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Diabetic Nephropathy: A Review on Clinical Characteristics and Treatment Strategy with Allopathic and Herbal Medicine Systems

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ABSTRACT: Nearly 50% diabetic patients experience diabetic nephropathy, which is a key contributor to ESKD. Hemodialysis or a renal transplantation is the only options for treating ESKD, which also raises the danger of myocardial morbidity besides death. Evidence of DKD, which progresses from microalbuminuria to overt nephropathy or macroalbuminuria to ESRF, will appear in 20–30% of all diabetic individuals. Thickened glomerular basement membranes (GBM), little mesangial enlargement, and hyaline arteriolar accumulation make up the first lesions. The mesangial matrix eventually increases noticeably as a result of mesangiolysis and ferocious mesangial repair. The term "diabetic kidney disease" (DKD) refers to extensive circumstances in which a person has diabetes with either albuminuria or diminished renal function. Upgraded glycation final products with receptors are examples of glucose-dependent pathways involved in metabolic processes. Numerous hormones acting on blood vessels, such as those found in RAAS, are among the hemodynamic variables. It is thought that a common distinct and signaling pathway, (nuclear factor kappa-light-chain-enhancer of activated B cells and proteinkinase C) with related ROS initiation, interacts with these hemodynamic parameters and metabolism. The cornerstone of treatment continues to be maintaining appropriate blood pressure and glucose management to stop the diabetic nephropathy advancement. Renoprotective medicines, which disrupt RAAS, are found to be very helpful in the management of hypertensive and normotensive Type-1 and Type-2 diabetic individuals.

KEYWORDS: Diabetic nephropathy, RAAS, ESKD, ACE Inhibitors, DPP-4 inhibitors, SGLT-2 inhibitors.

I. INTRODUCTION

The symptoms of Diabetic nephropathy (DN) can be identified by a steady deterioration in renal capacity and chronic albuminuria. "DN" denotes the proximity of a distinctive pattern of nephritic disorder, which affects 20–50% of diabetics. 28% of patients undergoing renal replacement treatment (RRT) for ESKD, since it is commonest root of illness in a larger civilization. DN is associated with an increase in myocardial morbidness and destruction plus arterial hypertension in people with T1DM & T2DM [1]. Well-proven tactics, such RAAS have allowed for notable patient outcomes in the treatment of DN during the past 40 years [2]. Individuals acquire chronic kidney disease (CKD) at significantly different rates, and regression of albuminuria is common. The use of recently developed medications, such as SGLT2 inhibitors, aids in the improvement of disease state [3]. DKD describes preserving albuminuria or eGFR decline originating diabetes-related renal pathology. Regarding albuminuria, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD will be followed. The KDIGO guidelines suggest three classes to indicate the disease intensity and are mentioned in Table-1.

II. EPIDEMIOLOGY

More than half of people with type 2 diabetes and a third of people with type 1 diabetes will eventually develop diabetic kidney damage. One of the most common, difficult and costly long-term consequences of diabetes [4]. Increased urinary albumin excretion is observed in between 30-50% of people with type 2 diabetes, and in approximately 20% of people, the eGFR is less than 60 ml/min/1.73 m2. After a median follow-up of 15 years, the UK Prospective Diabetes Study found that 28% of patients had albuminuria and an eGFR < 60 ml/min/1.73 m2. If T2DM manifests between the ages of 15 and 24, the lifetime risk of significant albuminuria is around 100%. In T1DM,

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albuminuria is usually observed at a yearly incidence of 2% to 3%, but in T2DM, it is approximately 8%. Low eGFR happens between 2% and 4% of the time, regardless of the type of diabetes. It is challenging to pinpoint the precise proportion of patients with diabetes-related CKD because people with diabetes may also have other causes of the disease and kidney biopsies are rarely performed to confirm the diagnosis. Acute kidney injury (AKI), glomerular atherosclerosis, obesity, dyslipidemia, hypertension, and age-related kidney loss are among other common causes of chronic kidney disease (CKD), especially in people with type 2 diabetes. Patients with type 2 diabetes are younger and healthier at diagnosis and have fewer comorbidities than patients with T2DM, resulting in a lower prevalence of CKD. It is likely that the diverse etiology of CKD in T2DM patients is less representative of DKD than is CKD in T1DM individuals [5].

III. RISK FACTORS

The three primary modifiable hazards associated with DN patients are dyslipidemia, hypertension, and glycemic control. The risk variables that cannot be changed are age, race, and genetic makeup. Patients with a family history of DN are more susceptible to developing it. The racial groups most at risk are male Pima Indians, African Americans, Mexican Americans, and Mexican Americans. ACE, ALR2, APOC1, APOE, EPO, eNOS, HSPG2, VEGF, FRMD3, CARS, UNC13B, CPVL/CHN2, and GREM1 are among the genes linked to DN [6].

				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
Green: Low Risk (if no other markers of kidney disease, no CKD)
Yellow: Moderately Increased Risk
Orange: High Risk
Red: Very High Risk
Deep Red: Highest Risk

Figure 1: Diabetic Nephropathy Guidelines

IV. CLINICAL PRESENTATION OF DIABETIC NEPHROPATHY

DN is characterized by stubborn albuminuria (type A3) and concomitant retinopathy. Diabetic glomerulopathy is undoubtedly evident in T1D when these features are present [7]. It is rare for T1D patients to develop DN within the first decade of diagnosis.; nevertheless, between 10 and 20 years after diagnosis, DN frequency increases by about 3%

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year. 15% of T1DM patients have moderate albuminuria (A2), and 15% more have severe albuminuria (A3). The likelihood of developing DN is lower in people with normal renal function and normal urinary albumin excretion after 30 years of treatment for T1D, 20 years after the incidence has declined [8]. Since type 2 diabetes accounts for 90% of all diabetes cases worldwide, most DN cases are primarily caused by T2D. The epidemiology of DN in T2D is more diverse than in T1D [9]. Albuminuria is more challenging to diagnose because to the large Intraindividual differences in albumin excretion. In a group of patients with chronic kidney disease and proteinuria who provided three separate urine samples, the ACR coefficient of variation was 29.7% (in random samples) and 32.5% (in early morning samples) [10-12]. All people with diabetes should undergo an annual ACR screening test for moderate albuminuria (A2) however, follow-up testing is necessary to confirm elevated results. Physicians need to be aware of illnesses that can be misdiagnosed and leads to brief rise in albuminuria. Menstruation, heart failure, severe hypertension, an active inflammatory or systemic sickness, an active UTI, excessive physical activity during the preceding 12 to 24 hours, and severe hyperglycemia are a few of these [13-14]. Furthermore, in certain instances, non-proteinuric DN has been connected to the typical histological anomalies of diabetic glomerulopathy. It appears that proteinuria levels remain a significant predictor of risk of advancement in various types of chronic kidney disease (CKD), with non-proteinuric diabetic kidney disease (DN) having a better prognosis [15–17].

V. CLINICAL PERSPECTIVES FOR DKD DIAGNOSIS

A. SCREENING

American Diabetic Association & KDIGO imply that renal activity and albuminuria ought to be evaluated in all diabetics in evaluation and yearly afterward in T2DM; in T1DM, this may start five years following the diagnosis. ACR values, especially from samples taken in the morning, are the most effective way to diagnose albuminuria. Renal function should be evaluated by eGFR calculation depend on serum creatinine; the CKD EPI method is advised because of its exceptional performance with 60-90 mL/min/1.73 m2 of eGFR range [18–19].

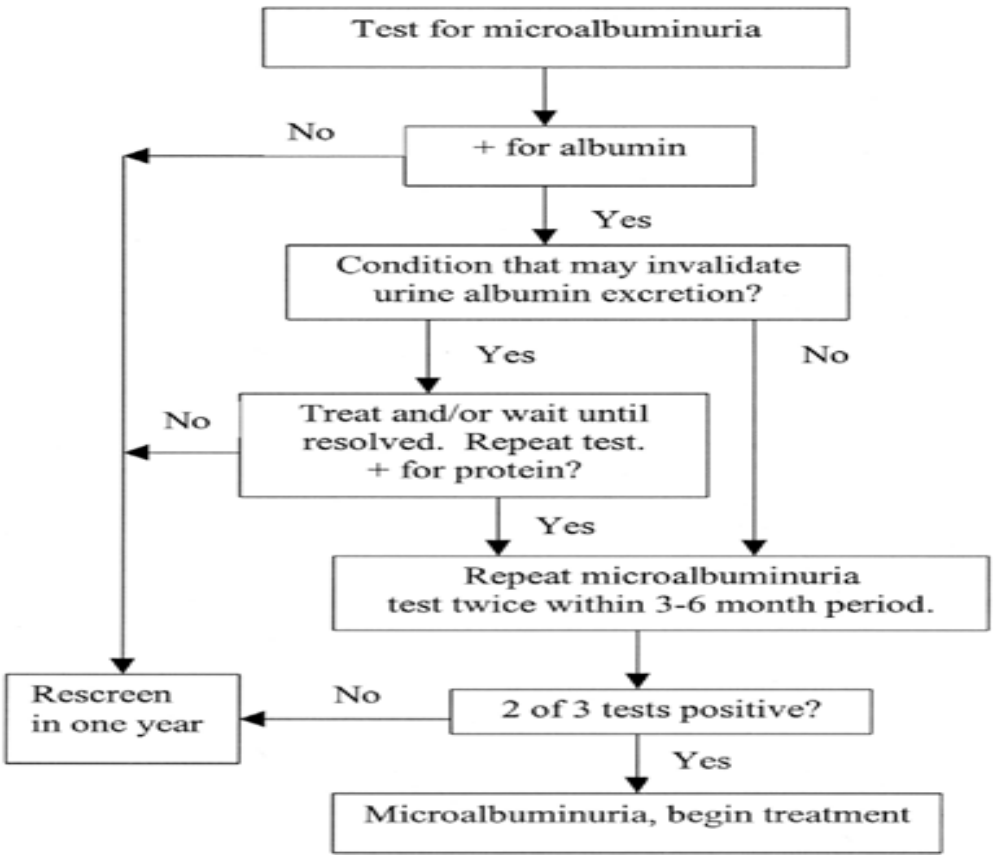

Figure 2: Screening test for Microalbumin uria (NKF KDOQI Guidelines)

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B. ABNORMALITY CONFIRMATION

An individual must have at least two raised ACR readings that are more than 3 months apart before they are regarded to have increased albuminuria. Frequent testing within three to six months must confirm any observed drop in eGFR or rise in albuminuria. Two eGFR readings that are at least ninety days apart and fewer than 60 mL/min/1.73 m^2 is required to diagnose CKD.

C. FEATURES INDICATING ALTERNATIVE CKD FORM

Albuminuria that develops suddenly or an eGFR drop that is fast (>5 mL/min/year) are not signs of DN. Finding earlier cases for AKI, are continuously presumed to be connected to the outbreak & course of CKD, will be made easier with the use of serial eGFR patterns [20–22].

VI. PATHOPHYSIOLOGY

There are several pathophysiological mechanisms behind the creation of the DN. Hyperglycemia is the primary cause of both structural and functional abnormalities, including microalbuminuria, glomerular hyperfiltration, and glomerular and tubular epithelial hypertrophy. After these modifications, thicker glomerular basement membranes grow, mesangial matrix accumulates, overt proteinuria occurs, and ultimately glomerulosclerosis and ESRD develops.

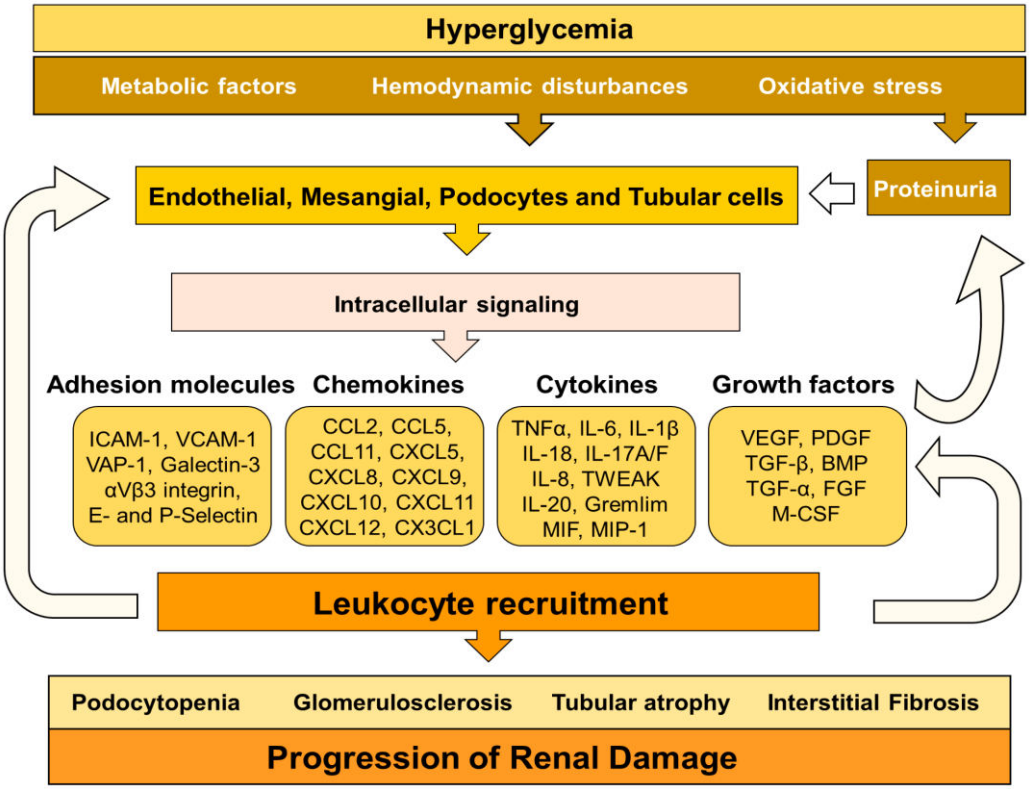

Figure 3: Mediators & Pathways involved in pathophysiology of DN

A. HAEMODYNAMIC PATHWAY

Very early in the development of DN, there are glomerular hemodynamic alterations that include hyperfiltration and hyperperfusion damage. More so on the afferent side, reduction in afferent and efferent arteriolar resistance results in higher glomerular capillary pressure, improving the trans-capillary hydraulic pressure gradient and increases glomerular plasma flow [23-24]. Increased mesangial cell matrix formation, rigidness of renal basement membrane, and increased intraglomerular fluid pressure are the alterations that cause glomerulosclerosis [25-27]. The effects of ANG-II on renal cells' hemodynamics, trophic responses, inflammatory responses, and fibrinogenesis are stimulated by hyperglycemia [28-29]. Vascular endothelial growth factors (VEGF), as well as cytokines like transforming growth factor-beta (TGF-), are the agents that

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trigger hyperfiltration damage.15 TGF- is credited with playing a crucial part in diabetic vascular dysregulation. The technique involves boosting arginine resynthesis and endothelial NO synthase (eNOS) mRNA expression to produce more NO [30-31].

B. PATHOLOGICAL CHANGES

Diabetes mellitus results in glomerulosclerosis, vascular conditions, and alterations to the tubulointerstitium with tubular atrophy and interstitial fibrosis, among other renal compartment injuries [32-36]. Expansion of the mesangial region is a result of an increase in extracellular matrix. Due to the impact of hyperglycemia, mesangial cell proliferation enters the G1 phase of the cell cycle via P 27Kip1. The mediator of G1-phase arrest, P 27Kip 1, is likewise enhanced by ANG-II. Increased glucose-mediated mesangial damage due to ANG-II blockade [37]. The first year following the initiation of T1DM is when glomerular basement membrane (GBM) thickening begins, and it continues slowly for many years. Collagen type IV deposition increases, although heparin sulfate expression and the degree of sulfation both decline. The GBM comprises chains 3, 4, and 5 of type IV collagen, as opposed to the mesangial matrix, which mostly expresses chains 1 and 2 [38-39]. GBM is immediately covered by glomerular epithelial cells (podocytes). Studies on humans demonstrate that proteinuria is associated with a decline in the number of podocytes throughout time. Damage to podocytes happens immediately before glomerulosclerosis and tubulointerstitial damage appear [40].

C. CYTOKINES AND GROWTH FACTORS

Growth factors, cytokines, chemokines, and vasoactive substances have all been linked to altered DN structure. One of the most popular and well-researched growth factors in DN is insulin-like growth factors (IGFs). Hyperglycemia induces an early and transient rise in renal IGF-I protein [41-48].

D. PYLOL PATHWAY

More glucose enters the polyol pathway as a result of an enhanced absorption of glucose by the cell. The pylol route involves the conversion of glucose to sorbitol by aldose reductase and subsequently to fructose by sorbitol dehydrogenase. In order to convert glucose to sorbitol, NADPH-depleting cells are needed. A precursor of AGEs is the intermediate threedeoxyglucone [49-53].

E. PROTEIN KINASE PATHWAY

Mechanisms of DN, including a rise in TGF-54, have been related to an enhanced flow of glucose through the hexosamine pathway. In this process, glycolysis-derived fructose-6-phosphate is changed into glucosamine-6-phosphate. N-acetylglucosamine promotes TGF- transcription by glycosylating the transcription factor Sp1. Upstream stimulatory factors (USFs), which transactivate the TGF-1 promoter, are expressed more often in response to an increase in flux through the hexosamine pathway. Diarylglycerol (DAG), which is produced from dihydroxyacetone phosphate, is likewise increased by intracellular glucose buildup. Increased DAG molecules trigger isoforms of PKC, which then cause reactive oxygen species (ROS) to stimulate MAPKs [54].

F. METABOLIC PATHWAY

The mesangial cell matrix is produced, mesangial cells expand, mesangial cells apoptose, and mesangial cells undergo structural changes as a result of the activation of multiple metabolic pathways by the glucose transporter-1 (GLUT-1) protein.40 Extracellular glucose transporters (GLUT-4) that are insulin-sensitive are expressed by mesangial cells. Advanced glycosylation end products (AGE) are produced by non-enzymatic glycosylation. Protein kinase C (PKC) is activated, the polyol pathway is accelerated, and VEGF, TGF-, IL-1, IL-6, IL-18, and tumor necrosis factor alpha (TNF-) are all activated as a result.

G. OXIDATIVE STRESS

The increased production of ROS stimulates a number of metabolic processes, including TGF-, AGE formation, PKC pathways, and ANG-II. Hyperglycemia causes an increase in the overproduction of reactive oxygen species (ROS) and oxidative stress in diabetes. Peroxidation of cell membrane lipids, protein oxidation, renal vasoconstriction, and DNA damage are all brought on by ROS.

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H. ADVANCED GLYCATION END PRODUCTS

Long-term hyperglycemia results from the excess glucose combining with free amino acids or tissue proteins, which causes the DN to develop, first creating reversible early glycosylation products and then irreversible AGE. Because of the rise in AGEs, the glomerular epithelial cells' matrix proteins accumulate, collagenase activity declines, and the tight connection between the cells becomes defective [55].

I. TRANSFORMING GROWTH FACTORS- B REFERENCES CHANGES

Transformational growth factor results in nephro hypertrophy and the enlargement of mesangial matrix in DN. In the renal cells of strptozotocin diabetic rats, high amounts of TGF-B have been detected [56-57]. Reduced production of renal bone morphogenic proteins counteracts TGF-1's profibrogenic effects 7.61 The increased collagen production and cellular enlargement caused by TGF-1 ultimately result in DN. The platelet derived beta growth factor (PDGF-) alters the glomerulus' histology [58-59].

J. NUCLEAR FACTOR-KB

Nuclear factor-B is crucial for cell viability and when it is inhibited, apoptosis results. Recent research has demonstrated that NF-B regulates the TGF-1 intracellular messenger pathway and causes the synthesis of monocyte hemoattractant amino acids (MCP) in mesangial cells in response to stretch and high glucose [60-63].

K. PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR- Γ

A pharmacological target for the insulin sensitizers known as thiazolidinediones (TZDs), PPAR- is a nuclear transcriptional factor. According to preliminary investigations, TZDs may improve microalbuminuric type-2 diabetes patients' urine albumin excretion [64-65]. In rats with streptozotocin-induced diabetes, TZDs exert antiproteinuric effects apart from their ability to make the animals more sensitive to insulin. A relative PPAR- relative deficiency in diabetes may be compensated for by PPAR- ligand in diabetics glomeruli and mesangial cells that are exposed to high sugar [66-67].

L. HYPOXIA AND DIABETIC NEPHROPATHY

Anemia quickens the pathophysiology's advancement in DN patients. Erythropoietin therapy administered early on reduces the course of renal disease. Interstitial fibrosis is made worse by renal hypoxia brought on by anemia, which stimulates TGF- and VEGF [68-71].

M. SWELLING AND DIABETIC NEPHROPATHY

On biopsy, cells of inflammation (mononuclear cell infiltration) are seen in the tubular and glomer regions [72-74]. MCP-1, RANTES, and MCP-1 expression in tubules are all increased by hyperglycemia. High hyperglycemia triggers the production of ROS and accelerates the production of AGE. Reactive oxygen species promote the production of ANG-II locally, which raises proteinuria and boosts tubular ANG-II synthesis [75-77]. AGE production is also accelerated by angiotensin II. TGF- and CTGF are two of these cytokines that directly promote the formation of extracellular matrix, whereas MCP-1 mediates inflammation. As a result of the process, fibrosis of the tissues and destruction are observed [78-79].

N. FUNCTION OF RAAS

The renin-angiotensin-aldosterone system (RAAS) is inhibited, which normalizes glomerular and systemic hypertension as well as has anti-fibrotic and anti-inflammatory effects. Proteinuria in DN is also decreased by RAAS inhibition. Chymase is an ANG-II-forming enzyme that is up-regulated in the glomeruli of people with nephropathy brought on by type-2 diabetes and is not inhibited by ACE inhibitors. The local rise in ANG-II concentrations in the podocytes is responsible for the reduction of nephrin synthesis and the increased protein ultrafiltration that results [80-84]. It has been observed that ANG-II causes tubular inflammation and fibrosis via increasing protein reabsorption in the tubules. Three weeks after streptozotocin treatment, the aldosterone antagonist spironolactone promoted collagen deposition in rats. Spiranolactone also reduced the expression of TGF-1 in this model. Eplerenone, a more recent aldosterone antagonist, lowers microalbuminuria in diabetics [85-88].

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VII. MANAGEMENT AND TREATMENT OF DIABETIC NEPHROPATHY

A. PHARMACOLOGICAL MANAGEMENT (DRUG THERAPY)

- **Metformin**
  The therapeutic benefits of metformin are produced by activating the AMPK pathway. MTOR is inhibited as a result of AMPK activation by metformin. Hyperglycemia-induced podocyte apoptosis is inhibited by metformin. Activation of AMPK and suppression of mTOR signaling together provide this effect [89].
- **ACE-1 Inhibitors**
  Patients having hypertension, diabetes and diabetic nephropathy, ACE-I and ARBs are regarded as the preferred medications. Studies have shown that ACE-I and ARBs have kidney preventive reactions in diabetic patients, assuring them preferred medications for hypertension treatment in those who have both hypertension and diabetes. ACE-1 inhibitors act by blocking ACE preventing conversion of angiotensin-I to angiotensin-II. Additionally, ACE-I prevents the breakdown of vasodilators such bradykinin [90-91]
- **GLP-1 Agonist**
  Antioxidative activities of GLP-1. Rats lacking GLP-1 receptors exhibit accelerated mesangial growth, elevated UAE, increased glomerular ROS, elevated renal NADPH oxidase, and enhanced glomerular ROS. Mammalian mesangial cells' expression of TGF-1 and CCN2 is inhibited by GLP-1 agonists [92-93].
- **Dipeptidyl Peptidase-4 Inhibitors**
  Vildagliptin had a substantial 44.6% reduction in UAE. Sitagliptin dramatically lowers UAE as compared to other oral hypoglycemic medications that also reduced HbA1c. Linagliptin stands out among DPP-4 inhibitors since it does not require dosage change with GFR reduction. Linagliptin blunts pathogenic TGF- signaling and reintroduce healthy equilibrium of VEGF receptors by directly inhibiting the DPP-4-integrin-1 interaction. Observed following switching from Sitagliptin to Alogliptin is a decreased UAE [94-98].
- **SGLT-2 Inhibitors**
  The suppression of SGLT-2 results in afferent constriction of a drop in renal blood flow, lower hyperfiltration, and lower renal damage. This enhances the distal salt supply and thus increases the formation of adenosine. An average follow-up for 3.4 years, losartan was determined to minimizing the ESRD risk in T2DM patients by 28%, whereas empagliflozin achieved a 55% reduction during an average follow-up period of 3.1 years. Empagliflozin reduced the development of overt albuminuria by 38% and the onset or severity of nephropathy by 39% and the rise in blood creatinine by 44% in the study.[100–99].
- **Statins**
  Because statins reduce the risk of atherosclerotic cardiovascular disease in people with chronic kidney disease, they are recommended for patients with DN. In addition, they have practically no effect on the development of chronic kidney disease. Compared to placebo, statins did not reduce the risk of stroke or all-cause mortality in people with chronic kidney disease and diabetes. [101–102].

B. HERBAL TREATMENT (AYURVEDIC TREATMENT)

- ***Indian Milkvetch (Astragalus membranaceus)***
  Astragalus the infusion shows a more beneficial effect in DN consumers including kidney protection and systemic state enhancement (serum albumin level). Astragalus is and its active ingredient extracts have been incorporated in clinical treatment of early DN with fulfilling safety profiles, partially for their protection against oxidative damage as a free rna.

- ***Milk thistle (Silybum marianum)***
  The effects of milk thistle (Silybum marianum) on the kidney are quite similar to those on the liver. A fascinating body of clinical data backs up the plant's use in nephrology. Significant thiol deficit was present in ESRD patients, and this condition was associated with markedly reduced T-lymphocyte activation and elevated TNF-a production. In vivo and in vitro, silymarin therapy returned the thiol status to its usual level within 72 hours. The normalizing impact on immunoregulatory deficiencies was displayed by a rise in T-cell activation and a fall in TNF-a release. Silymarin increases the production of proteins and cell renewal through RNA Polymerase-I stimulation in the renal epithelium.

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- ***Turmeric (Curcuma longa)***
  Ayurvedic and conventional Indian medicine have both employed turmeric (Curcuma longa) for managing diabetes. Because it lowers glycemia and hyperlipidemia,Its active ingredient, curcumin, has attracted interest as a potential treatment for diabetes and its consequences. Curcumin can relieve kidney damage. The substance improves the excretion of urea and creatinine and increases the level of urea nitrogen in the blood.Additionally, albuminuria and enzymuria levels drop.

- ***Breviscapine***
  Refined flavonoid extract from Erigeron breviscapus has a number of pharmacological uses, including the ability to inhibit protein kinase C and act as an anti-oxidative stress agent. By regulating B-cell lymphoma communication, breviscapine can prevent podocyte death in diabetic rat models. With a decrease in the albumin excretion rate and 24-hour urine protein values, the chemical can lower urinary protein levels, which may help explain how breviscapine protects the kidneys in individuals with DN.

- ***Ginkgo biloba extract (GbE)***
  It has been demonstrated to have a variety of pharmacological effects. In clinical studies, GbE may lower the risk of toxicity and maintain therapeutic efficacy, and it has been used to treat cardiac and neurological disorders. GbE protects human lens epithelial cells against apoptosis that is brought on by excessive glucose levels. When DN occurs in its early stages, when microalbuminuria predominates, GbE is frequently administered as a supplement to enhance albuminuria and the functioning of the kidneys [103].

- ***Cashew (Anacardium occidentale)***
  It lessens the functional and histological changes in the kidneys brought on by diabetes. Insulin (5 IU/kg) was given to albino rats in graduated dosages along with this plant's hexane extract by gavage (150 and 300 mg/kg/day). In diabetic rats, there was a considerable fall in RBS, overall protein excretion, glycosuria, and urea [104].

- ***Kalmegh (Andrographis paniculata)***
  Substantial blood glucose decrease resulted from chronically administering paniculata to diabetic mice for four weeks after alloxan induction [105].

- ***Kusmanda (Benincasa cerifera)***
  Benincasa cerifera fruits have the ability to scavenge free radicals. Benincasa cerifera inhibits lipid peroxidation, guards against a serious rise in reactive oxygen species, and shields the kidneys from decreased glutathione and super oxide dismutase depletion [106].

- ***Red Cabbage (Brassica oleracea)***
  It has anti-oxidant and antihyperglycemic effects and is mostly consumed as vegetables. Isothiocyanates and anthocyanins, which are the main components, lessen oxidative renal damage caused by diabetes. Vitamins A, B, and C are all present in its extract and all three have a preventive function against oxidative damage. Consuming red cabbage polar extract on a daily basis (1gm/kg body weight) reduces oxidative stress and the development of diabetic nephropathy [107-108].

- ***Green Tea (Camellia sinensis)***
  Green tea reduces renal damage by preventing renal oxidative stress caused by high blood pressure and diabetes [109].

- ***Dalchini (Cinnamomum zeylanicum)***
  Cinnamon oil has been investigated against alloxan (150 mg/kg I.P.) induced diabetic nephropathy to see how well it treats early stage diabetic nephropathy due to its antioxidant and anti-diabetic effects. The findings showed that more than 98% of cinnamaldehyde was present in the volatile oil from cinnamon, and that it offers dose-dependently considerable protection against kidney damage caused by alloxan.[110].

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- ***Lingzhi Mushroom (Ganoderma lucidum)***
  Ganoderma lucidum polysaccharide lowered creatinine in the serum and blood nitrogen from urea levels as well as urine albumin excretion in streptozotocin-induced diabetic mice as compared to diabetes model mice in a dose-dependent manner. It can help diabetic mice with metabolic problems and stop or slow the advancement of diabetic renal issues [111].

- ***Soyabean (Glycine max)***
  Soyabean prevents the morphological deterioration of the kidney caused by diabetes mellitus, slowing the course of diabetic nephropathy. Docosahexaenoic acid is produced when polyunsaturated fatty acids are transformed into it. Renal illness is one of several inflammatory models and disorders where increased synthesis of this complex lipid has been related to benefit. In individuals with nephritic syndrome who are non-diabetic, soyabeans have been proven to lower urine albumin excretion and total cholesterol. It includes vitamins, minerals including calcium, folic acid, and iron, as well as carbs, fat, and protein [112].

- ***Bidaria Tingens Deche (Gymnema montanum)***
  It is an indigenous plant species from India that has long been used to treat and control diabetes. The raised blood glucose, renal indicators, and lipid peroxidation markers were considerably restored by the ethanolic extract of Gymnema montanum at a dosage of 200 mg/kg body weight, and the levels of antioxidants in diabetic kidney were enhanced [113].

- ***True Indigo Leaves (Indigofera tinctoria Leaves)***
  The extract from the leaves demonstrated nephroprotective qualities by increasing renal clearance of creatinine and reducing renal total protein loss. The effects of Indigofera tinctoria leaves on the pancreas and liver were shown by investigations on the organ's to body weight ratio [114].

- ***Linseed (Linum usitatissimum)***
  In obese spontaneously hypertensive rats, dietary protein replacement with flaxseed meal has been demonstrated to lessen proteinuria and glomerular and tubulointerstitial lesions. The amount of protein consumed and glycemic management had little bearing on the decrease in proteinuria and kidney damage [115].

- ***American Ginseng (Panax quinquefolius)***
  The effects of American ginseng and heat-processed American ginseng on streptozotocin (STZ)-induced diabetes in rats showed a loss of body weight and a boost in kidney weight, dietary intake, and volume of urine, while oral ingestion of heat-processed American ginseng at a dose of 100mg/kg of body weight per day for 20 days attenuated these diabetes-induced physical abnormalities. The high urine protein levels in diabetic control rats were dramatically reduced in terms of the renal function markers [116].

- ***Scented Solomons Seal (Polygonatum odoratum)***
  The ethanol extract and soluble fragments were assessed using an in vitro bovine serum albumin-glucose test and an in vivo model of kidney enhanced glycation end-product (AGE) formation in diabetic rats treated with streptozotocin. The positive control, aminoguanidine, was shown to be less efficient at inhibiting AGE development than isolates. The findings suggest that this plant has potential as a unique natural remedy for treating diabetes problems [117].

- ***Red Sandal Wood (Pterocarpus santalinus)***
  Pterocarpus santalinus treatment enhanced glucose tolerance tests and markedly lowered blood sugar. There was a decrease in HbA1c following consistent long-term blood glucose control. The red sandalwood extract further demonstrated its antioxidant benefits by lowering malondialdehyde (MDA) levels in brain, liver and muscle tissues. Furthermore, as shown by thiobarbituric acid reactive substance (TBARS), the extract resulted in lowering the lipid peroxidase production and rise in antioxidants. The use of the aqueous extract of P. santalinus enhanced the masses of the brain, liver, and heart as well as lipid peroxidation and glycemia [118].

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- ***Rhubarb (Rheum officinal)***
  Affected rats brought on by partial nephrectomy and streptozotocin injection received rhubarb extract orally. Elevated blood sugar levels were seen as a result. Additionally, it was noted that hyperlipidemia had improved and that urine urea nitrogen and creatinine excretion had speeded up [119].

- ***Grape Vine (Vitis vinifera)***
  Rats given STZ injections saw substantial drops in body weight, polyuria, proteinuria, and blood glucose levels. Rats with diabetes showed renal impairment, as shown by decreased urea and creatinine clearance, proteinuria, and an important oxidative stress elevation, shown by lipid peroxidation and the activity of important antioxidant enzymes. In diabetic rats, resveratol treatment dramatically reduced renal impairment and oxidative stress.

C. NON-PHARMACOLOGICAL MANAGEMENT includes:

- Loss of weight,
- Enhanced exercise,
- Decrease in salt consumption, and
- Giving up smoking

Other considerations should be made in addition to the measures listed above. This includes decreasing cholesterol and quitting smoking. Lipid-lowering treatment directly slows the development of DN. While some studies have shown lipid reduction assists to preserve eGFR/diminished albuminuria in CKD, it has not been convincingly proved that this will diminish glomerulosclerosis or hyperlipidaemia [120].

VIII. CONCLUSION

Diabetic kidney disease is a considerable provocation which complicates treatment of numerous diabetic patients and is the utmost origin of ESKD. DKD being there has a well fortified connection with cardiovascular events and has a vital hold on endurance. Humans vary in their disease presentation and prognosis; nonalbuminuric DKD and elevated albuminuria regression values are two examples we can see now a days in the society. However, hypertension along with elevated albuminurea levels continues to be a significant predictor of patients at higher risk of disease progression. The deliberate kidney disease management plan for DKD includes blood pressure reduction, RAAS inhibition, and glucose control. This strategy also combines with cardiovascular risk reduction. Combining all of the aforementioned therapies in an efficient manner lowers the chances of cardiovascular events, mortality, and other microvascular complications as well as the development of DKD. Clinical recommendations have been made by several worldwide bodies in clinical practice; these should be customized for every single patient.

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