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REVIEW ARTICLE

A Review on Diabetic Nephropathy

D. Saikoteswar Sarma*, Dr. M. Alagusundaram, N. Viharika, SK. Asha

Jagan's College of Pharmacy, Jangala Kandriga (V), Muthukuru (M), Nellore, Andhra Pradesh, India.

ABSTRACT

Diabetic Nephropathy is defined as a persistent albuminuria and more commonly diagnosed by a urinary excretion of more than 300 mg/24 hour. It develops in around one third of patients with diabetes, with the Asia, Pacific region being the most severely affected. It is one of the causes of renal failure and end-stage renal disease. Factors like smoking and diastolic blood pressure have been found to be associated with microalbuminuria. Oxidative stress may play a key role in the pathogenesis of diabetic nephropathy. Role of traditional herbs and medicines in the treatment of diabetic nephropathy needs attention especially in India, where certain fruits and herbs are thought to have positive effects on health. Certain herbs such as Anacardiumoccidentale, Benincasacerifera, Brassica oleracea and Terminaliachebula etc. have shown positive effects in diabetic nephropathy. Therefore, there has been great interest in studying the inherent, renal protective role of the different antihyperglycemic agents. This review will shed light on the pathophysiology, screening, and diagnosis of diabetic kidney disease. It will also discuss the treatment and prevention of diabetic nephropathy, with a specific focus on comparing the mechanisms, safety profiles, and efficacy of the different antihyperglycemic medications.

Keywords: Diabetic nephropathy, microalbuminuria, pathogenesis, Herbal Medicines and their treatment.

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Corresponding Author
D. Saikoteswar Sarma
Jagan's College of Pharmacy,
Jangala Kandriga (V), Muthukuru (M),
Nellore, Andhra Pradesh, India.
MS-ID: JPBMAL3556

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CONTENTS

1. Introduction

Diabetes mellitus (DM) is the most frequent cause of chronic kidney failure in both developed and developing countries [1]. Diabetic nephropathy, also known as Kimmelstiel Wilson syndrome or nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis, is a clinical syndrome characterized by albuminuria (>300

mg/day or >200 mcg/min) confirmed on at least two occasions 3-6 months apart, permanent and irreversible decrease in glomerular filtration rate (GFR), and arterial hypertension[2].

The syndrome was first described by a British physician Clifford Wilson (1906-1997) and American physician Paul Kimmelstiel (1900-1970) in 1936. Diabetic nephropathy is a chronic complication of both type 1 DM (beta cell destruction – absolute lack of insulin) and type 2 DM (insulin resistance and/or decreased secretion of insulin[3]. There are five stages in the development of diabetic nephropathy.

STAGE 1: Stage of Hyper fusion and Hyperfiltration

In this stage, GFR is either normal or increased. Stage I lasts approximately five years from the onset of the disease. The size of the kidneys is increased by approximately 20% and renal plasma flow is increased by 10%-15%, while albuminuria and blood pressure remain within the normal range.

STAGE 2: Silent Stage

This stage starts approximately two years after the onset of the disease and is characterized by kidney damage with basement membrane thickening and mesangial proliferation. There are still no clinical signs of the disease. GFR returns to normal values. Many patients remain in this stage until the end of their life.

STAGE 3: Microalbuminuria Stage

The microalbuminuria stage (albumin 30-300 mg/dU) or initial nephropathy. This is the first clinically detectable sign of glomerular damage. It usually occurs five to ten years after the onset of the disease. Blood pressure may be increased or normal. Approximately 40% of patients reach this stage.

STAGE 4: Overt Diabetic Nephropathy

Chronic kidney failure (CKF) is the irreversible stage. Proteinuria develops (albumin > 300 mg/dU), GFR decreases below 60 mL/min/1.73 m2, and blood pressure increases above normal values.

STAGE 5: End Stage Renal Failure

Terminal kidney failure (TKF) (GFR < 15 mL/min/1.73 m2). Approximately 50% of the patients with TKF require kidney replacement therapy (peritoneal dialysis, haemodialysis, kidney transplantation) [4]. In the initial stages of diabetic nephropathy, increased kidney size and changed Doppler indicators may be the early morphological signs of renal damage, while proteinuria and GFR are the best indicators of the degree of the damage[5].

Epidemiology

In patients with type 2 DM, the prevalence varies between 5% and 20% on average. Diabetic nephropathy is more frequent in African Americans, Asian Americans, and Native Americans. The occurrence of diabetic nephropathy in Pima Indians is very interesting, indeed. According to a study published in 1990, around 50% of Pima Indians with type 2 DM developed nephropathy after 20 years of the disease, and 15% of them were already in the terminal stage of kidney failure[7]. In the United States, the occurrence of diabetic nephropathy in patients beginning kidney replacement therapy doubled in the 1991-2001 period. Fortunately, the trend has been decreasing, most likely due to the better prevention and earlier diagnosis and treatment of DM.

2. Pathology

The severity of glomerular damage is proportional to GFR value, DM duration, and blood glucose regulation [8]. The main pathohystological changes in diabetic nephropathy include the thickening of the glomerular basement membrane (GBM), mesangial expansion, nodular sclerosis – Kimmelstiel-Wilson change, diffuse glomerular sclerosis, tubular interstitial fibrosis, and arteriosclerosis and hyalinosis of kidney blood vessels (Figures 1-3)[9].

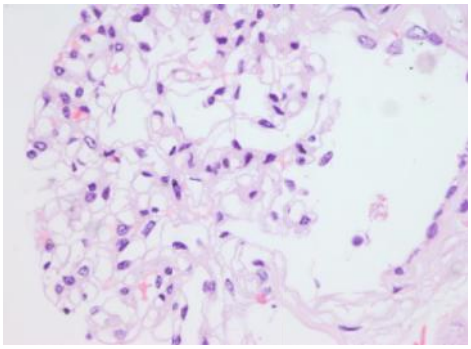

Figure 1: Photography shows delicate structure of normal glomerulus with thin glomerular basement membrane and unrecognizable mesangium. HE stain, X.

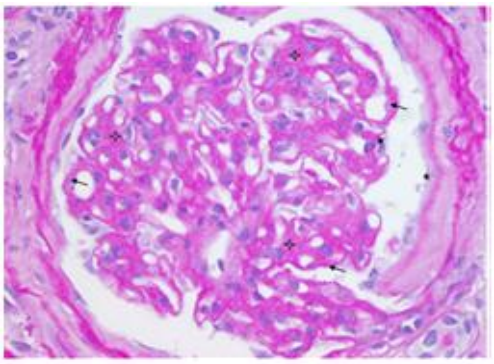

Figure 2: Class II b diabetic nephropathy. Diffuse expansion of mesangium (star) and diffuse thickening of the glomerular basement membrane (arrow). PAS stain, X400.

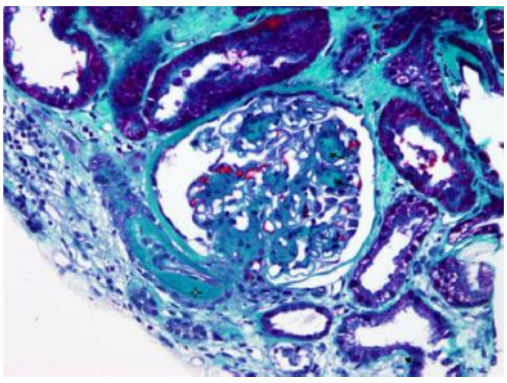

Figure 3.Class III diabetic nephropathy.Sclerotic nodule (Kimmelstiel–Wilson) in nodular diabetic nephropathy

(arrow). Afferent and efferent arteriolar hyalinosis is characteristic for diabetic nephropathy (star). The arrow in the lower right corner indicates thickening of the tubular basement membrane. Mallory stain, X 100.

Among other pathological lesions, we should mention hyalinosis, the so-called fibrin cap, which consists of accumulated hyaline material between endothelial cells and glomerular basement membrane (Figure 4). Fibrin cap is present in approximately 60% of the cases and is believed to be associated with chronic ischemia[10].

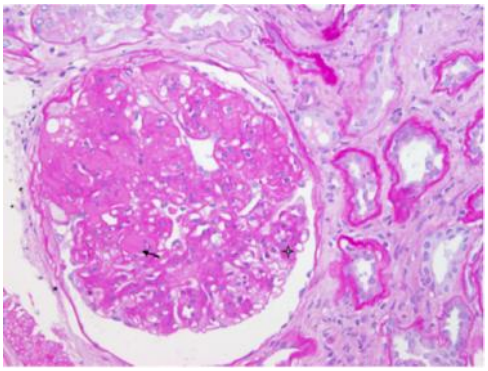

Figure 4: Fibrin cap (arrow) is characteristic for diabetic nephropathy. It is caused by insulation and accumulation of glycosilated plasma proteins between the glomerular endothelium and the glomerular basement membrane. Diffuse expansion of mesangium is designated by four point star. PAS stain, X 200.

There is a significant overlap between the described changes in patients in different stages of albuminuria, independent of their type of DM8. The expansion of mesangium and glomerular sclerosis do not occur simultaneously indicates their different pathogenesis within diabetic nephropathy.

Pathogenesis

Pathogenesis of diabetic nephropathy is very complicated and results from the interaction of hemodynamic and metabolic factors.

Glomerular hyper filtration

Increased intraglomerular pressure and hyper filtration are early changes in the development of diabetic nephropathy as many as 40% newly found DM cases had increased glomerular filtration[11].

Hormones

The infusion of somatostatin analogues (octreotide) partly led to the decrease in hyper filtration and kidney size, glycemic regulation, plasma glucagon, and growth hormone levels remained unchanged.

The addition of angiotensin-converting enzyme inhibitor (ACEI) resulted in a decrease in blood pressure in both men and women, but GFR decreased only in women.

Sorbitol

The enzyme aldose reductase converts intracellular glucose to sorbitol, which remains in the cell. Although research in patients with type 1 DM and known hyper filtration has shown that the infusion of aldose reductase inhibitor (tolrestat) decreases GFR to normal values, a possible therapeutic use of this agent should be confirmed in more studies.

Increased sodium reabsorption and tubuloglomerular feedback

Increased renal tubular sodium reabsorption due to increased sodium-glucose co transport leads to the increase in extracellular fluid volume, which then increases GFR. This causes the afferent arteriole dilation and leads to an increase in the GFR. In this case, the renal hyper filtration response to the imbalance caused by increased sodium reabsorption in the proximal tubules consequently increases fluid retention.

Poor control of metabolic factors

Glycation end-products

Part of the excess glucose in chronic hyperglycemia binds to free amino acids of circulating or tissue proteins. This non-enzymatic process produces reversible early glycation products, and later, irreversible advanced glycation end products (AGEs), which accumulate in the tissues and contribute to the development of microvascular complications of DM.

Hyperglycemia

The evidence from in vitro studies shows that hyperglycemia has a direct effect on mesangial cell proliferation, matrix expansion, glycosylation of glomerular proteins[12] .

Protein kinase C

The activation of protein kinase C (PKC) is one of the main mediators of hyperglycemia induced tissue injury. PKC activation leads to increased vascular permeability, increased synthesis of extracellular matrix components, and increased production of reactive oxygen species (ROS), which are important mediators of kidney injury[15].

Heparanase Expression

The regulation of heparanase expression plays an important role in the pathogenesis of diabetic nephropathy. The reduction in heparin sulphate on the surface of endothelial cell changes the negative charge of glycocalyx and consequently increases albumin permeability of the glomerular filtration membrane.

Reactive Oxygen Species

Increasing evidence shows the importance of reactive oxygen species (ROS) in the pathogenesis of diabetic nephropathy. ROS activate all importantpathogenetic mechanisms, such as increased production of AGEs, increased glucose entry into the polyol pathway, and PKC activation.

Prorenin

Increased serum prorenin plays a role in the development of diabetic nephropathy in children and adolescents. Prorenin binds to a specific tissue receptor, leading to the activation of the signal pathway of mitogen-activating protein kinases (MAPK), which potentiate the development of kidney damage.

Cytokines and Growth Factors

Hyperglycemia stimulates increased expression of different growth factors and activation of cytokines, which overall contributes to further kidney damage.

Nephrine Expression: Nephrine is a transmembrane protein, the main structural element in slit diaphragm and as

such, it is important for the maintenance of filtration membrane integrity. More recent studies have shown the association between the decreased expression of nephrine and albuminuria progression in the model of human diabetic nephropathy[16].

3. Signs and Symptoms

Main symptoms of diabetic nephropathy include an increase in blood pressure (hypertension) and fluid retention in the body. Other complications include arteriosclerosis of the renal artery and proteinuria. Diabetic nephropathy has no symptoms throughout its early course. They develop in late stages and may be a result of excretion of high amounts of protein in the urine or due to renal failure:

Edema: swelling, usually around the eyes in the mornings; later, general body swelling may result, such as swelling of the legs

- Foamy appearance or excessive frothing of the urine (caused by the proteinuria)
- Unintentional weight gain (from fluid accumulation)
- Anorexia (poor appetite)
- Nausea and vomiting
- Generalized itching
- Frequent hiccups
- Malaise (general ill feeling)
- Fatigue
- Headache

RISK FACTORS

There are several risk factors for the development of diabetic nephropathy. They can be divided into those that cannot be altered (genetic factors, age, and race) and those that can and must be changed (hyperglycemia, hypertension, dyslipidemia, and GFR).

Genetic Predisposition

Genetic predisposition substantially determines the occurrence and severity of diabetic nephropathy. The likeliness of diabetic nephropathy is higher in siblings and children of parents with diabetic nephropathy, independently of the type of DM[17]. There is a 14% probability for a child of the parents without proteinuria to develop clinical proteinuria, 23% probabilities in cases where one of the parents has proteinuria, and 46% probability in case that both parents have proteinuria.

Race

The incidence of diabetic nephropathy is increased in African American, Mexican American, and Asian Indian ethnic groups. Occurrence and severity of the disease are higher in Blacks American Mexicans, and especially in Pima Indians in the North West part of the United States. This observation in genetically incongruent populations suggests that socioeconomic factors, such as nutrition and poor control of glycemia, blood pressure, and body weight, play the key role.

Age

In patients with type 2 DM, age and duration of DM increase the risk for albuminuria. In the population study of 1586 Pima Indians with type 2 DM, subjects diagnosed with DM before age 20 had a higher risk of developing terminal kidney failure. The risk of terminal kidney failure in patients with type 1 DM was low if the disease was diagnosed by the age of 5.

Glomerular Filtration Rate

Increased GFR at diagnosis is a risk factor for the development of diabetic nephropathy. In approximately half of the patients with type 1 DM lasting up to five years, GFR value is approximately 25-50% above normal range. These patients have a higher risk of developing diabetic nephropathy.

Glycemic Regulation

Diabetic nephropathy often develops in patients with poor glycemic control. The degree of glycemic control is an important predictor of terminal kidney failure. The prevalence of terminal kidney failure was 36% in patients with the worst glycemic control in comparison with 9% in the group with well-controlled glycaemia. It is generally accepted that the degree of glycemic control is a very important risk factor for the development diabetic nephropathy.

Increased Blood Pressure

There is a high prevalence rate of hypertension in patients with type 1 DM (40%) and type 2 DM (70%), even before albuminuria can be found. Evidence from several large clinical studies (UKPDS, ADVANCE) indicates a causal relationship between the increased arterial pressure and diabetic nephropathy.

Overweight

High body mass index (BMI) increases the risk of development of chronic kidney disease in patients with DM. Furthermore, adequate diet and reduction in body weight decrease proteinuria and improve kidney function in these patients. The role of overweight as a risk factor for diabetic nephropathy (independent of DM and glycemic control) has not been clearly confirmed.

Smoking

Although recent studies have shown the association between smoking and progression of diabetic nephropathy, did not confirm the association between smoking and decreased GFR rate in patients with DM with or without ACEI therapy[18].

Oral Contraception

The use of oral contraceptives and development of diabetic nephropathy. Each of the above-described factors increases the risk of diabetic nephropathy, but none is predictive enough for the development of diabetic nephropathy in an individual patient.

4. Screening and Diagnosis

Historically, the term “diabetic nephropathy” has been used loosely to describe the pathologic effect of diabetes on renal function. However, there are key definitions and stages of this process to assist with diagnosis and management. DKD is the finding of proteinuria in a person with diabetes, regardless of the presence of pathologic changes or a decreased glomerular filtration rate (GFR). Diabetic glomerulopathy on the other hand, is a term reserved for biopsy-proven renal disease caused by diabetes. Measuring serum albumin on spot urine tests is

the first step in screening and diagnosis of diabetic nephropathy as recommended by most professional medical societies concerned with diabetes and kidney disease[20].

Albuminuria remains the only biomarker acceptable for diagnostic purposes, although some growth factors are expected to replace albuminuria in future. It is known that values of TGF beta, vascular endothelial growth factor (VEGF), and CTGF are increased in the plasma and urine of patients with diabetic nephropathy.

Treatment

Diabetic nephropathy is treated with medicines that lower blood pressure and protect the kidneys. If a person is taking other medicines, especially non-steroidal anti-inflammatory drugs (NSAIDS), the medicines that damage the kidneys, should be avoided. It is also important to keep the blood sugar as close to normal as possible.

Conventional medicines that are used to treat diabetic nephropathy include[25]:

Angiotensin

Converting Enzyme Inhibition:

These include captopril, lisinopril, ramipril and enalapril. They have been shown to protect kidney function in people with Type I diabetes, even in those who do not have high blood pressure. They can lower the amount of protein being lost in the urine.

Angiotensin II Receptor Blockers (ARBs):

They include candesartan, irbesartan, losartan, and telmisartan. The combination of these medicines may provide greater protection to kidneys than either medicine alone.

Calcium Channel Blockers (CCBs):

These lower blood pressures by making it easier for blood to flow through the vessels. Examples include diltiazem, verapamil, amlodipine and nifedipine**.**

Diuretics:

Medicines such as chlorthalidone, hydrochlorothiazide or spironolactone help lower blood pressure by removing sodium and water from the body.

Beta-blockers:

These lower blood pressure by slowing down heart beat and reducing the amount of blood pumped with each heart beat. Examples include atenolol, carvedilol and metoprolol.

Some of the herbs reported to be effective in diabetic nephropathy are:

Anacardiumoccidentale:

It reduces diabetes induced functional and histological alterations in the kidneys. Hypoglycaemic action of this plant is seen in experimental type I diabetes. Streptozotocin induced diabetes in rats has been reported to be associated with functional and morphological changes in the kidney

Astragaluspropinquu

It improves the pathogenesis and development of diabetic nephropathy which is closely associated with the changes of plasma Endothelin I (ET-I) levels and platelet function.

Benincasacerifera

They are widely used as a vegetable in India and other tropical countries. They are also used in urinary infections, epilepsy, peptic ulcer and haemorrhages from internal organs.

Benincasacerifera

Prevents lipid peroxidation and protects the kidneys from severe increase of reactive oxygen species and depletion of superoxide dismutase and reduced glutathione.

Brassica oleracea

It has anti-oxidant and anti hyperglycaemic activity. Main constituents are the isothiocyanates and anthocyanins, reduces oxidative diabetic nephropathy.

Cinnamomumzeylanicum

The ameliorative effect of the cinnamon oil upon early stage diabetic nephropathy due to its antioxidant and anti diabetic effect has been studied against alloxan (150 mg/kg I.P) induced diabetic nephropathy.

Glycine max

Soyabean decreases the progression of diabetic nephropathy. It prevents morphological destruction of the kidney associated with diabetes mellitus.

Indigoferatinctoria

Leaves The extract from leaves improved renal creatinine clearance and reduced renal total protein loss demonstrating nephroprotective properties.

Terminaliachebula

It has anti-oxidant and free radical scavenging properties and mainly used in Ayurveda in the treatment of diabetes, asthma, sorethroat, vomiting, hiccough, diarrhoea, bleeding, piles, gout, heart and bladder diseases.

Strict Glycemic Control

The effect of strict glycemic control depends on the DM stage in which it was started and consequent normalization of glucose metabolism. Intensified insulin therapy has the following effects on the kidney:

- It partly decreases glomerular hypertrophy and hyperfiltration, both of which are important risk factors for permanent glomerular damage.
- It postpones the development of albuminuria. Intensified insulin therapy that
- Keeps glucose values within normal ranges decreases the development or progress of diabetic nephropathy.
- In some patients, the thickness of glomerular and tubular basement membranes and
- Mesangial cell number becomes normal and glomerular nodules disappear.

Strict Blood Pressure Control

Strict blood pressure control is important in the prevention of progress of diabetic nephropathy and other complications in patients with type 2 DM. The optimum lower range of systolic blood pressure is not clearly defined.

A reduction in systolic blood pressure by 10 mm Hg decreases the risk of development of diabetic complications by 12%; the risk is the lowest where systolic blood pressure values are below 120 mm Hg.

According to the current Guidelines on Arterial Hypertension Treatment, the target blood pressure in patients with DM should be <130/80 mm Hg. Antihypertensive therapy may be started even when blood pressure values are in the upper normal range.

The Role of Other Factors

Transforming growth factor beta (TGF-beta) has effects on cell hypertrophy and increased collagen synthesis. Inhibition of TGF-beta in experimental DM model

prevented the development and progression of diabetic nephropathy. Experimental studies have shown that non-dihydropyridine calcium channel blocker (diltiazem) slows down the progression of most morphological changes in diabetic nephropathy. On the other hand, diltiazem monotherapy leads to the increased tubulointerstitial fibrosis and global, but not segmental, glomerulosclerosis. This negative effect of diltiazem can be corrected by ACEI therapy.

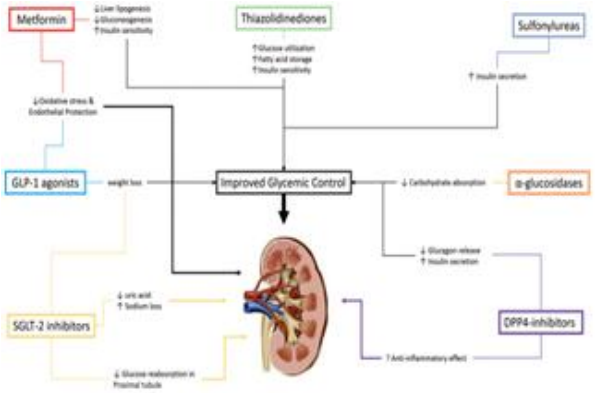

Figure 5. The different anti hyperglycaemic agents exhibit their renal protective properties through hyperglycemia-dependent and independent mechanisms. This figure attempts to map out our understanding of some of these mechanisms.

New Treatment Strategies

Current treatment has not always been effective in all patients. Therefore, new treatment options are being investigated. High doses of thiamine and its derivative benfotiamine (S-benzoyl thiamine Omonophosphate) were shown to slow down the development of microalbuminuria in animal models, most likely by decreasing the activation of PKC, protein glycation, and oxidative stress. In experimental animals treated with ALT-711, which metabolizes AGEs, a decrease in blood pressure and kidney damage was observed. PKC-beta inhibitor (ruboxistaurin) normalizes GFR, reduces or decreases albuminuria, and improves kidney function in experimental animals. Pimagedin (second generation AGE inhibitor) reduces albuminuria and GFR decrease in patients with type 1 DM and proteinuria[23].

5. Conclusion

In the last several years, we have witnessed an enormous progress made not only in our understanding of the risk factors and mechanism of the development of diabetic nephropathy, but also in the treatment possibilities aimed at preventing the progression of diabetic nephropathy. Early detection of this chronic DM complication along with the treatment of main risk factors (hyperglycemia, hypertension, and dyslipidemia) and use of renoprotective drugs (ACEI and ARB) may decrease the progression of this kidney disease. The treatment of increased blood pressure is a priority. All listed measures lead to a decrease in the overall and cardiovascular mortality in patients with DM.

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