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PATHOGENESIS OF DIABETIC NEPHROPATHY AND POTENTIAL THERAPEUTIC EFFECT OF CURCUMIN: A REVIEW

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ABSTRACT

Chronic diabetes mellitus is associated with various complications such as retinopathy, neuropathy, nephropathy, cardiomyopathy, vasculopathy, dermatopathy and encephalopathy. Nephropathy is one of the major complications of diabetes mellitus, and the morbidity and mortality due to diabetic nephropathy is constantly progressing in industrialized nations. Diabetic nephropathy is a leading cause of end-stage renal failure worldwide. Its morphologic characteristics include glomerular hypertrophy, basement membrane thickening, mesangial expansion, tubular atrophy, interstitial fibrosis and arteriolar thickening. Numerous reports have demonstrated that oxidative stress induced by diabetes plays an important role in the development and progression of diabetic vascular complications including nephropathy. Biomarkers for oxidative damage to DNA, lipids, and proteins are also supporting the concept of increased oxidative stress in diabetes and diabetic nephropathy. The present review has been undertaken to communicate the pathogenesis of diabetic nephropathy, the role of oxidative stress and reactive oxygen species as well as antioxidant property of Curcumin in ameliorating diabetic nephropathy.

KEYWORDS: **Diabetic nephropathy, Renal failure, Curcumin, Reactive oxygen species, Hyperglycemia**

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INTRODUCTION

'Nephropathy' refers to the kidney disease or damage. Diabetic nephropathy (DN) is damage to kidneys due to diabetes[1]. In severe cases it can lead to kidney failure. Diabetic nephropathy is a major microvascular complication, representing the leading cause of end-stage renal disease and glomerulosclerosis in the world, and a major cause of morbidity and mortality in both type 1 and type 2 diabetic subjects[2-3]. Diabetic nephropathy (DN) has been found to be the most common cause of end-stage renal disease requiring dialysis in the many countries. Between 20% and 40% of patients with diabetes ultimately develop nephropathy, although the reason why not all patients with diabetes develop this complication is unknown.[4] Presence of numerous micro blood vessels in the kidney which filter waste from blood is the main cause of diabetic nephropathy. High blood sugar from diabetes leads to damage of these blood vessels[5-6]. Over time, the kidney isn't able to work completely and this leads to kidney failure. Clinical hallmarks of diabetic nephropathy include a progressive increase in urinary albumin excretion and a decline in glomerular filtration rate (GFR), which occurs in association with an increase in the blood pressure, ultimately leading to end-stage renal failure[7]. DN is characterized by early glomerular hypertrophy, hyper-filtration, and accumulation of extracellular matrix (ECM) components such as fibronectin (FN)[8]. The disease is later stimulated by transforming growth factor-beta 1 (TGF-β1), triggering the thickening of glomerular and tubular basement membranes, which ultimately progress to glomerulosclerosis and renal fibrosis [9].

Multiple mechanisms contribute to the development and outcome of DN, such as oxidative stress, lipid disorders, renal hemodynamic changes, increased non-enzymatic glycosylation of proteins, the activation of the polyol pathway and the mitogen activated protein kinase signaling pathway[10]. Diabetic nephropathy has several distinct phases of development. Functional changes occur in the nephrons at the level of the glomerulus, including glomerular hyperfiltration and hyperperfusion, before the onset of any measurable clinical changes, subsequently leading to thickening of the glomerular basement membrane and glomerular hypertrophy[11]. The DN is diagnosed using simple tests that check for a protein called albumin in the urine. Urine does not usually contain proteins. But in the early stages of kidney damage, a small concentration of this protein may be found in the urine, because the kidneys aren't able to filter properly. Finding the kidney damage early can keep it from getting worse[3-4]. So it's important for diabetic patients to undergo regular testing. Current therapies that aim to lower blood glucose level are not effective in blocking renal damage, and co treatment with renoprotective drugs often results in toxicity[12]. Consequently, there remains an urgent need of developing an effective therapy for preserving normal renal function and to prevent or slow the progression of diabetic nephropathy. Diabetic nephropathy has been reported as one of the leading causes of chronic renal failure in India also. It has been reported that among 4837 patients with chronic renal failure seen over a period of 10 years, the prevalence of diabetic nephropathy was 30.3% followed by chronic interstitial nephritis (23.0%) and chronic glomerulonephritis (17.7%) [13-14].

POSSIBLE PATHOGENIC MECHANISMS IN DIABETIC NEPHROPATHY

The pathogenesis of diabetic nephropathy is still not fully understood but is considered to be multifactorial in nature. Interactions of hemodynamic and metabolic factors along with the glycosylation of glomerular proteins are all thought to be involved in the pathogenesis of diabetic nephropathy[12–15]. In insulin-dependent diabetic patients with poor glucose control, which may initially increase albumin excretion rate, an early rise of arterial pressure and smoking were implicated in the development of persistent microalbuminuria[16]. There are evidences that genetic predisposition plays a major role in development of diabetic nephropathy, clustering within families, both in IDDM and NIDDM[17-18] .

HEMODYNAMIC FACTORS

Hemodynamic factors that contribute to the development of diabetic nephropathy include increased systemic and intraglomerular pressure, as well as activation of vasoactive hormone pathways including the renin angiotensin system and endothelin[12]. These hemodynamic pathways activate the intracellular second messengers such as Protein kinase C (PKC), Mitogen activated protein (MAP kinase), nuclear transcription factors, vascular endothelial growth factor (VEGF), cytokines and Transforming growth factors (TGF-β)[19]. Glucose dependent pathways are also activated within the diabetic kidney which increase the oxidative stress, free radicals generation and further activate renal polyol pathway causing accumulation of advanced glycation end products (AGEs)[20]. In combination, these pathways ultimately lead to increased renal albumin permeability and extracellular matrix accumulation, resulting in an increase in proteinuria, glomerulosclerosis and ultimately development of tubulointerstitial fibrosis[21].

HEMODYNAMIC CHANGES

The early signs of glomerular hyperperfusion and hyperfiltration result from decreased resistance in both the afferent and efferent arterioles of the glomerulus. Many factors have been reported to be involved in this defective auto regulation, including prostanoids, nitric oxide, vascular endothelial growth factor (VEGF; now formally known as VEGF-A), TGF-β1, and the renin–angiotensin system, specifically angiotensin II[22-25]. These early hemodynamic changes facilitate albumin leakage from the glomerular capillaries and overproduction of mesangial cell matrix. These also result in thickening of the glomerular basement membrane and injury to podocytes[26]. In addition, increased mechanical strain resulting from these hemodynamic changes can induce localized release of certain cytokines and growth factors[27]. The renal hemodynamic changes are mediated partly by the actions of vasoactive hormones, such as angiotensin II and endothelin. Glomerular hypertension and hyperfiltration contribute to the development of diabetic nephropathy because use of renin–angiotensin blockers preserves kidney function and morphology. Blockade of the renin–angiotensin–aldosterone system antagonizes the profibrotic effects of angiotensin II by reducing its stimulation of TGF-β1[24-26].

METABOLIC FACTORS

An early sign of diabetic nephropathy is the increased quantity of urinary protein, manifested by “albuminuria,” which correlates with, and can predict, the progression of renal damage[27]. It is established that albuminuria derives primarily from defects in the glomerular filtration barrier[28]. Advanced glycation end products (AGEs) are proteins or lipids that become glycated after exposure to sugars. AGEs are prevalent in the diabetic vasculature and contribute to the development of atherosclerosis. The presence and accumulation of AGEs in many different cell types affect extracellular and intracellular structure and function. AGEs contribute to a variety of microvascular and macrovascular complications through the formation of cross-links between molecules in the basement membrane of the extracellular matrix and by engaging the receptor for advanced glycation end products (RAGE)[29-30]. The advanced glycation pathway is of particular importance not only in the development of diabetic nephropathy, but also in enhanced arterial and myocardial stiffening. Once AGE related cross-links are formed on proteins, they become resistant to proteolytic degradation and contribute to the diabetic nephropathy[30-31].

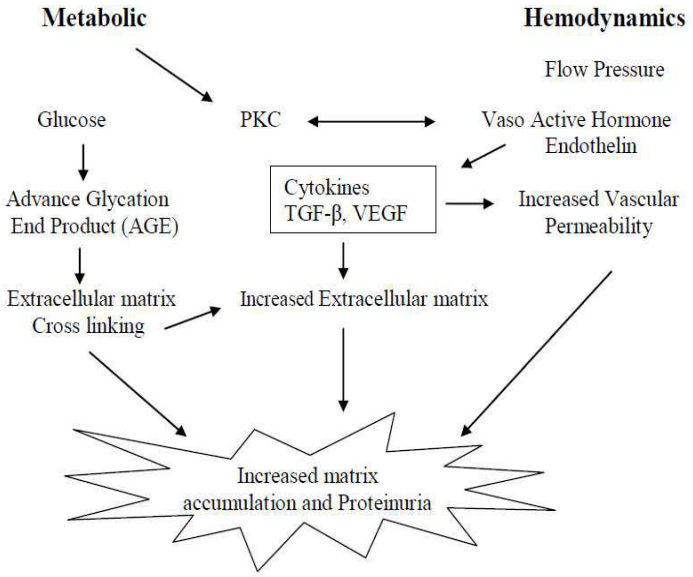

Figure 1
Involvement of various metabolic and hemodynamic factors in Diabetic Nephropathy

OXIDATIVE STRESS, REACTIVE OXYGEN SPECIES AND DIABETIC NEPHROPATHY

Diabetes has been established as the leading cause of end-stage renal disease (ESRD), accounting for nearly half of all new patients and chronic kidney disease (CKD) is an independent risk factor for all-cause and cardiovascular mortalities[1-3]. Hyperglycemia, a well recognized pathogenetic factor of long-term complications in diabetes mellitus, not only generates more reactive oxygen species but also attenuates antioxidative mechanisms through glycation of the scavenging enzymes[4]. Therefore, oxidative stress has been considered to be a common pathogenetic factor of the diabetic complications including nephropathy.

OXIDATIVE STRESS

Oxidative stress in the body represents an imbalance between the production of free radicals and reactive oxygen species (ROS) generation. The ability of anti oxidant defence mechanisms to detoxify the reactive intermediates[31]. All forms of life maintain a reducing environment within their cells. This reducing environment is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy[32]. Disturbances in this normal redox state can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA.

REACTIVE OXYGEN SPECIES

Reactive oxygen species plays an important role in the regulation of normal cellular function[33]. When ROS are produced in excess they can have detrimental effects, a state known as oxidative stress. ROS comprises free radicals and non free radicals[33]. Free radicals, i.e. Superoxide anion (O_2^-), hydroxyl radical (OH^-) and nitric oxide (NO^-), are unstable atoms or molecules with an unpaired electron. Non free radicals like hydrogen peroxide (H_2O_2), have paired electrons but due to their natural instability they can easily become free radicals[34].

OXIDATIVE STRESS MARKERS IN DIABETIC NEPHROPATHY

The oxidation products of biological components are generally accepted as markers of oxidative stress and they include lipid peroxides, malondialdehyde, 4-hydroxy-2-nonenal, isoprostane (a product of oxidation of arachidonic acid), 8-hydroxydeoxyguanosine (8-OHdG), thymine glycol, protein carbonyl, hydroxyleucine, hydrovaline, and

nitrotyrosine[35-36]. Increased urinary 8-OHdG levels have been reported in patients with diabetes and in diabetic rodents[37-39], and Because of their reactive chemical property to directly oxidize and damage DNA, protein, lipid, and carbohydrate, ROS are believed to play a key role in the pathogenesis of late diabetic complications. ROS mediate hyperglycemia-induced activation of signal transduction cascades and transcription factors leading to transcriptional activation of profibrotic genes[40-42]. Numerous studies on experimental models of both immune and nonimmune glomerular injury demonstrated ROS to be primary mediators in the pathogenesis of these disorders and showed that the kidney is, in fact, susceptible to oxidative stress[43]. Lee *et al.* reviewed ROS-regulated signaling pathways leading to extracellular matrix (ECM) deposition in diabetic kidney[44]. ROS generated by hyperglycemia activate various signal transduction cascade viz Protein Kinase C (PKC), Mitogen Activated Protein Kinase (MAPK) and transcription factors like nuclear factor kappa-B (NF-κB), TGF-β1 and fibronectin in the renal cells. Moreover antioxidants effectively inhibit high glucose and H_2O_2 induced activation[45-47].

ROLE OF ANTIOXIDANTS IN DIABETIC NEPHROPATHY

Antioxidants are molecules that significantly inhibit oxidation of target molecules at lower concentrations than those of the oxidizable target molecules[48]. Antioxidative effects can be achieved in three different ways:

(1) sequestering free transitional metal ions,
(2) catalyzing the breakdown of oxidants generated in situ,
(3) scavenging free radicals to produce relatively unreactive antioxidant radicals.

Large quantities of ROS are cytotoxic. In contrast, ROS at low doses activate the transcription factor NF-KB, a pleiotropic regulator of many "response to-injury" genes, and alter intracellular signal transduction pathways, gene expression, and cell proliferation[49]. Linkage of renal injury to oxidative stress has been demonstrated by studies using rats placed on diets deficient in the antioxidants such as selenium and vitamin E [50-51]. ROS scavangers such as antioxidant enzymes and antioxidant molecules can help balance the ROS activity and toxicity. The use of these ROS scavangers has shown to reduce the diabetic nephropathy in animal studies. Vitamin E, an antioxidant molecule has been shown to exhibit additional anti inflammatory effects. It also has the ability to inhibit fibroblast and platelet adhesion and release [45-46].

CURCUMIN AS ANTIOXIDANT IN DIABETIC NEPHROPATHY

There is an increasing demand for natural antidiabetic medicines that do not have the same side effects as modern drugs. Curcumin is the active ingredient of turmeric powder with a variety of biological activities including antioxidative activity. Curcumin, a phytochemical found in the spice turmeric, has been used in India for centuries, and it has no known side effects. It has been shown to have some beneficial effects against various chronic illnesses. Many of these therapeutic actions can be attributed to its potent anti-oxidant and anti-inflammatory activities [52-53]. In view of the oxidative stress and inflammatory mechanisms of DM, Curcumin can be considered suitable for the prevention and amelioration of diabetes. Curcumin is used as an antioxidant for the treatment of diabetic nephropathy [54]. Curcumin is the main biological active phytochemical component of turmeric which is a member of the *Curcuma* botanical group (Family Zingiberaceae). Curcumin, a major polyphenol from the golden spice Curcuma longa commonly known as turmeric, has been recently discovered to have renoprotective effects on diabetic nephropathy (DN)[55]. Extensive studies within the last half a century have demonstrated the protective action of curcumin in almost all the disorders of the body. The molecule is known to possess many pharmacological properties viz. antimicrobial, anti-inflammatory, antihypertensive, antihyperlipidemic, antitumor, anticancer, antiphlogistic, antidiabetic, antipsoriasis, antithrombotic and antihepatotoxic along with other useful biological properties[56]. The activation of SphK1-S1P (sphingosine kinase-1) signaling pathway induced by hyperglycemia and oxidative stress play important roles in renal fibrosis and DN[57]. Curcumin possesses

anti-oxidant and anti-inflammation properties. Therefore, the involvement of the renoprotective function of Curcumin in the SphK1-S1P signaling pathway and in preventing diabetic renal fibrosis needs investigation. Several studies have indicated a beneficial role of Curcumin in terms of anti-oxidant, anti-tumourgenic and anti-inflammatory properties. It was previously reported that Curcumin has a glucose-lowering activity in streptozotocin (STZ)-induced type 1 diabetic rats, STZ-nicotinamide induced type 2 diabetic rats, ob/ob mice and db/db mice[58]. Moreover, it has also been shown that it could prevents diabetes-induced oxidative protein and DNA damage in association with decreasing nitric oxide synthase levels in cardiac tissue. Accumulating evidences suggest that Curcumin has a diverse range of molecular targets. Among its molecular targets are transcription factors, transcriptional coactivator (e.g. p300), growth factors and their receptors, cytokines, enzymes and genes regulating the cell proliferation and apoptosis as well as inhibits the activity of several protein kinases such as phosphorylase kinase, PKC and protamine kinase[56]. It has been previously demonstrated that, although LOX-1and LDL expression rises with DM, Curcumin delivery leads to the suppression of this increase in LOX-1 levels in the dorsal root ganglia (DRG) through its role as a non-specific LOX-1 inhibitor. It is able to perform these actions without affecting oxLDLlevels[59].

Therefore, through curcumin's suppression of LOX-1 upregulation it may be able to provide an intervention leading to a potential clinical therapy to prevent the neurodegenerative effects due to DM. It is well reported that Curcumin attenuates the upregulated inflammatory mediators that occur during hyperglycemia in experimental rats[60]. Several studies have indicated that Diabetic kidney posses excessive lipid deposits, curcumin, a polyphenol, attenuate the tissue dyslipidemic condition through activation of 5' adenosine monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation and suppression of sterol regulatory element-binding protein (SREBP)-1c in the kidney and would prevent renal progression in experimental type 1 diabetic rats.

CONCLUDING REMARKS

Diabetic nephropathy (DN), one of the major micro vascular complications of diabetes, has become the main cause of end-stage renal disease requiring dialysis. A large body of evidence indicates that oxidative stress is the common denominator link for the major pathways involved in the development and progression of diabetic micro- as well as macro-vascular complications of diabetes. Hyperglycemia causes the autoxidation of glucose, glycation of proteins and the activation of polyol metabolism. These changes accelerate generation of Reactive Oxygen Species (ROS) and increases in oxidative chemical modification of lipids, DNA and proteins in various tissues. Excessive generation of free radicals modulate activation of protein kinase C, mitogen-activated protein kinases, various cytokines and transcription factors which eventually cause increased expression of extracellular matrix (ECM) genes with progression to fibrosis and end stage renal disease. Curcumin, a phytochemical found in the spice turmeric, has been used in India for centuries, and it has no known side effects. It has been shown to have some beneficial effects against various chronic illnesses. Many of these therapeutic actions can be attributed to its potent anti-oxidant and anti-inflammatory activities. In view of the oxidative stress and inflammatory mechanisms of diabetic nephropathy, Curcumin can be considered suitable for the prevention and amelioration of diabetic nephropathy.

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