelial cells. The hyperglycemic condition induces reactive oxygen species, which activate this pathway [51]. The nuclear factor-2 erythroid related factor (Nrf2)-keep 1 pathway has also been linked to the progression of DKD [52]. In the experimental paradigm of streptozotocin-induced diabetic mice on an apolipoprotein E-deficient background, pharmacological activation of Nrf2 reduces cytokine production, M1 macrophage accumulation, and the formation of an atherosclerotic plaque lipid core[53].Furthermore, its activation reduces oxidative stress, TGF expression, and extracellular matrix proteins in the glomerulus of streptozotocin-induced diabetic mice, which improves the pathogenic alterations [54].The enzyme isoforms of the NADPH oxidase (NOX) enzyme are involved in the formation of reactive oxygen species, which cause kidney cell injury in DKD. In mouse models of DN, GKT137831, a NOX1/4 inhibitor, has been demonstrated to be helpful[55].MCP-1, or proinflammatory chemokine ligand 2, has been linked to the development of DN and has emerged as a new therapy target. Albuminuria was reduced in mouse models treated with NOX-E36, a chemokine ligand 2 inhibitor [56].as described in **(table2).**

Evaluation of patients with diabetic nephropathy

Following confirmation of the diagnosis of micro- or macroalbuminuria, patients should have a thorough examination, which should include a urine test. Other etiologies should be investigated, as well as renal function and the presence of other comorbidities.

Differential diagnosis

The history, physical examination, laboratory evaluation, and imaging of the kidneys are commonly used to make a differential diagnosis. Renal biopsy is only advised in exceptional circumstances. Diabetic nephropathy can be easily diagnosed in long-term type 1 diabetic patients (10 years of diabetes), especially if retinopathy is also present. Proteinuric type 2 diabetic patients with retinopathy are likely to have typical diabetic nephropathy. However, certain people with type 2 diabetes face diagnostic uncertainty because the beginning of diabetes is unknown, and retinopathy is absent in a significant number of these patients (28 %) [57].

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

Symptoms of urinary tract illnesses, such as blockage, infection, or stones, can be detected during urination. A rash on the skin or arthritis could be signs of systemic lupus erythematosus or cryoglobulinemia. The presence of risk factors for parenterally transmitted disease may raise suspicions of HIV, hepatitis C, or hepatitis B-related kidney disease. Proteinuria and/or hypertension during childhood or pregnancy may indicate a different type of glomerulonephritis.A family history of renal illness indicates the polycystic renal disease and other type of genetic disease[58].

Although the criteria for renal biopsy are not clearly defined in type 1 diabetes, proteinuria in combination with a short history of diabetes and rapid decrease of renal function, especially in the absence of diabetic nephropathy, has been employed[59]. On the other hand nephropathies, either isolated or superimposed over diabetic glomerulosclerosis, were seen in 46 and 19 percent of 68 Chinese individuals with type 2 diabetes, respectively. A biopsy was performed because of proteinuria of 1 g/24 h, renal damage in the absence of retinopathy, or unexplained hematuria[60].

Monitoring of renal function

GFR is the best indicator of overall kidney function, and it should be measured or estimated in diabetic patients with micro- and macro-albuminuria. GFR levels in micro-albuminuric patients may remain steady, although a subset of patients has had a rapid decline in GFR levels[61]. GFR falls by around 1.2 ml min1 month1 in type 1 macro-albuminuric patients without treatment interventions[62].GFR decline is more varied in persons with type 2 diabetes. Although some individuals' GFR may remain steady for lengthy periods of time, one research observed a mean drop of 0.5 ml min1 month 1[63,64].

Comorbid associations

It's very crucial to look into retinopathy. Because retinopathy is common in the presence of diabetic nephropathy and is a clue for its diagnosis, this should ideally be done by an expert ophthalmologist. Diabetic retinopathy was found to be a predictor of diabetes nephropathy in type 2 diabetic patients in prospective investigations[65,66].Because both microvascular diseases (diabetic nephropathy and diabetic retinopathy) share common causes, such as poor glycemic, blood pressure, and cholesterol control, retinopathy is most likely a risk marker rather than a risk factor in and of itself. Other diabetes sequelae, such as peripheral and autonomic neuropathy, should be assessed as well, because they are more common in individuals with diabetic nephropathy and are linked to higher morbidity and death[67,68].Carotid disease, peripheral artery disease, and atherosclerotic plaques are some of the other atherosclerotic complications. Renal artery stenosis should be checked as well. Acute renal failure can be caused by radiocontrast agents used in angiography. Up to 35% of diabetes individuals, particularly in patients with impaired renal function[69].Prior hydration and delivery of an iso-osmolar contrast medium can help prevent this[70].In diabetic individuals, magnetic resonance angiography is the preferred approach for detecting renal artery stenosis. Captopril renal scintigraphy and duplex Doppler ultrasonography imaging of the renal arteries are two more approaches; however, they

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 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

have poorer sensitivity. In patients with impaired renal function (serum creatinine 2.0 mg/dl), captopril renal scintigraphy has limits, and Doppler ultrasonography is highly dependent on operator skill [71].

CONCLUSIONS:

Several risk factors are linked to the development and progression of DN. Furthermore, because DN patients are typically older, have had diabetes for a longer period of time, and are more likely to have co-morbidities, the therapeutic regimen for DN is usually multi-factorial, encompassing tight glycemic control, blood pressure control with RAS inhibitors, lipid-lowering agents, weight loss, protein restriction, and smoking cessation. The advancement of DN cannot be prevented, even if blood glucose and blood pressure levels are effectively controlled and nonspecific interventions are taken. Many diabetes people acquire end-stage renal disease (ESRD), and disproportionate health-care spending becomes a huge socioeconomic burden A multi-factorial strategy focusing on glucose, lipids, and blood pressure, as well as renin angiotensin system blocking and lifestyle changes, has improved renal and cardiovascular prognosis and reduced death by half. Recent evidence suggests that new glucose lowering medications have pleiotropic effects on kidney endpoints. It's also being looked into if inhibiting aldosterone could be a new therapy option. Consequently, while diabetic nephropathy remains a significant burden, the prognosis has improved, and new approaches for further improvement are currently being evaluated in renal outcome studies.

Abbreviations

DN- Diabetic nephropathy
ESRD - End stage renal disease
RAS- Renin-angiotensin system
ACE- Angiotensin converting enzymne
ROS – Reactive oxygen species
PKC- protein kinase C
MAPK- Mitogen-activated protein kinase
TNF- Tumor necrosis factor
MCP-Monocyte chemoattractment protein
ICAM-1 Intercellular Adhesion molecule -1
IL-1- Interleukin -1
HbA1C- Hemoglobin A1C
SLGT2- Sodium glucose transport protein 2
GLP-1- Glucagon-like peptide-1
GFR- Glomerular filteration rate

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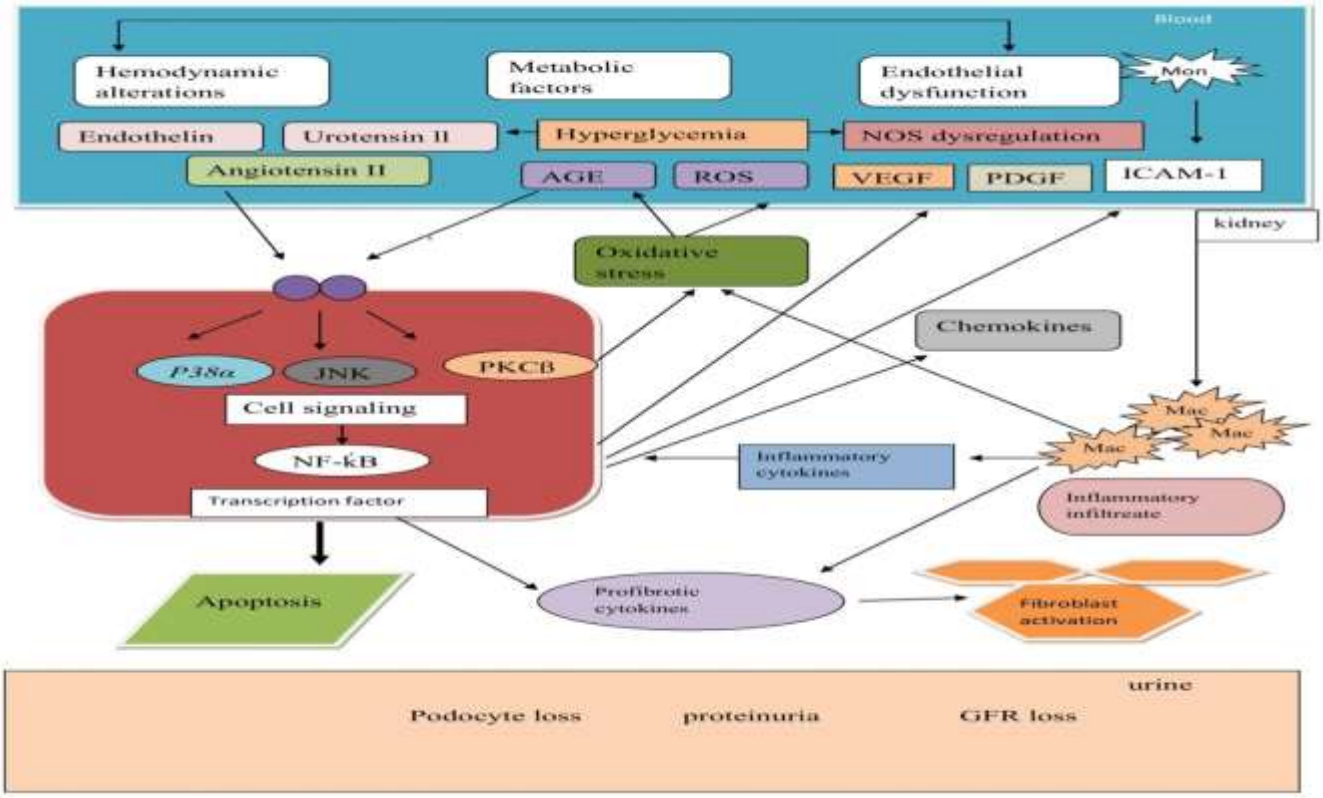

Figure 1 :- Overview of the pathological pathway in diabetic nephropathy

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

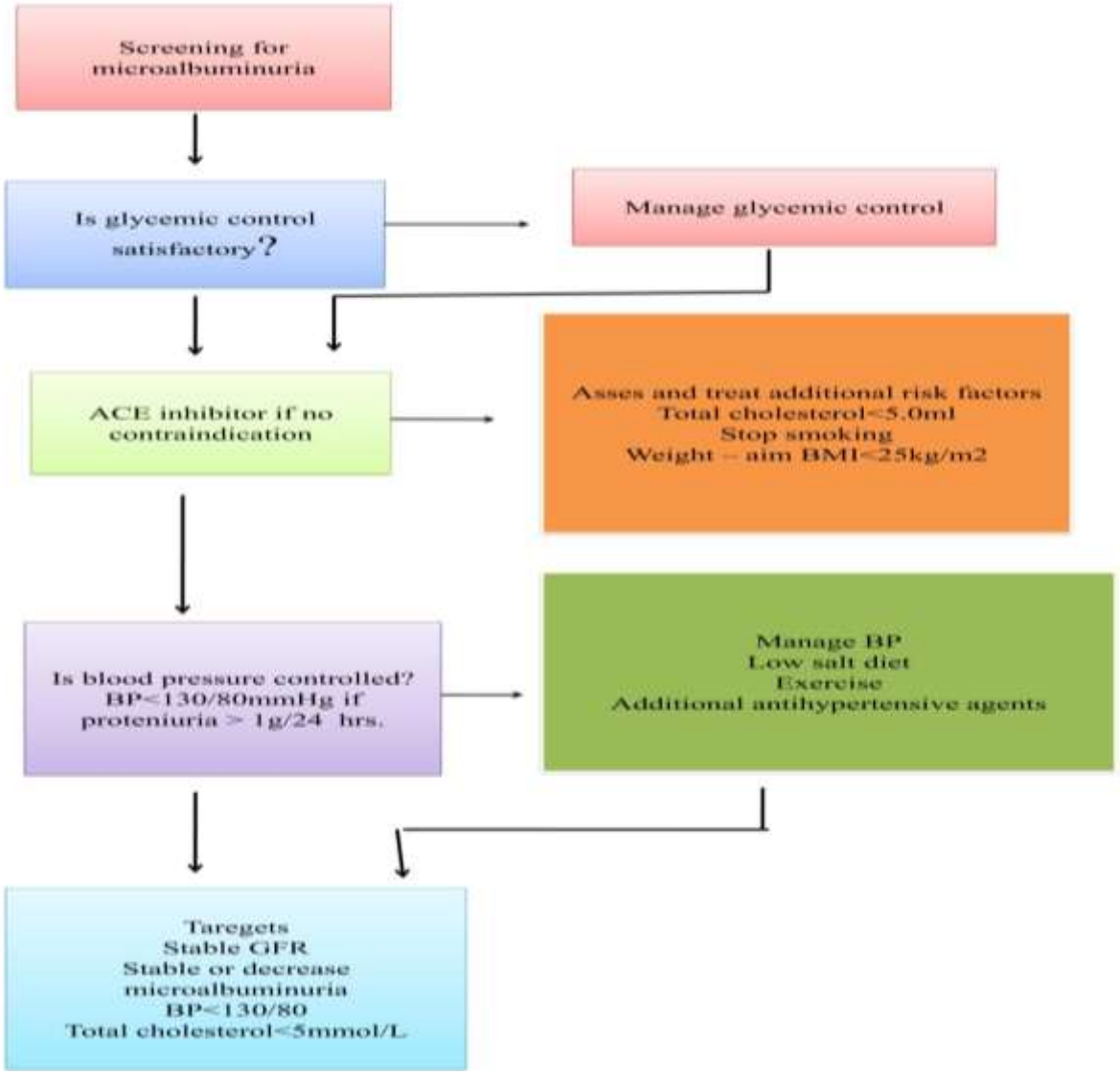

Figure 2:- Prevention and treatment of Diabetic Nephropathy

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

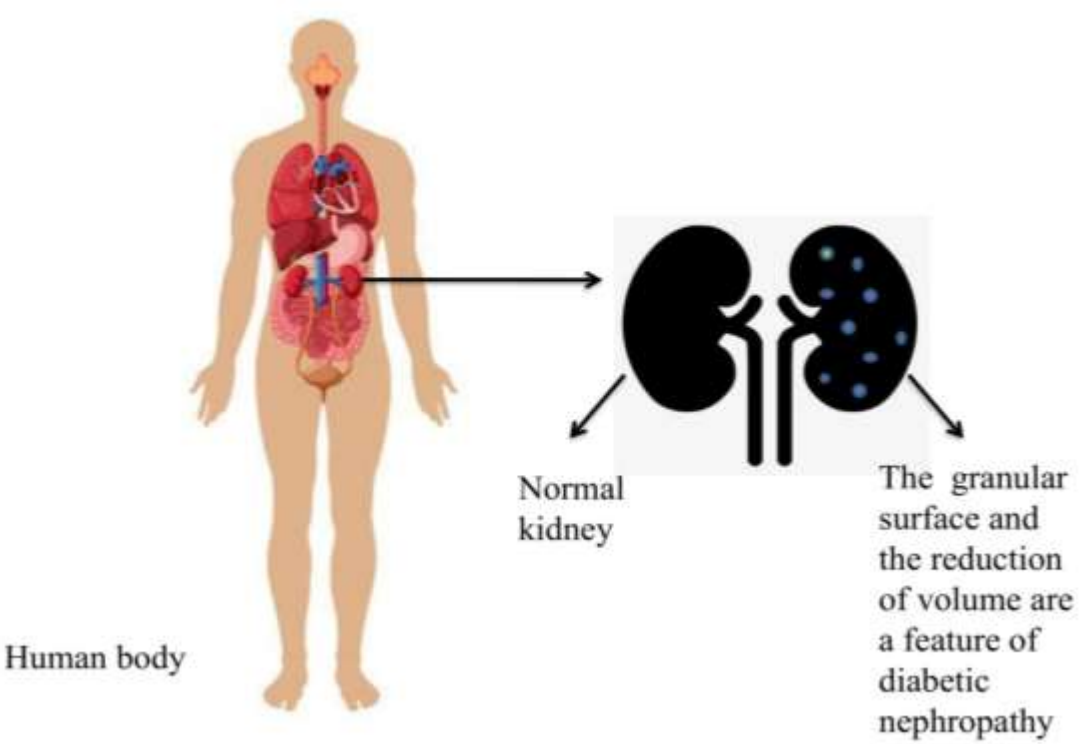

Figure 3:- Diabetic nephropathy

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

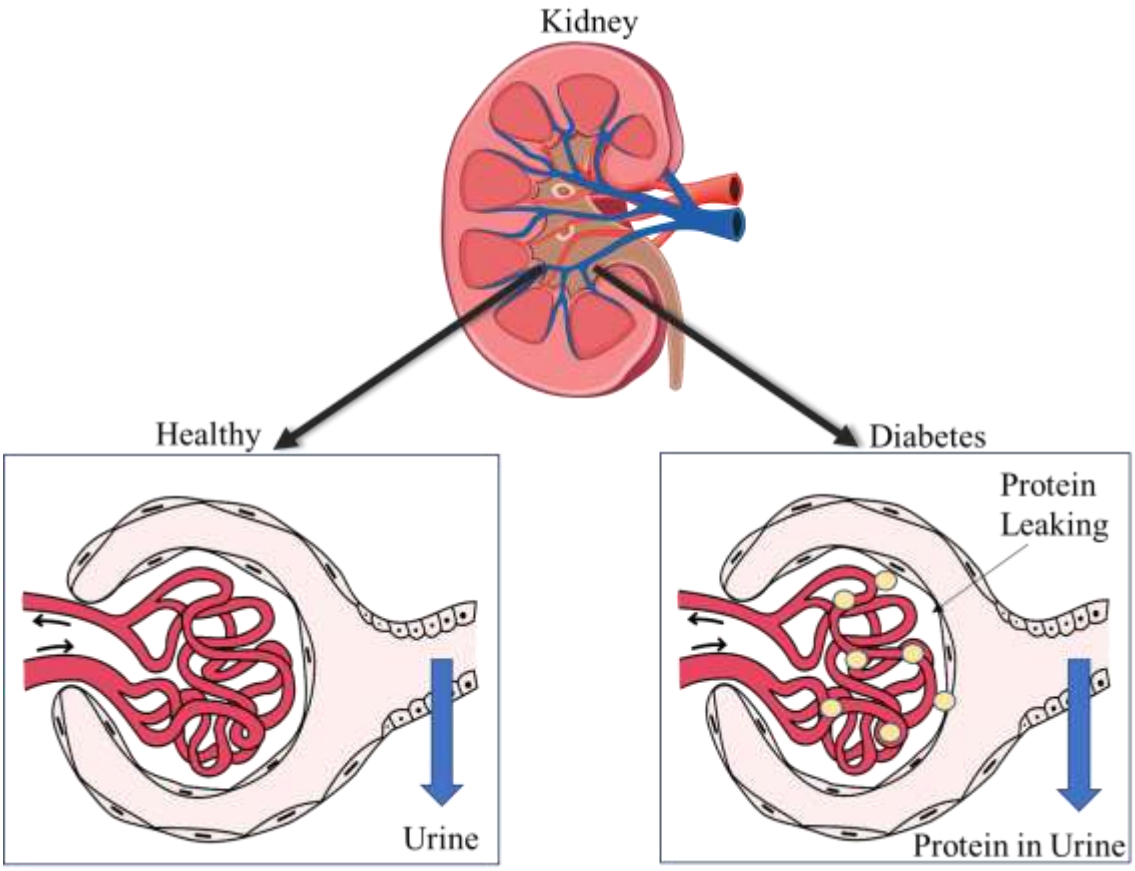

Figure 4:- Comparison between healthy and diseased kidney.

ISSN PRINT 2319 1775 Online 2320 7876

Table 2:- Review of drugs for DKD Treatment

Categories	Drugs	Studies	Outcomes/Status
Newly Approved Drugs			
SGLT2 inhibitor	Empagliflozin	NCT01392560 (clinicaltrials.gov) Wanner et al. 2016	Attenuaterenal hyperfiltration in subjects with type 1diabetes Slower progression of kidney disease
	Canagliflozin	Perkovic et al. 2019 Heerspink et al. 2017	Significantly lower risk of kidney failure Slower the progression of renal disease over 2 years in type 2 diabetes
	Dapagliflozin	Dekkers et al. , 2018 NCT02413398 (clinicaltrials.gov)	6 weeks of dapagliflozin decrease albuminuria and eGFR decrease from baseline in eGFR is greater with dapagliflozin than placebo at week 24 but eGFR return to baseline levels at week 27
Promising drugs in phase III clinical trials			
GLP-1 analog	Liraglutide	Marso et al. 2016 Mann et al. 2017	Lower rate of new onset of persistent macroalbuminuria and progression of DKD
	Semaglutide	Marso et al.2016	Lower rates of new or deteriorating nephropathy

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

Endothelin-1 receptor A antagonist	Avosentan	Mann et al. 2010	Reduce urinary albumin excretion Terminated early because of excessive cardiovascular events
	Atrasentan	de Zeeuw et al. 2014	Had a proteinuria-lowering effect Terminated early due to the recruitment issue
MRA	Apararenone (MT-3995)	NCT02676401 (clinicaltrials.gov)	Ongoing in Japan
	Esaxerenone	Kolkhof et al. 2017	In phase II and III randomized clinical trial
	Finerenone	Pitt et al. 2013 Bakris et al. 2015 NCT02540993 (clinicaltrials.gov) NCT02545049 (clinicaltrials.gov)	Reduce albuminuria Reduce albuminuria ina dose-dependent manner Ongoing Ongoing Ongoing
Antifibrotic therapy	Pirfenidone	Sharma et al. 2011 NCT02689778 (clinicaltrials.gov)	Have a mean increase of eGFR after 1 year of therapy in 1,200 mg/d Ongoing
	Pentoxifylline	Navarro-Gonzalez et al.2015 NCT03625648 NCT03664414 (clinicaltrials.gov)	Reduce albuminuria, slow progression of renal disease in patients with type 2 diabetes and stages 3-4 CKD Ongoing Ongoing

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

Potential drugs required further validations			
Anti-AGE drugs	Pyridoxamine	Williams et al. 2007	Not provide a significant renal protection in DKD patients
JAK-STAT inhibitor	Baricitinib	Tuttle et al. 2018	A phase II clinical trial showed a reduction of proteinuria
Nrf2 activator	Bardoxolone methyl	Pergola et al. 2011 de Zeeuw et al. 2013	Have no influence of albuminuria Increase the GFR in patients with type 2DM Phase III clinical study was terminated early because of more cardiovascular events
Nox1/4 inhibitor	GKT137831 APX-115	Gorin et al.2015 Cha et al.2017	A beneficial effect in murine models of DN A renal protective effect in an experimental animal model of diabetes
Inhibiton of chemokines cytokines	NOX-E36	Boels et al.2017 Menne et al.2017	A reduction in albuminuria in mouse models A phase II clinical trial demonstrated a reduced albuminuria in patients with T2DM and DN

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, Iss 03, 2022

Table 1:-Strategies and goals for reno and cardioprotection in patient with diabetic nephropathy

Intervention	**Micro-albuminuric**	**Macro-albuminuric**
ACE inhibitor and/or ARB and l owprotein diet (0.6– 0.8 g kg wt/day	Reduction of albuminuria or reversio n to normoalbuminuria GFR stabilization	Proteinuria as low as possi ble or 0.5 g/24- h and GFR decline 2 ml/ min year
Antihypertensive Agents	Blood pressure 130/80 or 125/75 mmHg†	
Strict glycemic control	A1c 7%	
Statins	LDL cholesterol 100 mg/dl‡	
Acetyl salicylic acid	Thrombosis prevention	
Smoking cessation	Prevention of atherosclerosis progression	