

## Review Article

# Molecular Mechanisms of Pathways in Diabetic Nephropathy Development in Patients with T2DM -A Review

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### Abstract

Diabetic nephropathy is related to increased mortality in diabetic patients and may be a major reason for end stage renal disease in most countries. The consequence of the combination of metabolic and hemodynamic pathway tends to be diabetic nephropathy. Glucose dependent pathways are activated with in diabetic kidney. This involves growing oxidative stress, and advanced glycated end-product accumulation. The pathogenesis of diabetic nephropathy also includes elevated systemic and intraglomerular pressure and also activation of multiple vasoactive hormone pathways, such as renin-angiotensin and endothelin. The aim of this review analysis is to gather knowledge of the molecular pathways and the factors involved in the pathogenesis of diabetic nephropathy.

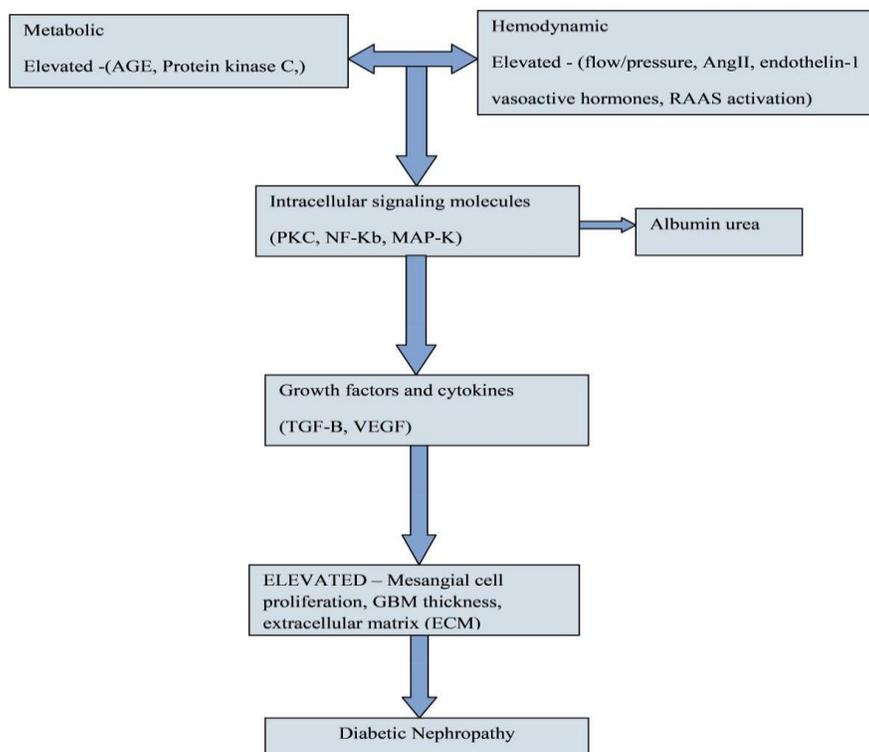
### 1. Introduction

Diabetic nephropathy is also known as Kimmelstiel Wilson Syndrome and was identified in 1936 by Clifford Wilson and Paul Kimmelstiel. Diabetic nephropathy is the product of associations between hemodynamic and metabolic factors [1]. Excessive systemic and intraglomerular strain, together with active multiple vasoactive hormone pathways including renin angiotensin and endothelin [2], is implicated in hemodynamic factors contributing to the production of diabetic nephropathy. These hemodynamic pathways activates intracellular second

messengers such as protein kinase C (PKC), mitogen-activated protein (MAPkinase) [3] and nuclear transcription factors such as the NF- $\kappa$ B and vascular endothelial growth factor, VEGF. Glucose-dependent pathways are most often triggered in the diabetic kidney and lead to increased oxidative stress, renal polyol formation [4] as well as aggregation of advanced glycation end products (AGEs). In addition, the effects of these processes gradually improve the permeability of renal albumins and extracellular matrix, which results in increased proteinuria, glomerulosclerosis and finally tubulointerstitial fibrosis. The impact of diabetic nephropathy on the expanded CKD and ESRD population is massive. Increased multifactorial treatment in patients with type 2 diabetes has resulted in decreased incidence of Controlled Steno Type 2 trials of micro-angiopathy and mortality; yet ESRD is that worldwide [5-7]. In these circumstances it will substantially enhance and encourage the creation of new therapeutically focused strategy through the discovery of inflammation-related molecules and pathways that are critically involved in the progression of diabetic nephropathy [8, 9]. The existing state of work in relation to molecules and pathways involved in diabetic nephropathy and its pathogenesis is discussed and the opportunities for diabetic nephropathy study are outlined in this analysis.

## 2. History of Diabetic Nephropathy

Diabetic nephropathy has a pathological background distinguished by the prior clinical period in which hyperglycaemia is followed by an improvement in GFR and microalbuminuria (Urinary albumin excretion of urine samples of up to 20–200 mg / min). Lifetime high glomerular flow and pressure and poor hyperglycaemic control eventually cause renal damage, leading to microalbuminuria progression to macroalbuminuria and a decline in the amount of GFR. In 20-40% of patients with type 2 diabetes over a 15-20-year span since the onset of the condition, development to macroalbuminuria (urinary albumin excretion > 200 mg / min) or active nephropathy is reported. Since macroalbuminuria exists, the rate of clearance of creatinine ranges significantly across individuals, with the estimated reduction in untreated individuals of 10 to 12 ml / min per year. The decline of GFR and the growth in final stage renal disease can be accelerated by hypertension and proteinuria [10, 11]. Furthermore, the incidence of cardiovascular disease is increased with microalbuminuria and proteinuria separate marks [12, 13]. While nephropathy typically exists in type 1 and type 2 diabetes, coronary losses in type 2 diseases are more prevalent from the outset. This is probably because Type 2, diagnosis, when macrovascular and microvascular complications are undetected, is usually diagnosed relatively late in the course of the disease.



**Figure 1:** Interrelationship of hemodynamic and metabolic pathway, cytokines and intracellular signalling molecules mediating diabetic nephropathy.

### 3. Hemodynamic pathway and their link with metabolic pathway

The early symptoms in both afferent and efferent glomerulin are glomerular hyperfusion and high filtration, which are the result of decreasing resistance. Afferent arteriole is more robust than efferent arteriole. A variety of causes, such as nitrogen oxide, prostanoids, VEGF, TGF- $\beta$ 1, and the rennin angiotensin mechanism, in particular angiotensin II, have been shown to be implicated in this deficient self-regulatory activity. Early hemodynamic changes limit glomerular capillary leakage and overproduction of the mesangial cell matrix as well as distribution and damage to podocytes of the glomerular basement membrane [14]. More mechanical pressure due to these hemodynamic shifts may also contribute to localized release of certain cytokines and growth factors [15]. Vasoactive hormone, like angiotensin II and endotheline, mediate changes in renal hemodynamics. The use of renin-angiotensin-blockers preserves kidney activity and anatomy which leads to the production of diabetic nephropathy. Blockage of the renin-angiotensin - aldosterone pathway by raising its TGF- $\beta$ 1 activation antagonizes the profibrotic activity of Angiotensin II [16]. The analysis of an animal model of diabetic nephropathy further confirms the idea that diabetic nephropathy underlies such profibrotic effects [17]. Proteinuria and strengthened glomerular structures were decreased by temporary (7 weeks) blockage of the renin – angiotensin network in prediabetic rats. In fact, an regulator of angiotensin-converting enzymes is decreased in TGF- $\beta$ 1 serum rates in patients with type-1 diabetes and nephropathy. Shows there is a link between decreased serum-and-urine TGF- $\beta$ 1 rates and the renewal as defined by glomerular filtration rate shifts.

#### 4. Reninangiotensin system in nephropathy

The renin-angiotensin aldosterone system is a hormonal system in the organism that is necessary to control blood pressure and fluid balance (RAAS). The main components of the system are three renin, angiotensin II and aldosterone hormones. The rate of renal blood flow is mostly controlled. Diabetes has been studied intensively. Previous research based on systematic RAS including information and findings were contradictory, motivating, restricting and the system was notified of almost any changes [18]. The controlling variables of systemic RAS as well as the multiple disease stages, many of these divergent observations may be clarified by organisms examined. For various diabetic types, the renal renin content is increased. This was commonly observed, however, compared to plasma renin levels. Suggested release into circulation of damaged rennin, Plasma rennin is reduced. Clinical diabetic nephropathy activity is attributable to nonenzymatic prorenin glycation with a lower renin transfer. Usually, nephropathy was known as a condition of low renin. However, the behavior of plasma renin does not necessarily reflect the operation of Kidney RAS. The challenge of precise calculation became a further issue, Angiotensin-II (Ang II) plasma, which is important because there could be discordance between the levels of plasma renin and Ang II. More details a big research recently centered on intrarenal RAS. There is ample evidence that local tissue RASs that are regulated are plasma-independent RAS. The glomerular Ang II receptor decrease in the diabetic rat was recorded 3 to 4 weeks after disease induction. Glomerular down regulation Ang II receptors suggest that intra-renal Ang II can be Upgraded. Ang II receptor density in the next tubules has been reduced and supplemented by diabetic rats shows Lowered AT1 receptor and mRNA expression [19]. Recently, AT1 It's been shown that mesangial receptor density has dropped Incubation of the cells into high-glucose media [20].

The biochemical impact of angiotensin II Members by means of different cell-surface receptors In the receptor family 7-transmembrane. The receptor angiotensin can be divided Type 1 (AT1) and 2 pharmacological classes Based on its differential affinities type 2 (AT2) Different antagonists of nonpeptides as stated above. Learning outcomes With the use of these antagonists, most suggested RAS functions that are classically recognized AT1 receptors are mediated [21]. In contrast The AT2 receptor, however, appears to be working as an AT1 receptor actions detrimental modulator [22-24].

#### 5. Interconnection of Nitric oxide and Reactive oxygen species with RAAS

NO(Nitric oxide), initially referred to as a "endothelial relaxing factor," is a signaling molecule that controls an omnipresent use Large variety of organ and cell roles, like renal hemodynamics, regulatory water and salt. NO is produced, L-arginine amino acid by one of three enzymatically Nitric synthesis: neuronal (NOS1 or nOS) nitric oxide synthesis, Endothelial or 'inducible' (NOS3 or eNOS), (NOS2 or iNOS). Numerous, though not all, intracellular trajectories. The activation of guanylate cyclase is mediated by NO, This raises cyclic guanosine intracellular levels Monophosphate. The mammalian kidney contains all three NOS isoforms the distribution patterns are both distinct and overlapping. Typically a NOS1 in the macula densa and glomerular parietal epithelium is highly expressed both the collection ducts and thin upward limb in the medulla. NOS 2 is found in glomerular endothelia capillaries and afferent and efferent, renal and descending vasa recta arteries, including in proximal tubules and medullary thick ascending limb. In addition to accurate arteries and vase-recta bundles nos3 is also expressed in tubules, including S3 proximal tubules segments, medullary thick ascending limb, and collecting pipes [25]. The result was conflicting both in vivo and in vitro studies regarding NOS expression and NO diabetes

production. In response to hyperglycemia, most, but not all, experiments in cultured cells find a decrease of NO output.

Angiotensin II has direct implications for the kidney as glomerular capillary pressure increases and increase-regulation of the renal wound response components increases. The early study has shown that, in response to high-volume glomerular damage, endothelial cell injury triggers glomerulosclerosis, and involves local up-regularization of angiotensin II synthesis with enhanced expression of TGF- $\beta$ 1 and matrix proteins [26]. The endothelium is synthesized to produce a constituent precursor of nitric oxide (NOS), nitric oxide is an endogenous vasodilator that prevents the development of the vascular smooth muscles and mesangial cell development. Nitric oxide antagonizes the vascular sound and development effects of angiotensin II and therefore lowers the angiotensin converting enzymes (ACE) and angiotensin II of type 1 (AT1). Increased compressive force and cyclic strain increase the NOS activity in endothelial cells, which may be involved in early phases of diabetic nephropathy: high expression of vascular activity of NOS is a homeostatic adaptation to enhanced hemodynamic workloads that can reduce organ failure. Through time, though, the diabetic nephropathy has evidently raising its bioactivity by nitric oxide, A hypertensive design of rat nitric oxide depletion showed that renal lesions were dramatically decreased after treatment with an AT1 receptor blocking agent (ARB) [27]. Throughout this research, the positive benefits of an ARB were independent of blood pressure control as, given a significant reduction throughout systolic blood pressure, hydralazine appeared to enhance renal function. This supports the idea of much more effective anti-hypertensive agents to prevent or avoid renal disease that decreases blood pressure and thus preserve the homeostatic equilibrium of angiotensin II and nitric Oxide in the vessel wall [28, 29]. A functional imbalance of angiotensin II and oxide in hypertensive organ injuries has a major pathogenic role: angiotensin II lowers nitric oxide bio-availability by encouraging oxidative stress. In the translation of molecules that promote the pathogens of mesangial and vascular smooth cell pathology, excess production of superoxide anion in reaction to angiotensin II is of central importance.

Blocking recurrent glomerular and tubulointerstitial damage from RAAS clinically and experimentally [30, 31]. In patients suffering from type 1 diabetes, the ACE inhibitors displayed slow down renal decrease, while ARBs exhibited major benefits for both an early stage (microalbuminuria) and at a later stage (proteinuria) of renal deterioration in patients with type 2 diabetes. ARB treatment in the Irbesartan Diabetic Nephropathy in the angiotensin II – Losartan Study (RENAAL) were correlated with substantial proteinuria decreases, independently of blood pressure reduction. The ARB treatments were identified as having a negative effect on blood pressure. In REENAAL, Proteinuria was an important indicator of renal and cardiovascular disease in Occurrences [32]. ARBs was close to ACE Inhibitors when providing for long-term Reno protection in type 2 diabetic patients and initial diabetic nephropathy [33]. Such reports highlight the significance of RAAS blockades as a method to enhance the health performance of renal disease patients.

## 6. Endothelin-1 (ET-1)

Endothelin-1 (ET- 1) is an extremely active, hypertension-inflammatory, vasoconstrictive peptide [34, 35]. The activity of ET-1 increases with a higher risk of renal disease in diabetes [36]. ET-1 promotes proteinuria and is

active in the inflammatory and fibrotic processes of the renal cells [37]. As predicted, in laboratory models of diabetic nephropathy, selected ET-1A receptor blockers were seen to lower both blood pressure and albuminuria [38, 39]. Although, disappointingly, after 4 months of median treatments for elevated cardiovascular potential complications in the avosentan group like (edema, heart failure, cardiovascular death) [40]. The Elevate research work examining the ET antagonist avosentan in conjunction with RAS blockade was reinstated prematurely. However, albuminuria with avosentan has decreased by 40 percent compared to placebo. Related decreases in albuminuria, with moderate edema being the most severe adverse effect, have been found in a smaller sample in which another ET antagonist, atrasentan, was applied to a form 2 RAAS blockade for diabetic nephropathy people [41]. The loss of 50:1 selectivity for the ET1A Receptor with a higher doses of avosentan (> 5 mg daily), resulting in sodium and fluid retention by antagonism to the ET1B receptor, may explain the differences in adverse effects between avosentan and atrasentan [42]. The risk of edema end heart failure in the Evolve study is supposed to be higher in this unwanted effect. In comparison, atrasentan gives a strong degree of ET-1A absorbing selectivity, which contributes to corresponding experiments with a better protection profile [43]. An initial randomized controlled atrasentan clinical trial consisted of 211 adults who received placebo or atrasentan (0.75 mg/1.25 mg) with T2D and DKD on maximum RAAS blocks [44]. Atrasentan-treated patients saw a 35% drop in albuminuria, with around 50 % of patients reporting an albuminuria drop of about 30%. During the 12-week course of the study there's no substantial shift in eGFR. The weight gain and anemia in the atrasentan groups were indicated, but the edema or heart disease was not greatly affected. Evidence of the more recent analysis of diabetic nephropathy With Atrasentan (SONAR) atrasentan treatment has shown a decrease in the incidence of a standardized renal endpoint versus placebo in more than 2,500 adults with T2D Atrasentan (6.0 percent) vs. placebo (6.9 percent) (doubling of serum creatinine or end-stage kidney disease) [45]. This research was performed in a patient population that was specifically chosen. Despite that, An preliminary 4-week 'enrichment' duration with all atrasentan patients was subject to randomization – approximately 50 percent with patients were 'respondents' as shown in the earlier study, and only people who had a 30 percent albuminuria change despite fluid retention were randomised. In order not to hit the key endpoint in the pre-specified time period, the SONAR experiment was terminated early, although this was predicted to occur in providing lower event rates overall. If such positive findings can contribute to more therapeutic advancement remains to be seen.

## 7. Intracellular signaling

### NF-KB

In the pathogenesis of diabetic nephropathy NFkB is the most significant transcription factor. One of the relevance of NFkB is to continually be found in cells, even in an inactive state, in regulation of cellular responses. Activating pathways downstream of NFkB does not therefore need a new protein synthesis, allowing NFkB to be a primary respondent to damaging cell stimuli. NFkB dimers are sequestered by a class of inhibitors in cells that are not activated, known as IκBs - NFkb dimers. The linkage of IκBs to NFkB precludes translocation to the nucleus and keeps NFkB inactive. The released NFkB can be entered and the expression NFkB-dependent can be activated after IκB degradation.

A class of inhibitors called IκBs (NFkB Inhibitors) is sequestered in non-stimulated cells. The binding of the IκBs to

NFκB impedes its translocation into the nucleus and keeps NFκB inactive in the cytoplasm. Activation of NFκB is initiated by degradation of IκBs in response to extracellular signals, primarily via activation of IκB kinase. The liberated NFκB can reach the nucleus and stimulate NFκB-dependent genes expression following IκB breakdown.

In diabetic nephropathy patients, NFκB is a key part of the interplay between metabolic and hemodynamic variables. In endothelial cells, vascular smooth muscle cells and proximal tubular cells, hyperglycemia can itself activate NFκB. 108,109 Mechanical strain in human mesangial cells leads to single-cyte chemotaxis through a mechanism which depends on NFκB and CCL2. In addition, increasing data suggest that NFκB is important to several linked pathways, including the activation of the renin angiotensin systems, the buildup of AGE and NADPH-related stress, that contribute to the structural and functional alterations found in diabetic nephropathy.

The activation of NFκB and the simultaneous upregulation of NFκB-dependent proinflammatory genes has been demonstrated in biopsy specimens from patients with T2DM and overt nephropathy. NFκB activities are mostly observed in the cortical tubular epithelium cells, and are, to a reduced extent, related to proteinuria and interstitial infiltration in certain glomerular cells (particularly podocytes).

The importance of NFκB to diabetic nephropathy development has been reaffirmed in the last several years. In vivo investigations, first, it has been established that the evo-flooding of diabetically nephropathically experienced temporary alterations in NFκB activity, and the NFκB appears to be a significant mediator of the angiotensin II effects, predestinally via the angiotensin type-1 receptor II.

Finally, a study of human kidney biopsy samples collected for the European Renal Complementary DNA Bank identified an ‘inflammatory signature’ relating to activation of the NFκB pathway in patients with progressive diabetic nephropathy. A specific NFκB promoter module in conjunction with interferon regulatory factor complexes, termed ‘NFκB\_IRFF\_01’, is thought to act as a master switch to activate this response.

## 8. Growth factor and cytokines

### TGF beta and VEGF

Several growth factors, cytokines, chemokines and vasoactive agents have been implicated in pathogenesis of diabetic nephropathy. TGF-β, a fibrotic cytokine, plays a central role in the development of renal hypertrophy and accumulation of ECM components [46]. In addition, there is increased infiltration of monocytes and macrophages into glomeruli early in diabetes. The release of growth factors and cytokines from these monocytes and macrophages (interleukin-8, monocyte chemoattractant peptide-1 etc.) may contribute to promotion of glomerular growth. There is increasing evidence that intrarenal renin-angiotensin system is activated in diabetic nephropathy [47]. There is enhanced expression of Ang II receptors and decreased degradation of Ang II thereby increasing the local effects of Ang II [48] which acts in synergy with hyperglycemia in Free radicals promoting, renal hypertrophy and ECM protein production. The vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), and insulin-like growth factor are other variables which contribute to the development of diabetes nephropathy (IGF) [49].

VEGF in nephropathic diabetic Vascular Endothelial Growth Factor (VEGF) is a promising option for endothelial diabetes mediation. VEGF in the renal is generated by glomerular epithelial cells under healthy settings, while mesangial and tube epithelial cells are usually not producing that growth factor. It was demonstrated that during hyperglycemia, overexpression of VEGF occurs through PKC activation [50]. Further, TGF- $\beta$ 1 which is over expressed in kidney also enhances VEGF expression [51]. Moreover, glomerular permeabilization by VEGF might induce both albuminuria and increased mesangial traffic of growth factors from the circulating blood. Hyperglycaemia increases VEGF excretion in the mesangial cell and podocyte via pathways involving PKC and extracellular signal regulated kinase (ERK) [52]. Receptors for VEGF in the glomerulus are found in the endothelial cells and it is thought that this growth factor increases the permeability of the glomerular endothelium and is therefore responsible for the hyperfiltration seen in early diabetic nephropathy. The excision of VEGF in the mesangial cell was also enhanced with mechanical strain imitating the sheer stress generated by hyperfiltration and elevated glomerular pressure. In a study demonstrating this effect it seemed that the effects of shear stress in mesangial cells are mediated via a pathway dependent on PKC and Protein Tyrosine Kinase (PTK) since the combined inhibition of these enzymes completely prevented the increased VEGF excretion in an in vitro experiment [53]. However, MC can also produce VEGF [54] and express VEGF receptors both in vitro and in pathological conditions [55]. Furthermore, VEGF binding to its receptors on MC induces both cell proliferation and collagen expression, providing a possible mechanism by which VEGF may contribute to glomerular hypertrophy/sclerosis [56]. In addition, VEGF potentially stimulate eNOS expression and activity in endothelial cells [57]. TGF- $\beta$ 1 in Diabetic Nephropathy the TGF- $\beta$  seems to play a central role as a mediator in the pathologic changes in the glomerulus. It has been shown that the AGE formation, PKC activation, angiotensin II, and shear stress increase TGF- $\beta$  expression [58]. TGF- $\beta$  is a potent growth factor promoting the deposition of ECM components, such as collagen I, IV and fibronectin. This leads to, the histologically evident glomerular expansion and thickening of the basement membrane. The effects of TGF- $\beta$  are mediated by the TGF- $\beta$  receptor type II while the Smad pathway is the downstream intracellular signaling pathway involved in TGF- $\beta$  signaling [59]. This cytokine play a central role in the development of renal hypertrophy and accumulation of ECM components in diabetes [60]. During hyperglycemia, mesangial and proximal tubular cells synthesise more TGF- $\beta$  than control. In addition, it has been demonstrated that intracellular glucosamine production resulting from glucose metabolism is responsible for the increased TGF- $\beta$ 1 production in mesangial cells. Several vasoactive factors such as AngII, thromboxane [61] & endothelin-1 [62] may exert part of their growth stimulating and profibrogenic action in diabetic renal diseases to the secondary induction of TGF- $\beta$ . Furthermore non-enzymatic glycation reactions leading to AGE [63], as well as the early Amadori glucose adducts in proteins such as serum albumin have [64] been shown to stimulate renal expression of TGF- $\beta$  [65]. Amadori glucose adducts in albumin also increase expression of TGF- $\beta$  type II receptors m-RNA and protein levels in mesangial cells.

### ***Renal syndromes of nephropathy***

*Tubulopathies*

*Renal Tubular Acidosis/Fanconi Syndrome*

*Sodium Wasting*

*Potassium Wasting*

*Nephrogenic Diabetes Insipidus*

*Nephrotic Syndrome/Proteinuria*

*Glomerular Disease*  
*Minimal Change Glomerulonephritis*  
*Focal Segmental Glomerulosclerosis*  
*Membranous Glomerulonephritis*  
*Other*  
*Thrombotic Microangiopathy*  
*Hemolytic uremic syndrome/ Thrombotic thrombocytopenic purpura*  
*Acute Kidney Injury*  
*Hemodynamic Disturbances*  
*Parenchymal Kidney Disease*  
*Collecting System Disease*  
*Chronic Kidney Disease*  
*Analgesic Nephropathy*  
*Chronic Tubulointerstitial Nephritis*  
*Secondary Progression of Toxin-induced Kidney Disease*

## 9. Conclusion

Complex relationships between hemodynamic and metabolic routes that contribute to diabetic nephropathy. Although proven therapy used in the appearance of symptoms include strict hyperglycemia regulation and the use of the rennin angiotensin system inhibitors, various metabolic pathway such as advanced glycation and particular protein kinase C isoforms provide essential hope for the future<sup>65</sup>. A mixture of therapies is expected which directly impact various phases in diabetic nephropathy pathophysiology. The development will need to be more minimized and diabetic nephropathy stopped in future.

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NA

## Conflicts of interest

All authors declare no conflict of interest to disclose.

## Ethics statement

This study doesn't involve animals or human subjects.

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