LEADING ARTICLE

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New Potential Agents in Treating Diabetic Kidney Disease

The Fourth Act

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Abstract

Despite the worldwide epidemic of chronic kidney disease complicating diabetes mellitus, current therapies directed against nephroprogression are limited to angiotensin conversion or receptor blockade. Nonetheless, additional therapeutic possibilities are slowly emerging. The diversity of therapies currently in development reflects the pathogenic complexity of diabetic nephropathy. The three most important candidate drugs currently in development include a glycosaminoglycan, a protein kinase C (PKC) inhibitor and an inhibitor of advanced glycation. In targeting primary mechanisms by which hyperglycaemia contributes to diabetic complications, these drugs could provide risk reduction complementary to the partial reduction proven for ACE inhibitors and angiotensin II receptor antagonists (angiotensin receptor blockers).

Glycosaminoglycans act to restore glycoproteins present in reduced amounts in the glomerular basement membrane and mesangium of diabetic animal models. Components of the drug sulodexide prevent pathological changes and proteinuria in diabetic rats. Reductions in albuminuria, a hallmark of early diabetic kidney disease, have been reported in initial human trials. In the US, a multicentre phase II study has been completed, with an interim analysis indicating reduction in urinary albumin losses. Pivotal phase II trials have begun in patients with type 2 diabetes. A second metabolic pathway of diabetic complications is overexpression of PKC. Several activators of this family of intracellular kinases have been identified and PKC activation may result in tissue damage through a variety of mechanisms. In animal models, the inhibitor ruboxistaurin reduces albuminuria, diabetic histological changes and kidney injury. Like sulodexide, drug development of ruboxistaurin has reached completion of a phase II evaluation with mixed results. The third metabolic target is the nonenzymatic formulation of advanced glycation end-products (AGEs) through well described biochemical pathways. Multiple pathways lead to AGE accumulation in tissues in diabetes and diverse AGE products are formed. AGE deposition has been implicated in animal models of diabetic nephropathy. The leading AGE inhibitor currently in development is pyridoxamine, which has multiple actions that inhibit glycation. Pyridoxamine is an efficient AGE inhibitor in experimental diabetes. A phase II study in diabetic patients with nephropathy reported mixed efficacy results and a favourable safety profile. Phase III evaluation of pyridoxamine has not begun.

These three classes of potential therapies, if successfully developed, will confirm that diabetic kidney disease has entered the era of biochemical treatments.

The projected increase in diabetes mellitus worldwide in the coming decades will create an unmet need for new therapies for diabetic complications.[1] Diabetic nephropathy is already the leading cause of end-stage renal disease (ESRD) in the US (figure 1), and elsewhere in the Western world, the most severe complication of diabetes and the major predictor of premature death.[2] The increase in dialysis enrolment in the US over the past decade has derived primarily from diabetic kidney disease, mostly attributed to type 2 diabetes, the net effect of a growing incidence of type 2 diabetic patients and more effective treatment of type 1 diabetic nephropathy in recent years.[3] Diabetic ESRD, for many years the only cause of end-stage renal failure increasing among all ethnic groups, continues at especially high incidence rates in the elderly, Blacks and Hispanics.[4] While the incidence of diabetic ESRD in the US has finally plateaued,[5] the condition is still managed at a cost of over $US15 billion annually in the US.[6]

Therapy for risk reduction in diabetic kidney disease in 2006 is a drama that currently has three acts: glycaemic control, antihypertensive treatment and angiotensin blockade with ACE inhibitors and/or angiotensin II receptor antagonists (angiotensin receptor blockers [ARBs]). Each is only partially effective, although when combined as part of intensive intervention reduces the risk of microvascular events by 50%.[7] For example, in controlled trials, a 22–34% reduction in microvascular complications such as nephropathy was achieved for every 1% reduction in glycosylated haemoglobin (HbA_{1C}).[8-10] Similarly, the risk of renal endpoints (death, dialysis, transplantation) was reduced by approximately 20% in the recent clinical trials of ARBs.[11-13] Therefore, a strategy of multitarget pharmacological therapy appears to be necessary for improving kidney outcomes. However, a decade into the ACE inhibitor/ARB treatment era, approval of additional therapies has proven difficult. With three acts in production, the fourth act (the emergence of new therapies) has proven the most difficult to complete.

The difficulty can be attributed to at least two problems: (i) proving benefit in trial patients already on standard ACE inhibitor/ARB therapy; and (ii) the absence of a single dominant metabolic target to complement the primary haemodynamic action of ARBs. The resulting need is for complementary treatments that can impact on the primary mecha-

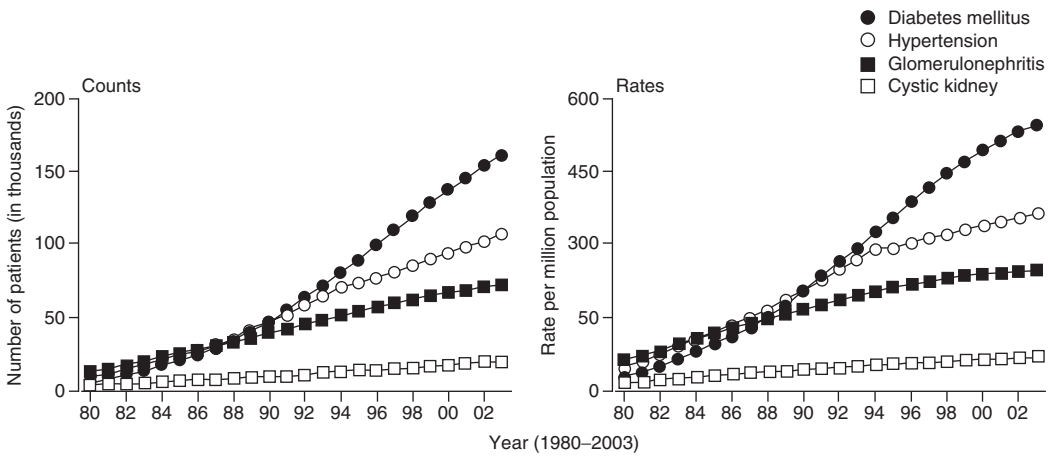

Fig. 1. Prevalent counts and adjusted rates of end-stage renal disease in the US, by primary diagnosis from 1980–2003.[5]

Table I. Potential new therapies for diabetic kidney disease

Study	Class	Drug	Current status
Gambaro et al.[15] Lewis et al.[16]	Glycosaminoglycan	Sulodexide	Phase III trials begun
Tuttle and Anderson[17]	Protein kinase C inhibitor	Ruboxistaurin	Phase III trial planned
Williams et al.[18]	AGE inhibitor	Pyridoxamine	Phase II studies completed

AGE = advanced glycation end-product.

nisms by which hyperglycaemia is pathogenic in diabetic kidney disease. The contribution of biochemical factors beyond blood glucose involves a complex interplay of multiple pathways.[14]

To the possible omission of other potential nephroprotective agents, this review focuses on what this author considers the most important classes (and representative drugs) advancing through clinical trials for diabetic kidney disease. Table I lists the status of these agents. Additional potential agents include the following:

1. The proliferator-activated hypolipidaemic drug fenofibrate, which has potential for the treatment of insulin resistance, dyslipidaemia and hypertension.[19] In a diabetic rat model, treatment with fenofibrate suppressed the overexpression of plasminogen activator inhibitor-1 and tumour growth factor (TGF)-β1.[20]
2. The oral endothelin antagonist SPP301, which decreased urinary albumin excretion over 12 weeks compared with placebo in 286 diabetic patients already on standard angiotensin inhibition.[21]
3. The experimental drug pirfenidone, which has been shown to reduce glomerulosclerosis and interstitial fibrosis in multiple animal models of kidney disease, and is undergoing phase II evaluation in diabetic kidney disease.
4. XL784, a metalloproteinase inhibitor proceeding through phase II evaluation for diabetic albuminuria.

1. Sulodexide

Glycosaminoglycan therapy has emerged as a potential treatment for diabetic nephropathy, based on the concept that, in addition to haemodynamic and oxidative stress, glomerular abnormalities in diabetes also involve critical loss of glycosaminoglycans. The term glycosaminoglycan refers to a category of related molecules that share common biological properties, including heparin, low molecular weight heparin, heparan sulfate and mixed glycosaminoglycan formulations such as sulodexide and danaparoid sodium.[15] Glycosaminoglycans are among the glomerular glycoproteins identified as biochemical components of the glomerular basement membrane (GBM) matrix structures. One glycosaminoglycan in particular, heparan sulfate, is thought to be a determinant of glomerular permeability *in vivo*.[22] Partial loss of anionic heparan sulfate occurs in the glomerular basement membrane in patients with diabetes.

Sulodexide is an oral formulation of the natural polysaccharide, glycosaminoglycan. The chemical name for sulodexide, a heparinoid compound, is glucuronyl glycosaminoglycan. The final drug mixture of sulodexide is a heterogeneous group of three naturally occurring glycosaminoglycan polysaccharide components, including approximately 80% low molecular weight heparin, 20% dermatan sulfate and <4% high molecular weight heparin, isolated from porcine intestinal mucosa, with a mean molecular weight of approximately 9000D. The drug is rapidly absorbed and depends in part on urinary elimination.[23] It is distinguishable from other glycosaminoglycans by having minimal or no demonstrable anticoagulation activity after oral administration in the doses being evaluated, and potential nephroprotective effects.

While its dominant action is uncertain, several physiological mechanisms could explain how provision of the glycosaminoglycan sulodexide might be nephroprotective in diabetic nephropathy.[24] Drugs such as sulodexide could potentially target metabolic defects of the mesangial matrix, the basement membrane and the endothelium. Treatment with

glycosaminoglycan agents is directed at restoring the glycoprotein content present in the GBM and mesangium in diabetic animal models.[25] The proteoglycan content of the GBM, for example, is known to be reduced in diabetes, perhaps due to upregulation of heparanase (HPR)-1, a heparan-sulfate-degrading endoglycosidase.[26] HPR-1 degrades heparan sulfate proteoglycans, a major component of the GBM. HPR-1 is upregulated with high glucose conditions. Secretion of active heparanase may be inititiated by protein kinase C (PKC) signalling.[27] Sulodexide inhibits HPR-1 activity *in vitro*.[28] Both low molecular weight heparin and dermatan sulfate have been shown to prevent reduction in charge density and structural changes in the GBM in experimental models,[25,29] although neither has been studied in the treatment of diabetic kidney patients. Gambaro et al.,[25] leading glycosaminoglycan investigators, have reported that glycosaminoglycans work primarily through activity on the synthesis of matrix and GBM molecules by glomerular cells. They include (i) inhibition of HPR-1 activity; (ii) prevention and correction of thickening of the GBM;[25,29] (iii) histochemical restoration of the ionic charge barrier of the GBM;[23,30] (iv) suppression of altered mesangial-cell proliferation;[31] (v) reduction of the TGFβ1 expression and mesangial matrix expansion; (vi) antithrombotic effects; and (vii) suppression of endothelin overproduction related to proteinuria.[32]

In a number of studies on the protective effects of administered glycosaminoglycans in experimental diabetic nephropathy,[33] a variety of glycosaminoglycans have been investigated. Gambaro et al.[29] initially reported several years ago that low molecular weight heparin and dermatan sulfate, components of sulodexide, were effective in preventing the pathological changes of GBM thickening and glomerular anionic charge reduction, as well as the onset of albuminuria, in streptozocin-diabetic rats treated for 8 months. Urinary albumin excretion did not rise, a desired effect, while no benefit in terms of renal function was reported. A follow-up study using a chemically modified heparin glycosaminoglycan with very low anticoagulant activity examined in more detail the effects of glycosaminoglycan formulations on possible regression of experimental diabetic nephropathy. Urinary albumin excretion was reduced by two-thirds. The study supported the previous observations that chronic glycosaminoglycan administration prevented pathological changes of diabetes. In rats with established disease, mild signs of diabetic nephropathy were reversed after several months of modified heparin therapy.[25]

Selected studies in the subsequent clinical development of sulodexide are shown in table II. The initial database has included eight small European clinical trials, a phase II European dose-ranging study (DiNAS; Diabetic Nephropathy and Albuminum Sulodexide) and ultimately a phase II study initiated in the US in 2004. The European trials enrolled a total of 185 type 1 and type 2 diabetic patients with micro- and macroalbuminuria.[34-41] Sulodexide was administered in dosages of 50–100 mg/day for <2 months in all but two studies. Reduction in albuminuria has been a consistent finding, ranging from 20–50% in microalbuminuric and 35–62% in macroalbuminuric patients,

Table II. Selected clinical studies of sulodexide in human diabetic nephropathy

Study	Type of diabetes mellitus	No. of pts	Duration (mo)	p-Value for AER reduction
Solini et al.[34]	Type 2	12	4	0.033
Velussi et al.[35]	Type 2	24	6	<0.01
Poplawska et al.[36]	Type 1	12	1	0.001
Dedov et al.[38]	Type 1	36	0.75	<0.005–<0.001
Szelanowska et al.[39]	Type 1	15	0.75	<0.0007
Skrha et al.[40]	Type 1 or type 2	53	0.75	<0.001
Sorrenti et al.[41]	Type 2	15	0.1	<0.05
Gambaro et al.[15]	Type 1 or type 2	223	4	<0.05

AER = albumin excretion rate.

and tending to persist for a period after drug discontinuation. Although a minority of patients in all eight trials were receiving concomitant ACE inhibitor therapy, over half of this subset also exhibited reductions in albuminuria.

In addition, the clinical safety and efficacy of sulodexide was evaluated in the phase II DiNAS trial[15], where 223 micro- and macroalbuminuric type 1 and type 2 diabetic patients were randomised to sulodexide 50, 100 or 200 mg/day, or placebo. After 4 months of treatment and an additional 4 months of observation, these dosages produced reductions in albuminuria of 30, 49 and 74%, respectively. At the highest dosage, urinary albumin excretion was normalised in 42% of patients versus 14% with placebo. Subgroup analysis indicated that sulodexide was equally effective in type 1 and type 2 diabetic patients, in patients treated with an ACE inhibitor versus those not, and in both micro- and macroalbuminuric patients. Follow-up evaluation after 16 weeks of treatment revealed that modest reductions in albuminuria were sustained in the 200 mg/day group, suggesting structural improvements in the diabetic kidney. During the DiNAS trial, only 14 adverse events and no serious adverse events were noted. Among the dosage subgroups, there were no differences in the adverse-event profiles.

A multicentre phase II pilot study has since been in progress in the US and completed enrolment in late 2004. An interim analysis was reported at the 2005 American Society of Nephrology meeting.[16] The effect of 6 months of sulodexide 200 or 400 mg/day compared with placebo was evaluated in 149 patients with type 2 diabetic nephropathy and microalbuminuria, concurrently treated with maximal ACE inhibitor or ARB therapy. The primary endpoint was remission or a 50% reduction from baseline in microalbuminuria. In the interim analysis of over three-quarters of enrolled patients, sulodexide significantly reduced albuminuria, including at the lower dosage.[16] The drug was well tolerated. A phase III study of sulodexide in overt type 2 diabetic nephropathy totalling 2000 patients and conducted by the Collaborative Study Group began in 2005,[16,42] and was followed by the start of a microalbuminuria study with sulodexide 200 mg/day in type 2 diabetic patients.[43] A separate small study[44] of 30 diabetic patients treated with sulodexide 50 mg/day has also reported reduction in albuminuria and favourable tolerability.

2. Ruboxistaurin

As an alternative to achieving euglycaemia, an alternative strategy would be to block pathways that are activated by hyperglycaemia.[45] Growing evidence indicates that high expression of PKC plays an important role in early tissue damage in diabetes.[46] PKC is a family of multifunctional intracellular serine-threonine kinases involved as signal transduction mediators, found throughout the body and leading to cell growth, fibrosis and tissue injury. At least 12 isoforms of PKC are known to exist.[17] PKC is activated in response to a variety of specific hormonal, neuronal and growth factor stimuli. Glucotoxins are known to induce cellular signaling alterations in the form of activation of protein kinase.[47] The classic activator of many PKC isoforms is diacylglycerol, which is produced in response to hyperglycaemia[48-50] (figure 2). Other isoforms are calcium-dependent or calcium- and diacylglycerol-dependent. Other metabolic activators of PKC have also been identified, including high levels of nonesterified fatty acids and amino acids[51,52] the intracellular concentration of which is heightened in states of hyperglycaemia. Cellular PKC activity can also be increased by glycation end-products and by a renin-angiotensin system activated by hyperglycaemia,[53,54] effects reduced by advanced glycation end-product (AGE) inhibition and ACE inhibition, respectively.[55,56] The activation of PKC creates involvement in the signal regulation of several physiological and pathological processes that are tissue-specific.[57] Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase upregulation, for example, is PKC dependent.[58]

PKC-β appears to play a role in the pathogenesis of kidney disease in diabetic animal models. PKC isoforms are chronically activated in multiple tissues including renal glomeruli and vascular tissues

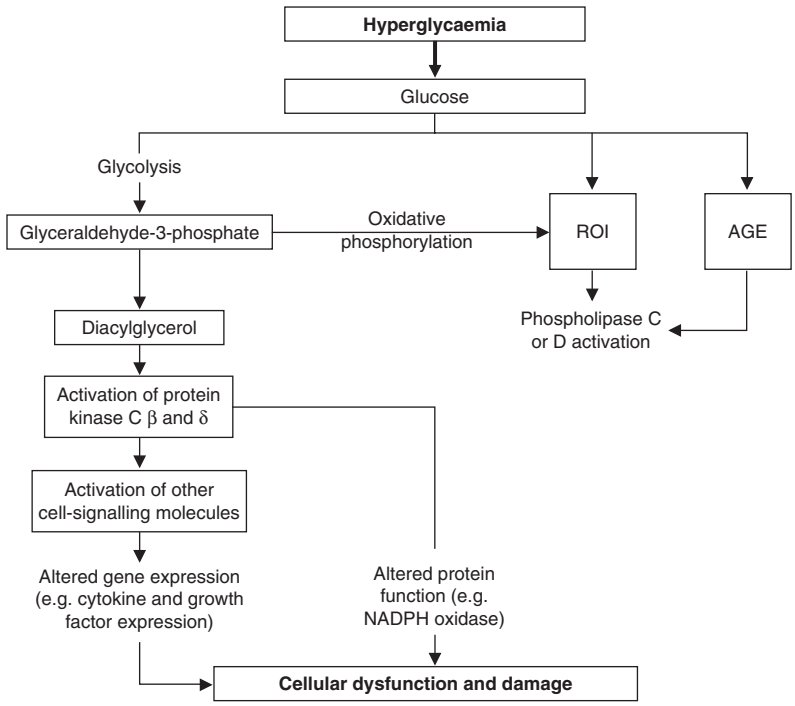

Fig. 2. Proposed pathway for pathological activation of protein kinase C in diabetes mellitus. **AGE** = advanced glycation end-product; **NADPH** = nicotinamide adenine dinucleotide phosphate; **ROI** = reactive oxygen intermediates.

in diabetic humans and animals. This activation induces kidney injury in the form of renal hyperfiltration, basement membrane thickening, glomerulosclerosis, endothelial dysfunction and increased capillary permeability.[47,59] PKC activation may cause kidney as well as vascular damage in diabetes through a variety of mechanisms. First, activation of PKC is a major signalling pathway for TGFβ to induce extracellular matrix production, an essential feature of diabetic nephropathy.[46] Secondly, PKC activates NADPH oxidase, leading to reactive oxygen species and oxidative stress in vascular tissues in diabetes.[60] Thirdly, glomerular endothelial nitric oxide inhibition by glucose was recently reported through a PKC mechanism.[61]

Therefore, inhibition of the activated PKC pathway could be beneficial in preventing both the micro- and macrovascular complications of diabetes. Discovered a decade ago, ruboxistaurin is a novel highly selective inhibitor of activation of certain PKC isoforms.[62,63] Pharmacological data recently reported described several metabolic pathways and intestinal excretion of the parent drug and metabolites.[64] The pharmacological actions of ruboxistaurin have been shown in several rodent models of diabetes to prevent vascular dysfunction. In a rat model of type 1 diabetic glomerulopathy induced by streptozotocin, ruboxistaurin normalised renal hyperfiltration and diminished albuminuria in association with normalising PKC activity.[65] In a separate study[66] of this model, ruboxistaurin prevented induction of pro-fibrotic factors and extracellular matrix proteins in glomeruli and cultured mesangial cells obtained from the diabetic animals. In other rat and mouse models, ruboxistaurin also reduced albuminuria, mesangial expansion and glomerular expression of TGFβ.[67,68] Ruboxistaurin has also been shown to reduce oxidative stress in glomeruli in rats with diabetes induced by streptozotocin,[51,69] through specific actions of decreasing NADPH subunit activity. A recent focus of PKC inhibition in diabetic nephropathy has been

tubulointerstitial injury, including TGFβ-rich macrophage accumulations in response to the chemokine osteopontin. In cell culture, PKC mediates this response. In diabetic rats, PKC inhibition with ruboxistaurin attenuated TGFβ activity and interstitial injury, suggesting a new mechanism for its protective effect on the kidney.[70]

Ruboxistaurin drug development moved forward with the recent publication of results of a phase II pilot study in type 2 diabetic nephropathy.[71] A total of 123 patients with persistent albuminuria despite standard of care for glycaemic control and ACE inhibitor or ARB therapy were enrolled in a double-blind, multicentre trial and treated with either ruboxistaurin 32 mg/day or placebo for 1 year. The primary efficacy endpoint was the reduction in urinary albumin excretion. While ruboxistaurin-treated patients experienced an average of 24% decrease in albuminuria, the reduction was not statistically different from the placebo group. Changes in estimated glomerular filtration rates also did not differ statistically between the groups. No significant safety concerns were evident. The results may be viewed as promising in that, although the study was not powered to definitively assess efficacy, albuminuria was reduced and renal function stabilised with treatment compared with baseline. Also of note, the recent PKC-DRS (Protein Kinase C beta Inhibitor Diabetic Retinopathy Study) study group report on ruboxistaurin in moderately severe diabetic retinopathy indicated mixed results with the experimental drug. Ruboxistaurin lacked efficacy in preventing progression of retinopathy itself to more severe stages, while reducing the risk of moderate vision loss.[72] The study drug was well tolerated without significant adverse effects over 36–46 months. Ruboxistaurin has also been investigated for the treatment of diabetic peripheral neuropathy. A recent phase II study reported no overall response to ruboxistaurin in the treatment of symptomatic diabetic neuropathy, although a subgroup of less severe patients appeared to benefit.[73] Subsequently, a new drug application has been filed in the US for the treatment of diabetic retinopathy.

3. Pyridoxamine

Evidence has grown, particularly over the last decade, to implicate the nonenzymatic formation of AGEs as a significant factor in the development of long-term complications of diabetes including nephropathy.[68,74-76] AGEs are diverse structures formed by a number of mechanisms in tissues and are biochemically active. Several pathways of protein damage by glycation reactions have been proposed *in vitro* and *in vivo*,[77] including protein modification via the Amadori pathway, via reactive carbonyl species and via reactive oxygen species. Chemical modification of amino groups on a variety of proteins (figure 3) by glucose, a reducing sugar, through a series of oxidative and nonoxidative reactions, is considered one of the pathogenic mechanisms of diabetic complications. The pathway to AGE formation consists of individual steps. Initially, glucose interacts with protein amino groups residing in extracellular tissues, in intracellular environs not regulated by insulin[78,79] and in skeletal muscle and liver. In the next step, a nearly irreversi-

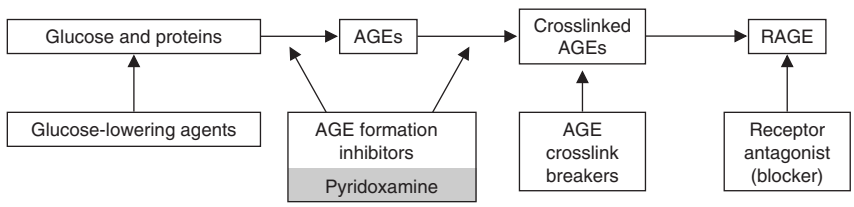

Fig. 3. Impact of advanced glycation end-product (AGE) inhibitors as shown in a simplified glycation pathway. **RAGE** = receptor for AGEs.

ble Amadori rearrangement proceeds, yielding proteins modified by intermediate Amadori products. These glycated proteins are then subject to slow oxidative breakdown and yield pathogenic AGEs, which accumulate on collagen and other long-lived molecules. The final step in some reactions is the formation of various types of crosslink structures between contiguous macromolecules. Many of the subsequent effects of AGEs are mediated by pathogenic signaling through the receptor for AGEs (RAGE).[80]

In reality more complex than portrayed in figure 3, AGE biochemistry indicates that a number of AGE pathways may produce AGE accumulation in diabetic tissues. Prolonged hyperglycaemia, dyslipidaemia and oxidative stress in diabetes may all result in the chronic production and tissue accumulation of AGEs.[81] Nonenzymatic glycation is enhanced in the presence of oxidative and carbonyl stress. *In vivo*, diverse sources of glycation products include, for example, those derived from breakdown of polyunsaturated lipids or from methyl glyoxal, a reactive intermediate molecule. The structure of several AGEs has been identified *in vitro*,[82] while only a few have been identified and characterised in tissues, including pentosidine, carboxylmethyllysine and pyralline.[83] Researchers have reported measurements of tissue as well as serum AGEs as markers of diabetic nephropathy. While progress has been slow in causally linking AGEs to diabetic kidney disease,[84] functional[85] and structural evidence does implicate AGE deposition in mesangial cells and animal models.[86] Additional support for a pathogenic role of AGEs comes from preclinical studies indicating that inhibition of AGE synthesis can ameliorate diabetic complications.[87] This therapeutic response seems to occur with AGE inhibitors[88-90] chemically disparate and possibly operating through separate mechanisms of action. Several approaches to AGE inhibition have been shown to confer some degree of renoprotection.[91] Faced with AGE structures that are diverse targets, and AGE mechanisms and *in vivo* effects that are biochemically complex, the result is that no AGE inhibitors have yet obtained regulatory approval.

Over the last decade, Hudson and colleagues[92] identified pyridoxamine as part of a new class of AGE inhibitors. Pyridoxamine is a post-Amadori AGE inhibitor, i.e. an 'Amadorin'.[77] Pyridoxamine entered clinical development as a potential inhibitor of AGEs that arise from the breakdown of glycated proteins (Amadori products). Its multiple actions have been reviewed by Voziyan and Hudson.[92] While the precise mode of action of this agent *in vivo* is not certain, it appears to inhibit glycation by blocking oxidative degradation of Amadori intermediates, scavenging toxic carbonyl products of glucose degradation and trapping reactive oxygen species.[92] It has been suggested that these balanced, moderate effects argue in favour of the safety and efficacy of the product. Pyridoxamine is one of three natural forms of pyridoxine (vitamin B6). It is normally minimally present in plasma, since it is formed by an intracellular process of transamination from pyridoxal 5′ phosphate, which is the major coenzymatic form of pyridoxine. Beneficial effects of other B group vitamin derivatives, such as benfotiamine, have also been reported.[93,94] To achieve concentrations of pyridoxamine believed to be therapeutic requires exogenous administration of pyridoxamine itself. Once achieved, several preclinical studies indicate that oral pyridoxamine is capable of preserving kidney function in type 1 and 2 diabetic nephropathy animal models,[95,96] including a preventive type 1 streptozocin-rat model and an intervention type 2 db/db mouse model where diabetic nephropathy was evidenced by histology and proteinuria. Recent studies have suggested that pyridoxamine is an efficient AGE inhibitor in various biological systems.[97] Pyridoxamine has been shown to inhibit lipaemia[95] and retinopathy[98] in experimental diabetes. Additional studies recently reported that carbonyl stress in diabetes resulted in weakening of cell-matrix interactions in renal glomeruli, contributing to fundamental change in mesangial expansion. Pyridoxamine protects this cell-matrix interaction.[99]

Pyridoxamine has been in development for the treatment of diabetic nephropathy, and has completed acute and chronic toxicology studies in animals,

as well as phase I and II clinical studies. A phase II study[18] was undertaken primarily to assess the safety and tolerability of oral pyridoxamine at a conservative dose of 50mg twice daily versus placebo in diabetic patients with overt diabetic nephropathy who were treated for 6 months at sites in the US. In this randomised, double-blind trial, a total of 128 patients with a serum creatinine <2 mg/dL and a calculated creatinine clearance of >40 mL/min were randomised and treated for 24 weeks. All patients were allowed to receive concurrent medications for the treatment of their diabetes, hypertension or kidney disease, including ACE inhibitors and ARBs. Because a previous report had suggested that megadoses of pyridoxine caused toxicity to nerves,[100] the analysis included a detailed neuropathy assessment. When pyridoxamine and placebo groups were compared, no differences in adverse events or deaths attributed to study drug were reported. No changes in neurological function due to the study drug were evident in specialised neurological testing. *Post hoc* efficacy analysis indicated that the rate of increase in serum creatinine over time in the pyridoxamine group tended to be less than with placebo. In the subset of subjects more likely to show progression of their renal disease (i.e. with poorer initial renal function, baseline serum creatinine levels >1.3 mg/dL), a significant treatment benefit was retrospectively determined. In patients with type 2 diabetes concurrently receiving either an ACE inhibitor or an ARB, and with a creatinine level of >1.3 mg/dL at baseline (similar to those studied in the widely cited Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study [RENAAL][13] and the Irbesartan in Diabetic Nephropathy Trial [IDNT]),[12] the rate of rise in serum creatinine was also slightly lower in the pyridoxamine than the placebo group. There were no significant reductions in mean albuminuria rates in the pyridoxamine group compared with placebo over the course of the trial. While additional phase II studies have been completed with pyridoxamine, no subsequent clinical trials of the drug have been registered at this time.

4. Conclusion

Established therapies for chronic kidney disease secondary to diabetes mellitus achieve patient risk reduction for ESRD. Additional risk reduction by complementary therapies has been difficult to prove, but is likely to emerge from three drug classes currently in clinical development: glycosaminoglycans, PKC inhibitors and AGE antagonists. Leading drugs in each class target primary mechanisms by which hyperglycaemia contributes to nephropathy complications. A strategy of multiple risk reductions in the future is likely to include pharmaceutical agents from these classes.

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