Effects of curcumin in experimental diabetic nephropathy

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ABSTRACT

Diabetic nephropathy (DN) is currently well established as the most common cause of end-stage renal disease in most parts of the world. Notwithstanding the expanding basic and clinical research in this field, the pathogenesis remains far from clear and hence the treatment of DN remains suboptimal. There is a critical need for the development of newer therapeutic strategies including alternative and complementary therapies. One of the natural products that was extensively studied in cancer and other chronic disease states such as diabetes is curcumin, an active ingredient in turmeric, a spice extensively used in India. In this manuscript, we present a critical review of the experimental and clinical evidence that supports the use of curcumin and its analogs in DN as well as the various proposed mechanisms for its biological actions in health and disease states.

INTRODUCTION

Diabetic nephropathy (DN) is one of the most serious complications of diabetes and results in end-stage renal disease (ESRD). DN is the most common cause of ESRD in the USA and in fact in most parts of the world.[1] Up to 30% of all subjects with diabetes, both type I and type II, develop DN. Currently, the treatment options of DN are limited and suboptimal since most patients continue to progress despite medical therapy. The mainstay of treatment involves control of systemic hypertension, blood sugar control, and use of inhibitors of renin-angiotensin system (RAS). Thus, there is an urgent need to understand the pathogenesis and seek innovative therapies to address DN.[2] We have recently evaluated the use of curcumin, a derivative of the commonly used spice turmeric, in the treatment of experimental DN and furthermore probed into mechanisms of its action. We found that such therapy is quite effective and safe and provides the necessary foundation for exploration in human clinical trials.

DIABETIC NEPHROPATHY

Nephropathy is an important complication of diabetes mellitus (DM) and contributes significantly to the morbidity and mortality. Nephropathy in DM is almost always progressive and may lead to ESRD, although many succumb to cardiovascular (CV) disease that is in turn accelerated by chronic kidney disease (CKD). It is estimated that the annual cost of caring for diabetes and its complications exceeds 240 billion dollars in the USA.[3] There is an imminent need to develop novel therapies to effectively decrease the CV burden that is significantly contributed by nephropathy in subjects with diabetes.

The onset of DN is often heralded by proteinuria, which typically starts as microalbuminuria, pathophysiologically often characterized by glomerular hyperfiltration, and progresses to overt proteinuria over a few years. This is accompanied by progressive loss of glomerular filtration rate (GFR) and hypertension which result in ESRD in a span of 3–5 years. Recent data indicate that a significant number of subjects with diabetes with microalbuminuria may spontaneously regress and not progress to overt proteinuria.[4] The kidneys are often grossly normal or enlarged in size with increased echogenicity on ultrasound. Early histological changes include glomerulomegaly, thickened basement membrane, mesangial expansion with increased cellularity, and matrix deposition. Later nodular and/or diffuse glomerulosclerosis ensues with ultimate glomerular demise. Simultaneously, progressive tubulointerstitial inflammation and sclerosis develop and, in some instances, may precede overt glomerular changes. The tubulointerstitial component may actually have a greater impact on the disease progression and renal failure than glomerular changes. There are also major hemodynamic changes that affect glomerular micro-vasculature as well as macro-vasculature, the latter leading to severe arteriolosclerosis. Alterations in vasoactive factors in the kidney leading to endothelial dysfunction, activation of RAS, hyperlipidemia,[5] hyperfiltration, and progressive atherosclerosis account for the vascular component of DN.[6] Despite the abundant literature, the pathophysiology of DN still remains very unclear.[7]

CURRENTLY APPROVED THERAPIES FOR DN

The current treatment options for DN are quite limited and not optimally effective. The main risk factors for the development of nephropathy are hypertension and uncontrolled hyperglycemia. Thus, the mainstay in the management of DN remains optimal control of hypertension and diabetes. In the past two decades, the use of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) to inhibit

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the RAS has remarkably improved the therapy of DN. Although these agents lower blood pressure (BP) by inhibiting the production or actions of angiotensin II, such effects also decrease renal protein excretion and slow the decline of GFR. These renoprotective effects, which are independent of BP control, could account for some of the decline in the incidence of ESRD from DN in the past decade. In addition, these agents could at least have a modest effect on lowering hyperglycemia.[8] While there is some additive effect when ACEi and ARBs are combined, the additional risk of hyperkalemia and acute kidney injury exceeds the modest anti-proteinuric benefit.

Dietary protein restriction has been shown in some studies to have a modest effect in slowing the progression of GFR in DN, although other studies have revealed conflicting data. The current consensus is to limit the protein intake to 0.8 g/kg body weight of high biological value protein while cautiously watching for protein malnutrition. Several other therapies have been tried with limited or no success. For example, inhibitors of advanced glycosylation end-products (AGE), such as aminoguanidine, were tried in clinical studies[9] after extensive experimental studies in vitro[10 11] and in vivo[12] validated its efficacy and safety in ameliorating DN. While phase I and II studies were impressive, the phase III study was prematurely terminated due to unexpected adverse events.[13] More recently, pyridoxamine, which also inhibits AGE, was evaluated in clinical studies to treat DN and the early studies failed to demonstrate a renoprotective effect as measured by serum creatinine (ΔScr).[14–16] Other agents such as inhibitors of transforming growth factor-β (TGF-β) and protein kinase C (PKC), which seemed promising in animal experiments, failed to show efficacy and/safety in human studies.[2]

Recently, bardoxolone methyl was shown to be safe and effective in slowing the progression of DN in phase II clinical studies.[17 18] Indeed, such therapy was associated with a modest improvement in GFR, an effect not seen with any known therapy so far. Bardoxolone is an antioxidant inflammatory modulator (AIM) and its mechanism of action is complex but involves activation of a nuclear factor Nrf-2. Based on the initial impressive results, an ambitious global phase III study was launched to evaluate its efficacy in advanced (stages IIIb and IV) DN. Unfortunately, the study was prematurely terminated due to a few deaths from heart failure.[19]

Thus, we do not currently have effective options to manage DN besides ACEi and ARBs. There is an imminent need to develop novel and effective therapies to prevent progression to ESRD and associated CV risk.

CINNAMON

Driven by the need to expand the therapeutic agents available to treat diabetes and its complications, a number of non-traditional and natural compounds have been evaluated both in experimental and clinical studies. One of such agents that received extensive attention was Cinnamon, derived from the bark of Cinnamomum trees. Administration of cinnamon augmented insulin sensitivity in animal models of diabetes.[20] In controlled clinical studies, cinnamon intake improved glycemic indices in poorly controlled diabetes[21] and reduced postprandial glucose levels in subjects without diabetes.[22]

CURCUMIN

Curcumin, an active chemical derived from a spice turmeric (*Curcuma longa*), is commonly used in India and South East Asia in cooking, cosmetics, as well for its medicinal effects for centuries. Its biological effects are believed to be mediated by antioxidant, anti-inflammatory, and antifibrotic mechanisms. Curcumin is chemically diferuloylmethane, a polyphenolic compound, and is generally sparingly soluble in water. Taken orally, the bioavailability of curcumin is limited, which has led recently to major efforts to develop more bioavailable forms.[23–25]

CURCUMIN AND DIABETES

Curcumin, an active derivative of turmeric, has been a part of Indian and Eastern traditional medicine for centuries and has been used in cooking materials and as a dietary supplement to prevent and treat diabetes. The scientific community has been engaged in intense experimental studies to confirm these widespread beliefs by in vivo and in vitro studies and even human clinical trials for the past 25 years and the results are not conclusive. However, there have been major efforts to understand the molecular mechanisms of the actions of curcumin in animal and human investigation. Besides antioxidant effects, curcumin seems to affect the sensitivity of insulin receptor and signaling pathways downstream to insulin receptor activation.[26] Curcumin has been shown in other studies to inhibit specifically glucose transporter 1 (GLUT1) in adipose and intestinal cells.[27] While the implications of such observations remain unclear, it is likely that the GLUT1 inhibition in intestinal cells may play a role in glucose absorption, thereby reducing hyperglycemia.

CURCUMIN—POTENTIAL THERAPEUTIC ROLE IN OTHER DISEASES

The therapeutic potential of curcumin has been evaluated in a variety of medical disorders including malignancies of several organs,[28–30] neurodegenerative conditions such as Alzheimer's disease,[31] Parkinson's disease,[32] CV disease,[23 33] diabetes,[26 27] inflammatory bowel disease,[34] wound healing[35] ocular conditions such as cataract,[36] age-related macular degeneration,[37] and even psychiatric conditions such as depression.[38] In all these studies, curcumin was found to be safe with no significant toxic effects but efficacy was demonstrable in most but not all the studies.

CURCUMIN IN DN

The effects of curcumin and its analogs have been evaluated both in experimental and clinical studies to assess its therapeutic potential. Several animal experiments and some clinical studies[39 40] have demonstrated beneficial effects of curcumin in DN. There are myriads of studies which were designed in particular to define the mechanism of action in cell culture and in vitro models. One of the early evidences of the beneficial effects of curcumin was published almost two decades ago in an animal study in which curcumin administration in the diet to streptozotocin (STZ)-induced diabetic rats decreased albuminuria and ameliorated renal structural lesions of diabetes.[41] A similar study in STZ rats showed that chronic oral administration of curcumin

reduced renal functional and structural damage by ameliorating oxidative stress.[42] More recently, Yang *et al*[43] demonstrated that short-term oral administration of curcumin reduced proteinuria in patients with diabetes by upregulating the nuclear receptor (transcription) factor 2 (NRF2) system and by anti-inflammatory effects. Chiu *et al*[44]

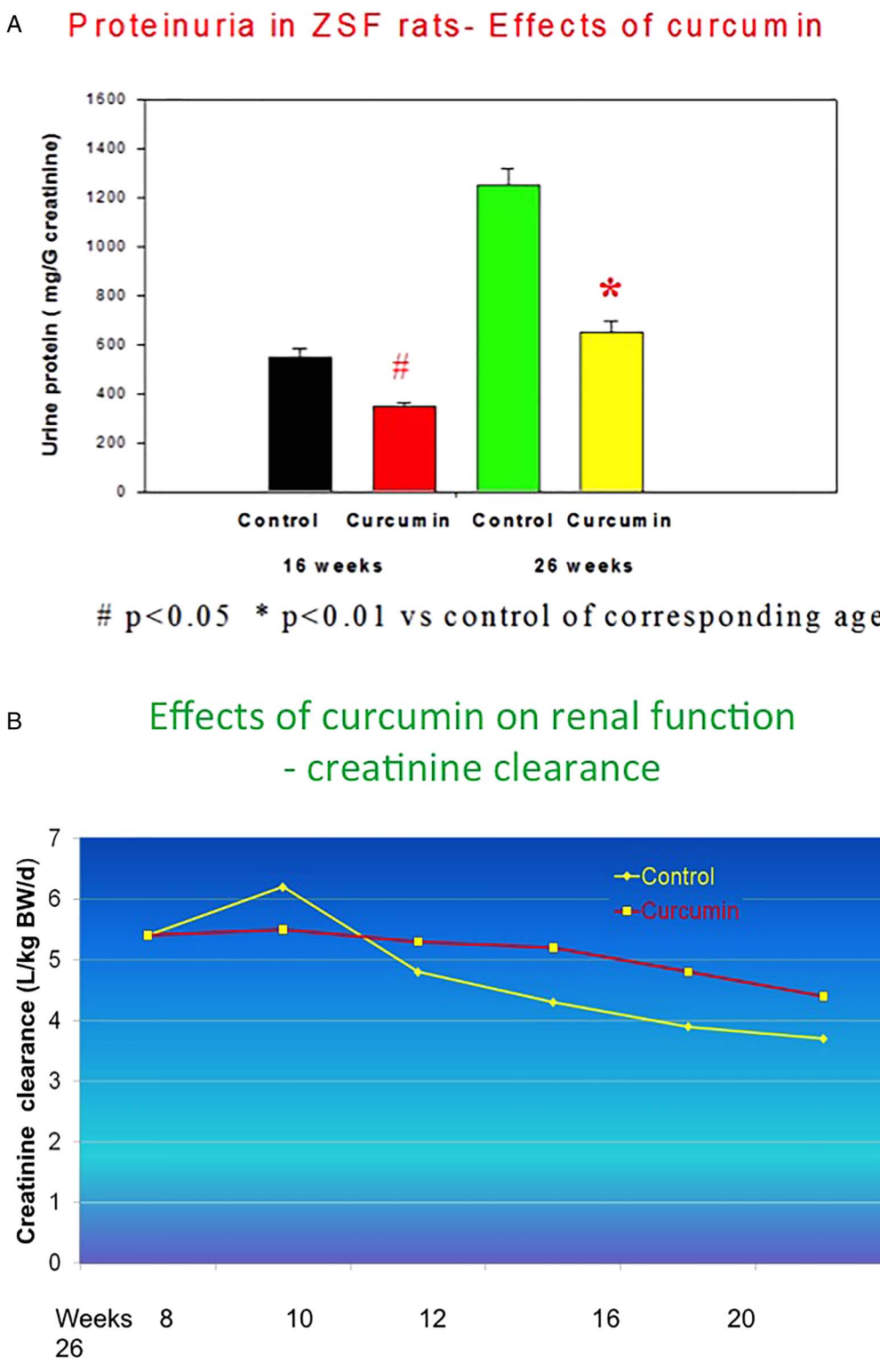

Figure 1 (A) Effect of chronic curcumin therapy urinary protein excretion rate. Both at 16 weeks and at 26 weeks, curcumin therapy lowered the urinary protein excretion rates significantly compared with control ZSF1 rats. (B) Effects of long-term administration of curcumin on GFR measured as endogenous creatinine clearance. The control rats exhibited a phase of hyperfiltration during 8–12 weeks, which was followed by a sustained and continuous fall of creatinine clearance. Curcumin-treated rats exhibited no hyperfiltration and demonstrated better preservation of GFR compared with control ZSF1 rats. BW, body weight.

showed that the beneficial effect of curcumin in STZ diabetic rats was mediated by its inhibitory effects on nuclear factor-κB (NF-κB) and TGF-β in the kidney, while others have demonstrated salutary effects at even a more proximal step involving inhibition of PKC-α and the PKC-β 1-extracellular signal–regulated kinase (ERK) signaling pathway.[45] Using a synthetic analog of curcumin C66 in cell culture studies, Pan *et al*[24 46] concluded that the inhibition of inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 by C66 was mediated by inhibitory effects on high-glucose-induced activation of c-Jun N-terminal kinase (JNK)/NF-κB signaling. Others have shown that inhibition of activator protein 1 (AP-1) activation through downregulation of the Sphingosine kinase 1-Sphingosine-1-phosphate (SphK1-S1P) signaling pathway may account for amelioration of experimental DN.[47] More recently, Soetikno *et al*[48] described the molecular basis of renoprotective effects of curcumin in DN underscoring the antioxidant and anti-inflammatory properties of curcumin and curcuminoids. Other recent investigations focused on the inhibitory effects of curcumin on microRNA, especially miR-124 on podocytes, to explain the renoprotective effects in DN.[49] Wu *et al*[50] showed that C66 contributes to renal protection by upregulation of NRF2 by activating miR200 and inhibiting miR21. Interestingly, some investigators have linked the renal effects of curcumin to prevention of epithelial-mesenchymal transformation (EMT) as a result of activation of NRF2 and heme oxygenase-1[51] or by suppressing the phosphorylation of cav-1 and increasing the stabilization of cav-1 and β-catenin.[52] More recent studies using podocyte cultures indicated that curcumin ameliorated podocyte apoptosis by regulating the link between ROS and cavelolin-1 phosphorylation.[53] Finally, Ho *et al*[54] focused on the role of wingless-type MMTV integration site (WNT) family β-catenin activation by curcumin, thereby leading to reduced superoxide dismutase activity and 8-hydroxy-2′-deoxyguanosine, TGF-β1, and fibronectin and thus ameliorating renal injury and fibrosis in DN.

EXPERIMENTAL DATA FROM OUR LABORATORY

Experimental studies performed in our laboratory evaluating the benefits of curcumin in experimental DN have in general produced positive results. We examined the effects of chronic administration of curcumin in obese Zucker diabetic-Spontaneously hypertensive Fatty rats (ZSF) rats, a murine model of nephropathy of type II diabetes, first characterized in our laboratory.[55] ZSF1 rats are transgenic rats developed by crossing Zucker diabetic fat (ZDF) rats with spontaneously hypertensive heart failure (SHHF) rats. Obese ZSF rats develop diabetes, hypertension, and other features of metabolic syndrome, while the lean counterparts have only hypertension. Nephropathy in such obese ZSF1 rats mimics human DN very closely, from a natural course and histological perspective, an essential requirement in animal models of human diseases to evaluate any compounds of therapeutic potential.[56] The course of DN in ZSF rats as well as many animal models of DN and human DN is characterized by progressive oxidative stress and nitric oxide (NO) deficiency, although in the initial phases of hyperfiltration there may be high NO levels.[57] Rats were given drinking water (control group) or curcumin at 1 mg/mL in drinking water (experimental group). To increase the solubility of curcumin in water, the water was preheated 90°C and then cooled before administration. This technique has been shown to enhance the curcumin solubility by several studies,[58 59] although the majority of curcumin remains in the solid phase. The absorbed amounts of curcumin have been shown to produce detectable plasma concentrations that yielded biological effects.

In our studies, rats were studied from the 8th week to 26th week while blood and urine samples were obtained at the 8th, 16th and 26th weeks. Curcumin did not affect the weight gains or food and water consumption by rats. Protein excretion rates increased incrementally with time in control rats while urine protein excretion was significantly lower in the curcumin treated rats at the 16th and 26th weeks (figure 1A). The GFR as measured by creatinine clearance was better preserved in the treated group compared with control rats (figure 1B). Furthermore, examination of renal tissue homogenates for protein expression by western blots showed significant reduction of TGF-β and vascular endothelial growth factor (VEGF) in curcumin-treated rats compared with control (figures 2A, B).

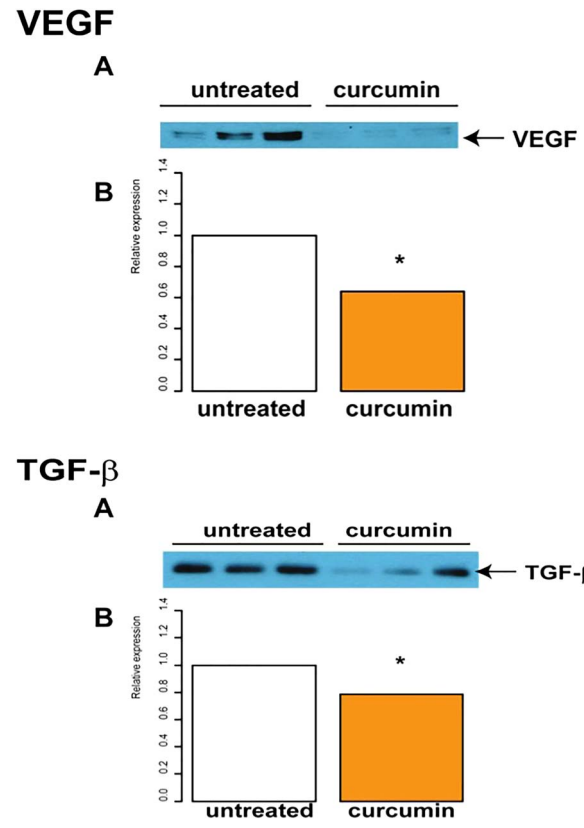

Figure 2 Effects of Curcumin on growth factors in the kidney. (A) Western blots demonstrating that kidneys from control rats exhibited an increased expression of vascular endothelial growth factor (VEGF) while curcumin-treated rats had diminished expression. (B) Renal tissue from control rats also exhibited increased expression transforming growth factor-β (TGF-β) while kidneys from rats receiving curcumin demonstrated significantly reduced expression. In each of these figures, panel A shows a representative Western blot while panel B shows the fold change of expression from pooled data from all western blots in that group. *p<0.05 vs untreated.

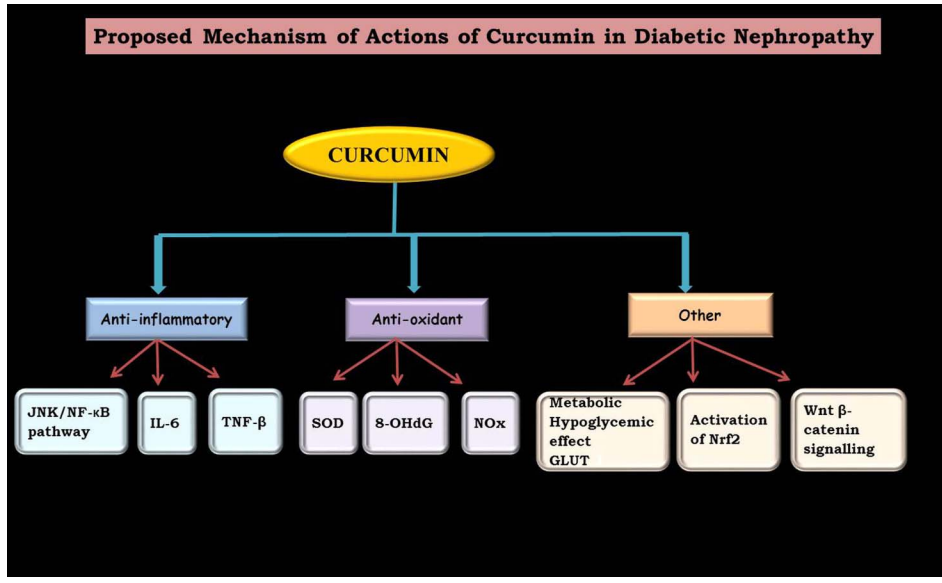

Figure 3 Proposed mechanisms of action of curcumin in diabetic nephropathy. Curcumin has been shown by several investigators including our group to have several renoprotective effects in clinical and experimental diabetic nephropathy. The mechanisms of such effects have been shown to involve multiple and different pathogenic and signaling pathways. In general, these reduce inflammation and oxidative stress in the kidney while there are also other metabolic pathways that curcumin modulates to affect renoprotection. 8-OHdG, *8-hydroxyl deoxyguanosine; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOX, nitric oxide metabolites, GLUT Glucose transporter; Nrf2, nuclear receptor (transcription) factor 2; SOD, Superoxide dismutase; TNF-β, tumor necrosis factor-β; Wnt- β, wingless-type MMTV integration site (WNT) family-β.

CONCLUSIONS

DN is a major and serious complication of diabetes and is the leading cause of ESRD. The available therapeutic options for DN are limited and only partly effective. Curcumin, an active ingredient of turmeric, has been found to be beneficial in many disorders[60] and is being actively investigated in diabetes[61] and its complications. This review summarizes many of the experimental and some clinical studies examining the safety and efficacy of curcumin DN with particular focus on the proposed molecular mechanisms (figure 3) of its action.[62] The overwhelming evidence supporting its salutary effects in DN warrants large-scale controlled randomized trials to validate its therapeutic potential.

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