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Review Article

DIABETIC NEPHROPATHY – GENESIS, PREVENTION AND TREATMENT

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ABSTRACT

Diabetic Nephropathy (DN) is the foremost reason of End Stage Renal Disease (ESRD) and a major cause of premature deaths amongst people with diabetes. It is one of the most common complications of diabetes mellitus (DM) and has majorly influenced patients' morbidity and mortality. About 50% of patients suffering from DM for more than 20 years develop this complication. The present review focuses on the global scenario of diabetic nephropathy and different molecular mechanisms involved in its pathogenesis i. e. increased formation of advanced glycation end products (AGEs), enhanced glucose flux into polyol and hexosamine pathways, activation of protein kinase C (PKC) and other proinflammatory transcription factors. This review also highlights the precautionary measures to be taken by people with diabetes along with the therapeutic interventions involving angiotensin converting enzyme (ACE) inhibitors, renin inhibitors, angiotensin receptor antagonists, aldosterone antagonists, protein kinase C inhibitors, mechanistic target of rapamycin (m-TOR) inhibitors, agents inhibiting plasminogen activator inhibitor-1 (PAI-1), advanced glycation end products inhibitors, anti-inflammatory agents and antioxidant agents.

Keywords: Diabetes Mellitus, Diabetic Nephropathy, End Stage Renal Disease, Advanced Glycation End Products, Protein Kinase C.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder manifested in the form of hyperglycemia as a consequence of defect in insulin secretion and/or insulin action along with an imbalance in the metabolism of carbohydrates, fats and proteins. The incidence of DM has reached epidemic proportions predominantly because of changes in lifestyle and increase in the prevalence of obesity, cystic fibrosis and mitochondrial defects [1,2]. On a global scale, it is a major public health concern as the number of people suffering due to diabetes has grown enormously. Recent statistics conducted in 2011 have stated the prevalence of 366 million people with diabetes worldwide, which is estimated to reach 552 million by 2030 [3]. The World Health Organization has envisaged a burgeoning rise in diabetes especially in countries like India, China and United States that are predicted to house the largest number of people with diabetes by 2025[4]. Diabetes Mellitus is categorized into two main types: Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus. Type 1 DM, formerly classified as insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes mellitus, is primarily caused by autoimmune pancreatic β- cell destruction.

It is characterized by an absolute deficiency of insulin and subjects with type 1 diabetes mellitus are prone to ketoacidosis. Type 2 DM, which results from defects in insulin secretion or due to insulin resistance, is a frequent form and accounts for more than 90% people suffering with diabetes [5-7]. Hyperglycemia is an established risk factor for the advancement of diabetes related macrovascular and microvascular complications that have a serious impact on a patient's quality of life [8,9].

Both type 1 and 2 DM progress to major health complications like heart disease, stroke, kidney disease, retinopathy, amputation and neuropathy which are the primary reasons for increasing mortality and morbidity rates [10].

Diabetic nephropathy

Diabetic Nephropathy (DN) is the principal reason of End-Stage Renal Disease (ESRD) and a major cause of premature deaths amongst patients with diabetes. This mortality is attributed to the occurrence of cardiovascular diseases which lead to a 15 fold increased risk in DN patients [11]. Prolonged hyperglycemia and poor blood pressure control are well known threats for the genesis and manifestation of DN [12]. DN is one of the most common complications of diabetes mellitus and has profound impact on delivery of healthcare. More than one-third of patients with type 1diabetes and a persistently increasing proportion of patients with type 2 diabetes develop renal complications. Approximately one-third of all the cases of ESRD are due to DN [13].

DN is predicted by persistent albuminuria (albumin excretion rate › 300 mg/24 hrs), diminished glomerular filtration rate and an elevated arterial blood pressure. Incipient DN is reflected by a small increase in urinary albumin excretion known as microalbuminuria (urinary albumin excretion rate (UAER): 20-200 mg/24 hrs) while overt DN is distinguished by the presence of macroalbuminuria or proteinuria (UAER › 200mg/24 hrs) [12]. DN is classified into several distinct phases. Early changes include glomerular hyperfiltration and hyperperfusion followed by a silent phase which is associated with subtle morphological changes such as thickening of the glomerular basement membrane, glomerular hypertrophy, mesangial expansion and a modest expansion of the tubulointerstitium. It is then followed by microalbuminuria. Post microalbuminuria stage, development of proteinuria with established hypertension defines the onset of overt nephropathy or macroproteinuria. This finally leads to end stage renal failure [14,15].

Global scenario of diabetic nephropathy

Analogous to the rising incidence in diabetes, a remarkable increase in the occurrence of DN has been noted along with an increasing number of patients requiring renal replacement therapy [16]. About 50% of patients suffering from DM for more than 20 years have been found to develop this complication. Although one third of people with type 1 diabetes develop DN, the number of type 2 diabetes patients requiring renal transplantation equals or exceeds that of type 1 owing to the escalating population of type 2 diabetes patients and genetic susceptibility along with hyperglycemia controlling the development of DN in people with type 1 diabetes.

The prevalence of DN is sharply increasing in the developing countries with the Asia –Pacific regions being the most severely affected ones. The risk of nephropathy in the case of type 2 diabetes differs with ethnicity ranging from 25% of individuals from European origin to about 50% in other ethnic groups such as Afro-Caribbean, Asian Indians, and Japanese. A strong familial clustering of diabetic nephropathy has been noted among people with type 2 diabetes in India [11].

Diabetes is the single most rising cause of end stage renal failure in Europe, particularly in Germany wherein the proportion of patients

admitted for renal replacement therapy has exceeded the figure reported from the United States [11-17].

Diabetic nephropathy in Type 1 and Type 2 Diabetes mellitus patients

As hyperglycemia is the main cause in the development of DN, the basic pathophysiological mechanisms giving rise to DN are similar in both type 1 and type 2 DM. However, in type 2 diabetes, other factors of metabolic syndrome may additionally harm the kidneys through uricaemia and obesity, independent of hyperglycemia [18].

In type 1 diabetes, microalbuminuria appears within 5 to 15 years after the onset of diabetes, followed by proteinuria which develops in the next 10 years in the absence of medical intervention. The rate of development of microalbuminuria and proteinuria in people with type 2 diabetes is comparable with that found in type 1 diabetes patients [19].

In both type 1 and type 2 diabetes, generalized endothelial dysfunction is associated with microalbuminuria. Microalbuminuria predicts the development of cardiovascular disorders especially in type 2 diabetes.

The clinical manifestations of DN are proteinuria, decreased glomerular filtration rate and high blood pressure. Both type 1 and type 2 diabetes are characterized by the same manifestations, but they differ only in the renal lesions underlying renal dysfunction. The lesions in type 2 are more varied with nonspecific and ischemic lesions being more uncontrolled. In type 1 diabetes, tubular, interstitial and arteriolar lesions are present and the most significant structural changes occur in the glomerulus. Despite the presence of proteinuria, a number of people with type 2 diabetes have been found to have a normal glomerular structure with or without tubule-interstitial or arteriolar abnormalities [20,21].

Molecular mechanisms of diabetic nephropathy

Various studies have postulated that hyperglycemia leads to the induction of oxidative stress, a condition which increases the production of reactive oxygen species (ROS) and decreases the antioxidant defence mechanisms of the cell. This imbalance results in the initiation of four major pathways involved in the pathogenesis of DN viz. AGEs, enhanced glucose flux into the polyol and hexosamine pathways and activation of PKC. This further triggers proinflammatory transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) resulting in increased inflammatory gene expression, increased expression of transforming growth factor-β (TGF- β) & activation of renin-angiotensin-aldosterone system (RAAS). Collectively these factors result in cell injury, apoptosis of podocytes and accumulation of extracellular matrix proteins in the glomeruli and tubulointerstitium [22].

Increased flux of glucose and other sugars through the polyol pathway

One of the possible reasons for the development of diabetic peripheral nephropathy is an abnormal functioning of the polyol pathway. The principal enzymes involved in this pathway are aldose reductase (AR) and sorbitol dehydrogenase (SDH). AR is found in various tissues of the body namely nerve, retina, lens, glomerulus and blood vessel wall [23,24]. Since glucose uptake in the abovementioned tissues occurs through an insulin independent mechanism, a rise in the intracellular glucose concentration is observed in parallel with an increasing blood glucose level in these tissues. The polyol pathway is involved in the reduction of sugars to their respective alcohol forms for e. g. glucose is converted to sorbitol and galactose to galactitol by the enzyme AR which is the rate limiting enzyme [25,26]. In the former mentioned conversion; nicotinamide adenine dinucleotide phosphate (NADPH), which acts as a cofactor, is converted into NADP. Sorbitol, thus formed, is oxidized to fructose by the enzyme SDH with NAD+ getting reduced to NADH [27]. Intracellular accumulation of sorbitol results in osmotic damage. Also oxidation of sorbitol causes an increase in the cytosolic ratio of NADH/NAD^+ thereby inhibiting the enzyme glyceraldehyde-3-phosphate dehydrogenase (GDPH) and increasing the intracellular concentrations of triose phosphate. Elevated levels of triose phosphate increase the formation of methylglyoxal (MG), a precursor of AGE, and enhance the production of diacylglycerol (DAG) via α-glycerol-3-phosphate which further activates PKC [25,26,28]. Activation of PKC increases the production of arachidonate and prostaglandin E_2 (PGE_2) both of which inhibit Na^+/K^+ ATPase. Thus leading to abnormal blood flow contractility and endothelial dysfunction [29].

NADPH is also required as a cofactor to regenerate reduced glutathione (GSH), an important scavenger of ROS [30,31]. Consumption of NADPH in the reduction of glucose to sorbitol results in the decrease of GSH thus exacerbating intracellular oxidative stress [29]. Hyperglycemia also inhibits glucose-6-phosphate dehydrogenase which is one of the major enzymes involved in the regeneration of NADPH.

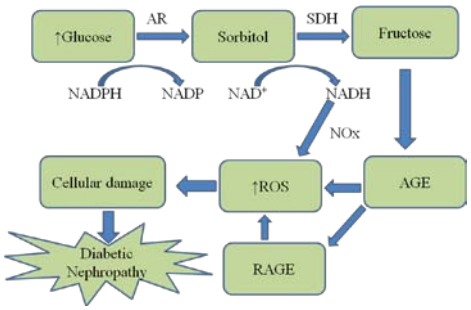

Fig. 1: It shows increased flux of glucose through the polyol pathway [25-27,30,31]

Increased intracellular formation of Advanced Glycation End Products (AGEs)

Nonenzymatic reaction between reducing sugars and amino groups of proteins, lipids and nucleic acids, also known as Malliard reaction, leads to the formation of Schiff's bases and Amadori products; thus finally leading to the production of AGEs [32,33]. The initial stage of the reaction leads to the formation of reversible glycosylated proteins termed as Schiff's bases. This stage is rapid and glucose dependent. It is followed by a much slower reaction ranging over a period of days resulting in the formation of the more stable Amadori products. These Amadori products undergo further irreversible rearrangement, oxidation and reduction reactions and form several advanced glycation end products such as pentosidine, N(carboxymethyl)lysine (CML), crossline and pyrolline [34-36]. Since these processes occur over a period of weeks, they affect long lived proteins e. g. glycated hemoglobin (HbA1c).

AGEs are produced intracellularly from auto-oxidation of glucose to glyoxal, decomposition of amadori products to 3-deoxyglucosone (3-DG) or fragmentation of glyceraldehyde-3-phosphate to yield MG. All these reactive intracellular dicarbonyls react with the amino groups of intracellular and extracellular proteins to form AGEs [34-36]. Structural components of tissue matrix such as basement membranes are important targets of AGEs. Angiotensin II (ANG II) triggers the AGEs process. CML and pentosidine accumulate in the expanded mesangial area and in the thickened glomerular capillary wall in the early phase of diabetic nephropathy [18]. AGEs are also formed through alternative glycolytic pathways along with dicarbonyl compounds which include MG, glyoxal and 3-DG [37]. The diagrammatic representation of same is in the figure 2.

AGEs exert their biological effects through receptor- as well as non-receptor mediated mechanisms. Their receptor mediated effects are brought about by receptor for advanced glycation end products (RAGE), which is a signal transduction receptor belonging to the immunoglobulin family and expressed on macrophages, renal mesangial cells, endothelial cells and podocytes. Binding of AGEs to RAGE leads to a cascade of events which includes increased cytosolic reactive oxygen species formation, stimulation of intracellular molecules such as PKC and NF-κB and activation as well as expression of a number of growth factors and cytokines such as TGF-

β and vascular endothelial growth factor (VEGF) which are involved in the pathogenesis of DN [38]. Certain *invitro* studies have proved the enhanced permeability of the glomerular basement membrane to albumin as a result of AGE formation on the intact glomerular basement membrane; thus resembling the abnormal permeability in diabetic nephropathy. Binding of AGE to its receptor on glomerular mesangial cells stimulates the secretion of platelet-derived growth factor (PDGF) which further mediates mesangial cells to produce type IV collagen, laminin and heparin sulphate proteoglycan.

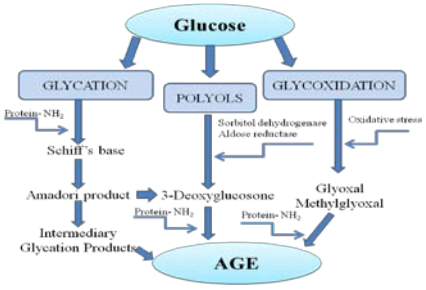

Fig. 2: It shows formation of advanced glycation end products (AGEs) by three different mechanisms [32-36]

Activation of protein kinase C

Protein kinase C, existing in several isoforms [39], phosphorylates many target proteins. Its activity is dependent on Ca^{2+} ions & phosphatidylserine and is greatly enhanced by DAG. Raised intracellular glucose levels enhance glucose flux through the glycolytic pathways which in turn increase the availability of triose phosphate; thus enhancing the de novo synthesis of DAG leading to excessive activation of PKC [40]. Also the increased cytosolic NADH/NAD^+associated with the polyol pathway and the inhibition of GDPH by intracellular ROS generated in mitochondria diverts glyceraldehyde-3-phosphate away from the glycolytic route and targets it towards the production of dihydroxyacetone phosphate and DAG [41]. Interaction between AGEs and their cell surface receptors results in enhanced activity of PKC.

Hyperglycemia increases PKC α-, β- and δ isoforms in the glomerulus of diabetic rats. Activation of PKC β-isoform results in decreased retinal and renal blood flow as a consequence of decreased production of vasodilator nitric oxide (NO) &/or increased production of endothelin-1(ET-1), a potent vasoconstrictor which further stimulates mitogen-activated protein kinase (MAPK) activity in the glomerular mesangial cells. Activation of PKC also contributes to the accumulation of microvascular matrix protein by inducing the expression of TGF-β1, fibronectin and type IV collagen in both cultural mesangial cells and in the glomeruli of diabetic rats [42].

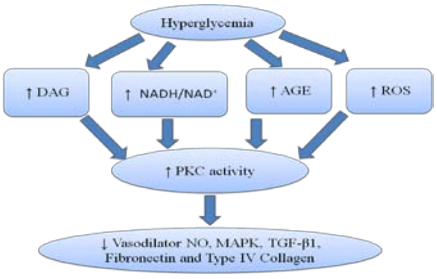

Fig. 3: It shows activation of protein kinase C and other mediators leading to DN [40,41,42]

Overactivity of hexosamine pathway

The hexosamine pathway plays a key role in causing diabetic complications. When glucose is high inside the cell, instead of getting metabolized through the glycolytic pathway, the fructose-6-phosphate formed from glucose-6-phosphate gets diverted into hexosamine pathway in which an enzyme, glutamine: fructose-6-phosphate amidotransferase converts fructose-6-phosphate to glucosamine-6-phosphate and finally to uridine di phosphate N-acetyl glucosamine.

The N-acetyl glucosamine increases transcription of genes such as TGF-α, TGF-β1, PAI-1, Sp-1 which further incorporate transition in protein function and thus, contribute to the pathogenesis of diabetic nephropathy [43].

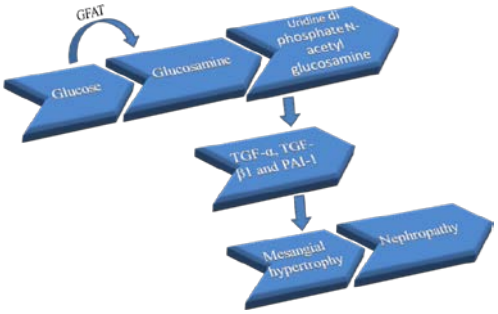

Fig. 4: It shows damage to the kidney tissues by hexosamine pathway [43]

In addition to these four major pathways, diabetic nephropathy can be caused through the intervention of other inflammatory mediators like m-TOR, PAI-1 etc.

Prevention of diabetic nephropathy

Glycemic control

Good glycemic control can prevent DN in both type I and type II diabetes [44]. According to the Diabetes Control & Complications Trial (DCCT), optimal control of blood glucose helps in retarding the development of diabetic nephropathy. However mere control of blood glucose does not prevent its progression, thus suggesting the need of alternative therapeutic strategies.

In Type 1 diabetes with microalbuminuria, improved blood glucose level and intensified insulin treatment has been found to prevent the aggravation of glomerulopathy [45,46]. Antihyperglycemics such as metformin [47] and sulfonylureas [48] which are renally excreted should not be prescribed in case of DN if renal function is persistently impaired (creatinine > 120μmol/litre) [49,50]. In such cases, sulfonylureas like gliazide can be administered whereas gliquidone and glipizide can be administered in case of uremia, a condition in which sulfonylureas like gliazide cannot be administered [51].

Dietary control

A good control on dietary protein intake, about 0.6-0.7 g/kg body weight/day, in patients with diabetes is found to have beneficial effects on glomerular filtration rate, creatinine clearance and albuminuria [11]. Vegetable protein sources have been proved to cause less damage to the kidneys as compared to animal sources [52]. Simultaneously, care should be taken to avert any unwanted side effects of low protein diet and thus, consultation of a nutritionist is advisable.

Increased levels of cholesterol and triglycerides are observed in type 1 & type 2 diabetes patients with microalbuminuria. Although the effects of hypolipidemics (lipid-lowering therapy) in such cases have not been reported, dietary restriction, weight reduction and improved metabolic control should be considered in all such patients.

Along with the conventional therapies, other dietary or lifestyle changes such as curbing down salt and alcohol intake, weight reduction, strict exercise regime etc. should be considered imperative.

Smoking cessation

Smoking should be discouraged in individuals with diabetes as it leads to oxidative stress, increased blood pressure [53], increased TGF- β level and impaired vasodilation, all of which are associated with the development and progression of diabetic nephropathy. Moreover, studies have shown that nephropathy progression increases in the case of smokers and also leads to Immunoglobulin A (IgA) nephropathy [54,55]. Thus, the presence of diabetes would further build up the possibilities of accelerating the progression of DN and worsen the overall prognosis.

Treatment of diabetic nephropathy

The therapeutic strategies which are currently employed for diabetic nephropathy include angiotensin converting enzyme (ACE) inhibitors, angiotensin-II AT1 receptor blockers and antioxidants all of which have been efficient in improving the functioning of the kidney but are ultimately incompetent in reversing the condition. Also, evidences suggest that the drugs belonging to these classes are capable only in the early stages of DN but prove to be ineffective in treating the late stage symptoms. Novel therapeutic interventions targeting the key biomarkers implicated in the pathogenesis of DN are being investigated to restrain the development and progression of this disease [44].

Agents modulating the Renin-Angiotensin-Aldosterone System (RAAS)

Angiotensinogen released by the liver, is converted to angiotensin I via plasma renin secreted by the juxtaglomerular cells in the kidney. Angiotensin I is further converted to angiotensin II by means of the angiotensin converting enzyme (ACE) present in the lungs [56]. Angiotensin II is a potent vasoactive peptide which increases blood pressure through constriction of blood vessels and stimulates the secretion of aldosterone from an adrenal cortex, resulting in the reabsorption of sodium and water [57]. It is a cogent growth modulator, a proinflammatory peptide which degrades bradykinin, a vasodilator. Augmented angiotensin II levels generate hypertrophy of mesangial and tubular epithelial cells and increase the expression of prosclerotic cytokine TGF-β. All these factors contribute to the development of nephropathy [58, 59].

Angiotensin-converting enzyme inhibitors (ACEI) viz. benazepril, lisinopril and angiotensin II receptor blockers (ARBs) viz. valsartan, losartan disrupt the renin-angiotensin system and predominantly function as renoprotective agents in both hypertensive and normotensive states [60]. ACEI demonstrate a superior protective effect in hypertensive type 1 and 2 individuals with diabetes than ARBs, irrespective of the phase of albuminuria. The latter proves to be effective only in the macroalbuminuria phase in both the types of diabetes and also decreases systemic vasoconstriction. A combinational therapy proves to be more efficient than individual drug in the macroalbuminuria phase e. g. benazepril and valsartan act synergistically and have an additive effect in preventing DN [61].

Direct renin inhibitors such as aliskiren inhibit the renin-angiotensin-aldosterone system (RAAS) and reduce the feedback effects more completely than ACEIs or ARBs; thus providing a superior renoprotection [62]. Angiotensin receptor antagonists like Candesartan, Irbesartan, Losartan, Valsartan and aldosterone antagonists like spironolactone demonstrate an inhibitory effect on the renin-angiotensin-aldosterone system and prohibit the progression of diabetic nephropathy.

Calcium channel blockers are diverse class of vasodilatory antihypertensive agents and they have been proved to delay the disease progression in DN. For example drugs like nicardipine, isradipine, etc. have been experimentally proved to be of immense therapeutic value in halting the furtherance of DN [44,13,11,51,60].

Agents inhibiting protein kinase C

Ruboxistaurin, an orally active selective inhibitor of the β-isoform of PKC has been found to reduce the actions of VEGF. It has also been found to stabilize glomerular hyperfiltration, reduce TGF-β levels along with subsequent reduction in proteinuria and also decrease osteopontin expression and subsequent macrophage infiltration in diabetic rats [62].

Agents inhibiting m-TOR (mechanistic target of rapamycin)

Originally known as mammalian target of rapamycin, m-TOR is a serine/threonine kinase which plays a crucial role in mediating cell size, mass, proliferation and survival. Over-spurring of the m-TOR pathway by excess food consumption may be vital factor underlying diabetes. This pathway is highly activated in progressive renal disorders including DN and causes renal hypertrophy in the early stages of diabetes.

Rapamycin (sirolimus) is a systemic and potent inhibitor of m-TOR. It has been found to markedly ameliorate pathological changes and renal dysfunction in diabetic db/db mice which were used as a model of ESRD associated with DN. It has also been proved significant in the reduction of fat deposits and attenuation of hyperinsulinemia.

Sirolimus decreases the expression and activity of glomerular TGF-β and VEGF and ameliorates renal inflammation, glomerular hypertrophy, and podocyte loss in rats.

Pentoxifylline has been reported to prohibit the renal expression of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6, leading to a decline in the urinary cytokine excretion and a reduction in albuminuria [62,63].

Agents inhibiting Advanced Glycation End Products (AGEs)

The diverse strategies targeting the AGE-RAGE interaction involve AGE formation inhibitors (ARBs, R-147176, aminoguanidine, 2-3-Diaminophenazine, thiamine pyrophosphate, benfotiamine, pyridoxamine), AGE cross-link breakers (alagebrium, PTB (N-phenylthiazolium bromide) and ALT-711), RAGE antagonists (PPAR-γ antagonists), AGE binder (Kremezin) and hypoxia-inducible factor (HIF) activators. Drugs such as losartan, olmesartan and hydralazine are well-known antihypertensive agents which inhibit the formation of AGEs [35,64,65].

Agents inhibiting Plasminogen Activator Inhibitor-1(PAI-1)

Plasminogen is converted to plasmin, which is involved in fibrinolysis, tissue remodeling and cell migration. This conversion is promoted by tissue type plasminogen activators and urokinase type activators. In diabetes, glycation of plasminogen occurs resulting into an impaired activation by plasminogen activators. Also the levels of these activators are high in diabetic plasma but are rendered biologically inactive due to their complex formation with plasminogen activator inhibitors-1 (PAI-1). This results into reduced conversion of plasminogen to plasmin leading to accumulation of extracellular matrix in the glomerulus, a characteristic feature of diabetic nephropathy. Binding of PAI-1 to the plasminogen activators regulates TGF-β expression and activates the extracellular regulated signal kinase/mitogen-activated protein kinase (ERK/MAPK) pathways. Rise in the level of PAI-1 inhibits usual fibrin clearance mechanism and encourages thrombosis resulting in fibrin accumulation in the basement membrane and interstitial tissue. PAI-1 is also involved in the renal fibrogenic process that occurs in chronic glomerulonephritis, DN, focal segmental glomerulosclerosis and other fibrotic renal diseases. The PAI-1 synthesis or its activity can be inhibited by specific antibodies, peptidic antagonists, antisense oligonucleotides or decoy nucleotides. Some novel, orally active, small molecule substances – TM-5001, TM-5007, TM-5275 – have been found to enhance fibrinolysis by inhibiting PAI-1 activity and the formation of complex with tissue plasminogen activator [66-68].

Antioxidant agents

Taurine, acetyl- L- carnitine, alpha lipolic acid, vitamin E, ascorbic acid, curcumin etc have shown significant reduction in the progression of DN. As oxidative stress is one of the major culprits leading to the progression of DN, inhibition of the same by antioxidant compounds can provide a holistic approach to treat DN along with the other forms of therapy [69].

Anti inflammatory agents

Hyperglycemia activates several inflammatory mediators such as TNF-α, TNF-β and NF-κB which are expressed in the form of cell injury, apoptosis of podocytes and accumulation of extracellular matrix proteins in the glomeruli and tubulointerstitium. These mediators additionally accompany and aggravate DN. Agents which can inhibit these mediators can be useful in the treatment of DN. Several anti-inflammatory drugs such as cyclooxygenase-2 inhibitors like meloxicam etc show beneficiary effect in chronic diabetes leading to nephropathy [70].

Aldose reductase inhibitors

Tolrestat, epalrestat, ranirestat and fidarestat are well-known aldose reductase inhibitors which have been reported in the treatment of various diabetic complications. Flavonoids such as quercetin, naringin, quercitrin, and myricitrin have been proved to play a significant role as aldose reductase inhibitors with reference to their effect on rat lenses. These drugs either individually or in combination can demonstrate a good therapeutic strategy for curbing diabetic nephropathy [71,72].

CONCLUSION

We can conclude that with the increasing prevalence of diabetic nephropathy globally, there is a need for early diagnosis and a therapeutic strategy which will halt its progression. Because of the complexity of this disease due to the simultaneous involvement of different pathways, one can conclude that there is a need for novel therapeutic interventions which will target the key biomarkers implicated in the pathogenesis of DN. In addition to this, a combination of the therapeutic interventions will be more beneficial in arresting the progression of diabetic nephropathy. Furthermore, slowing down the advancement of DN by maintaining a balanced glycemic control, blood pressure, dietary control and supplementary changes in the life style along with adequate exercise can provide a holistic approach in the prevention and treatment of DN.

CONFLICT OF INTERESTS

Declared None

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