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ADVANCED GLYCATION END PRODUCTS IN PROGRESSIVE COURSE OF DIABETIC NEPHROPATHY: EXPLORING INTERACTIVE ASSOCIATIONS

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ABSTRACT: Diabetic nephropathy is a major complication of diabetes and the most common cause of end stage renal damage (E.S.R.D). Diabetic nephropathy is a leading cause of morbidity and mortality and its prevalence is continuously increasing in industrialized nations. Hyperglycemias, hyperlipidaemia and hypertension are considered to be the major risk factors implicated in the progression of nephropathy. Possible mediators of untoward effects of hyperglycemias include advanced placation end products (AGEs) known to accumulate in diabetic subjects. However, mechanisms underlying the pathogenesis of diabetic nephropathy are not completely understood. AGEs have been recently reported to play an important role in the pathogenesis of diabetic complications, particularly in the progression nephropathy. At present, no promising therapy is available to treat patients with diabetic nephroapthy due to lack of understanding of mechanism involved in the pathogenesis of nephropathy. There have been wide-ranging reports underline the involvement of AGEs in progression of the diabetic nephropathy, but the exact mechanism is not known clear yet, Therefore in these review are trying to explore the interactive association of AGEs in diabetic nephropathy.

INTRODUCTION: Approximately 20–40% of patients with type-1 or type-2 diabetes mellitus (DM) develop diabetic nephropathy [1, 2]. Diabetic nephropathy is leading cause of End stage renal disease (ESRD) and most frequent cause of mortality. Possible mediators of undesirable events happened due to hyperglycemia include participation of advanced glycation end products (AGEs) known to accumulate in diabetic subjects [3, 4].

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The formation and accumulation of AGEs are characteristic features of aged or diabetic tissues and these products also have been strongly implicated in the pathogenesis of diabetic nephropathy complications [5, 6, 7, 8, 9, 10, 11] thus it accelerated our interest to assess these factors in this review. Better understanding of Advance glycation end product (AGEs) role in progression of diabetic nephropathy has a potential to lead to development of more effective drug.

Diabetic Nephropathy:

The classical definition of diabetic nephropathy is a progressive rise in urine albumin excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually ESRD [12, 13]. The diabetic nephropathy associated

with long-standing diabetes [14, 15]. Prevalence of diabetes mellitus is on the rise and it is estimated that there are 30 million diabetics in India, of which 6.6 million are expected to develop diabetic nephropathy (DN) [16]. The majority of diabetic patients starting DN therapy have been documented type-2 rather than type-1diabetes.Therefore it will be relevant to discuss nephropathy in both type-1 and type-2 diabetes [17].

Type-1 Diabetes:

The initial rise in protein excretion is small and highly selective, albumin being the main protein excreted in excess. At this stage, specific immunologically based assays detect small increases in urine albumin which are below the detection limit of conventional dipstick tests (**Table 1**).

TABLE 1: DEFINITIONS USED IN DIABETIC NEPHROPATHY

Albumin creatinine ratio (mg/mmol)	Normal	Microalbuminuria	Proteinuria
Men	<2.5	2.5–30	>30
Women	<3.5	3.5–30	>30
Albumin excretion Rate Overnight (μg/min)			
Men	<20	20–200	>200
Women	<30	30–300	>300

The microalbuminuria generally appears within 5–15 years duration of diabetes. Without specific intervention, over approximately a further 10 years, albumin excretion slowly increases through the microalbuminuric range, until dipstick positive or conventional proteinuria is present. Glomerular filtration generally does not begin to fall until proteinuria is present, when untreated; there is a progressive decline in glomerular filtration over a further 10 years, until ESRD is reached. Earlier literature suggested that the cumulative incidence of microalbuminuria after 30 years of type-1diabetes was approximately 50% and that 30%-40% of patients would develop proteinuria.

The incidence of proteinuria peaked at 4%-5% around 15-20 years' duration, with a smaller peak at 30-35 years' duration [18]. However, more recently, work has shown that the appearance of nephropathy may be delayed [19, 20, 21]. The cumulative incidence of microalbuminuria and proteinuria in several more recent studies is 35%-40% and 25% respectively after 25-30 years of diabetes. Initially studies suggested that 80% of type-1 diabetic patients with microalbuminuria would progress to proteinuria [22, 23].

However; recent studies suggest that around one third of microalbuminuric patients will revert to normal albumin excretion and only one third will progress to proteinuria [24, 25, 26]. In addition, in one small study, 24.4% of initially normoalbuminuric type-1 diabetic patients with duration of diabetes >30 years developed microalbuminuria or proteinuria in a seven-year follow-up [27]. Also in this study, 32% of the initially microalbuminuric patients progressed to proteinuria, in contrast to earlier suggestions that microalbuminuria in long-term duration diabetes was a benign condition [28].

Thus, the classical natural history of the development of nephropathy in type-1 diabetes is undoubtedly being modified. Microalbuminuria develops at around 2%-3% a year, with a cumulative incidence over a lifetime of diabetes of approximately 50%. Around one third of individuals with microalbuminuria will progress to proteinuria, at a rate of 2%-3% a year, and almost all proteinuric patients eventually develop ESRD. One small study has suggested that microalbuminuria and proteinuria may appear at any duration of diabetes, and patients with diabetes of long duration not protected kidney disease [13].

Type-2 diabetes:

The cumulative incidence of proteinuria in type-2 diabetic patients is similar to that of type-1 patients. Several studies have demonstrated rates of development of microalbuminuria and proteinuria in type-2 diabetic patients that are approximately comparable to those in type-1 patients [29, 30, 31]. In non-Caucasians, the cumulative risk of nephropathy is almost certainly higher and the disease may develop more rapidly than in Caucasian people. In Pima Indians (the most

intensively studied population) more than 50% develop proteinuria within 20 years of diabetes [31]. Longitudinal studies suggest that as in type-1 diabetes, glomerular filtration rate is preserved at the microalbuminuric stage. It is particularly concerning that the incidence of ESRD in the Pima Indians continues to rise despite improvements in blood glucose and blood pressure control. In other non-Caucasian populations, cross sectional studies indicate a prevalence of microalbuminuria of 30%–60% [32, 33, 34] and longitudinal studies suggest a rate of progression from normal albumin excretion to microalbuminuria of around 4% [35].

End-stage renal disease:

Worldwide, diabetic nephropathy is now the single commonest cause of entry to kidney replacement therapy (KRT) programmes [36]. In 2001, the incidence of ESRD disease caused by diabetes was 148 per million populations in the United States, 44.3% of the population beginning KRT having diabetes. However, the proportion of new entrants to KRT with diabetes varies widely geographically.

Other associations:

The two most important factors in the initiation and progression of nephropathy are blood glucose and blood pressure. Dyslipidaemia is deleterious, although there is no hard evidence yet [38].

Stages of Diabetic Nephropathy:

The kidney disease associated with long-standing diabetes. Kimmelstiel-Wilson disease (or Kimmelstiel-Wilson syndrome) or intercapillary glomerulonephritis is a type of diabetic nephropathy.

The natural history of diabetic Nephropathy evolves through 5 clinical stages; which are most clearly characterized in IDDM because its onset is distinct and precise in time as shown in **Table 2** [37, 38].

TABLE 2: **STAGES OF DIABETIC NEPHROPATHY** [37, 38]

Stage's	Clinical term	Histological Features	Functional Features	Clinical Features
Stage I	Initial Stage	Glomerular Hypertrophy	Increased GFR	Supra normal Clcr, Increased Kidney size.
Stage II	Early Renal involvement	GBM thickening Increased messangial matrix.	Increased GFR Normal UAE rate.	Supra normal Clcr,
Stage III	Incipient Nephropathy	Futhers GBM thickening and messangial matrix Expansion.	Increased UAE rate.	Persistently high UAE rates,Supranormal to normal Clcr,Increased in Blood pressure.
Stage IV	Clinical Nephropathy	Well-define diffuse and/or nodular diabetic glomerulosclerosis	Protenuria on routine urine analysis. Gradual reduction in GFR.	Proteinuria progressing to nephropatic syndrome , Established hypertention.Gradual increased in SCr.
Stage V	End Stage Renal Failure	Significant glomerular closure and obsolescence	GFR<15ml/min.	Hypertention.Anaemia, Uremic Syndrome.

Notes: Clcr: Creatinine Clearance, GFR: Glomerular filtration Rate, GBM: Glomerular basement membrane, SCr.: Serum Creatinine, UAE: Urinary albumin excretion.

Pathophysiology and factors associated with Diabetic nephropathy:

Diabetic nephropathy typically affects the network of tiny blood vessels (the microvasculature) in the glomerulus. Diabetic nephropathy includes the nephritic syndrome with excessive filtration of protein into the urine (proteinuria).When it is severe, diabetic nephropathy leads to kidney failure, ESRD, and the need for chronic dialysis or a kidney transplant. Long-standing hyperglycemia is known to be a significant risk factor for the development of diabetic nephropathy. Hyperglycemia may directly result in mesangial expansion. Increased mesangial stretch and pressure can stimulate this expansion, as of high glucose levels. TGF-β is particularly important in the mediation of expansion and later fibrosis via the stimulation of collagen and fibronectin [39, 40]. Besides, this TGF-β and various growth factors also play prominent role in membrane cholesterol

homeostasis [68]. Glucose can also bind reversibly and eventually irreversibly to proteins in the kidneys and circulation to form so-called advanced glycosylation end products (AGEs). AGEs can form complex cross-links over years of hyperglycemia and can contribute to renal damage by stimulation of growth and fibrotic factors via receptors for AGEs as shown in **Fig. 1**.

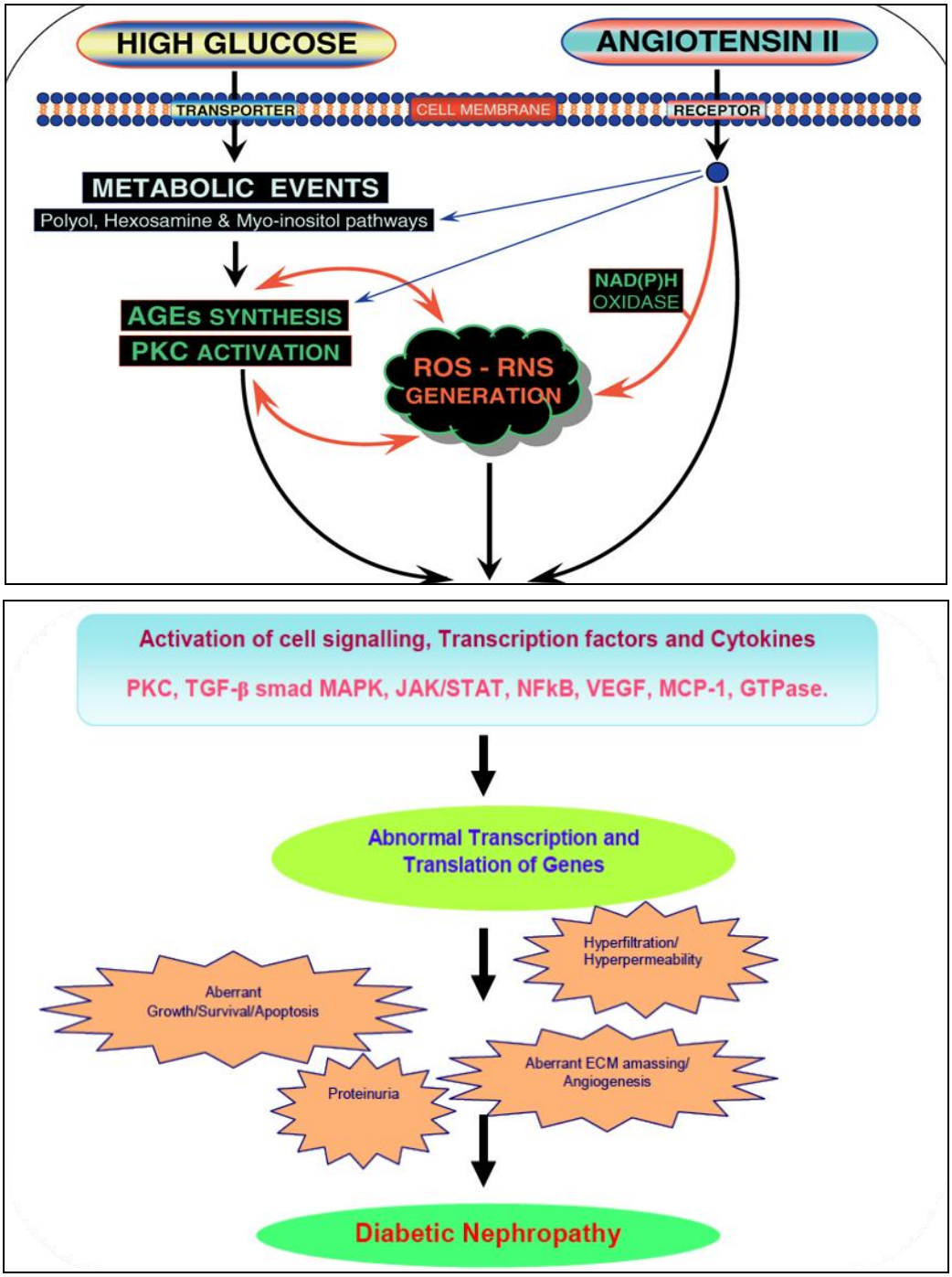

FIG.1: VARIOUS MECHANISMS RELEVANT TO HYPERGLYCAEMIA AND ADVANCED GLYCATION END PRODUCTS INDUCED ACTIVATION OF DIFFERENT SIGNALLING PATHWAYS WITH ALTERED EXPRESSION OF VARIOUS GENES AND CELLULAR DYSFUNCTIONS, LEADING TO DIABETIC NEPHROPATHY AND CHRONIC RENAL FAILUR

Notes: AGEs: Advanced Glycation End-products, PKC: Protein kinase C, ROS-RNS: Reactive oxygen species-reactive nitrogen species, NAD(P)H: nicotinamide adenine dinucleotide phosphate-oxidase, TGF-β smad: *Transforming growth factor beta* smad signalling, MAPK: *Mitogen-activated protein kinase*, JAK/STAT: Janus kinase/signal transducers and activators of transcription, NFkB: Nuclear factor kappa-light-chain-enhancer of activated B cells, VEGF: Vascular endothelial growth factor,MCP-1: Monocyte chemotactic protein 1,GTPase: Guanosine triphosphate enzyme

In addition, mediators of proliferation and expansion, including platelet-derived growth factor, TGF-β, and vascular endothelial growth factor (VEGF) that are elevated in diabetic nephropathy can contribute to further renal and micro vascular complications [39, 40]. Proteinuria, a marker and potential contributor to renal injury, accompanies diabetic nephropathy. Increased glomerular permeability will allow plasma proteins to escape into the urine. Some of these proteins will be taken up by the proximal tubular cells, which can initiate an inflammatory response that contributes to interstitial scarring eventually leading to fibrosis.

Tubulointerstitial fibrosis is seen in advanced stages of diabetic nephropathy and is a better predictor of renal failure than glomerular sclerosis. Hyperglycemia, angiotensin II, TGF-β, and likely proteinuria itself all play roles in stimulating this fibrosis. There is an epithelial-mesenchymal transition that takes place in the tubules, with proximal tubular cell conversion to fibroblast-like cells. These cells can then migrate into the interstitium and produce collagen and fibronectin that induced fibrotic event in diabetic nephropathy.

Advanced Glycation End-Products:

Advanced glycation end-products (AGEs), which are biochemical end-products of non-enzymatic glycation and are formed irreversibly in serum and tissues of diabetes, [41, 42, 43] were found to play a critical role in the development of diabetic nephropathy.

Advanced glycation end products (AGE) are formed by chemical reaction of carbohydrates with protein in a process known as the Maillard or browning reaction. The AGE formation process, or the Maillard reaction, begins from Schiff bases and the Amadori product.

Reducing sugars react non-enzymatically with amino groups of proteins to form Amadori products; Amadori product, a (1-amino-1-deoxyketose) produced by the reaction of the carbonyl group of a reducing sugar, like glucose, with proteins, lipids, and nucleic acid amino groups [44, 45]. The Amadori product is a precursor to AGEs, which are a more permanent, irreversible modification of proteins [46]. During Amadori reorganization, these highly reactive intermediate carbonyl groups, known as α-dicarbonyls or oxoaldehydes, products of which include 3-deoxyglucosone and methylglyoxal, accumulate [47, 48].

Such build-up is referred to as "carbonyl stress" [49]. The α-dicarbonyls have the ability to react with amino, sulfhydryl, and guanidine functional groups in proteins [50]. The reaction results in denaturation, browning, and cross-linking of the targeted proteins [50, 51]. In addition, the α-dicarbonyls can react with lysine and arginine functional groups on proteins, leading to the formation of stable AGE compounds, such as N^{ϵ}-(carboxymethyl) lysine (CML), which are non fluorescent AGEs [52].

Advanced Glycation End-Products in Progression of Diabetic Nephropathy:

The formation and accumulation of AGEs are characteristic features of aged or diabetic tissues and these products also have been strongly implicated in the pathogenesis of diabetic nephropathy complications [5, 6, 7, 8, 9, 10, 11]. AGEs are able to mediate diabetic complications by stimulating a number of mediators, including oxygen free radicals, cytokines, chemokines, adhesion molecules, TGF-β_1. In response to AGEs or high levels of glucose, a potent profibrotic growth factor transforming growth factor-β_1 (TGF-β_1) significantly increases and leads to fibrotic consequence [53,54].

The induction of TGF-β_1 emerges to be the key intermediate step for many AGE–RAGE (receptor for Adanced glycation end products)-mediated effects on cell growth and matrix homeostasis [55]. Engagement of AGEs to the receptor (RAGE) has been shown to play a critical role in diabetic complications, including diabetic nephropathy [56]. Indeed, AGE-induced tubular epithelial-to-mesenchymal transition (EMT) and renal fibrosis are RAGE dependent [56, 57].

Accumulation of AGEs closely correlates to TGF-β_1 expression in the kidney, and inhibitors to AGEs reduce overproduction of TGF-β_1 in diabetic animals independent of the glycemic status [58, 59]. All of these studies suggest a critical role for TGF-β_1 in AGE-mediated diabetic nephropathy. In

response to AGEs or high levels of glucose, a potent profibrotic growth factor transforming growth factor-β_1 (TGF-β_1) significantly increases and leads to fibrotic consequence [53,54.]

Available documentation addressed that the advanced glycation end-products (AGEs), which are biochemical end-products of nonenzymatic glycation were found to play a critical role in the development of diabetic nephropathy. In fact, this compelling evidence to suggest that the formation and accumulation of AGEs mediate the progressive alteration in renal architecture and loss of renal function and those inhibitors of advanced glycation prevent the progression of experimental diabetic nephropathy [42,58,60,61,62,63,64,65,66,67]. Drugs that either inhibit AGE formation or break the AGE crosslink showed a protective effect on experimental diabetic nephropathy [66, 67].

CONCLUSIONS AND FUTURE DIRECTION:

Diabetic nephropathy is leading cause of End stage renal disease (ESRD) and most frequent cause of mortality. At present no promising therapy available to diabetic nephropathy due to lack of understanding of signaling mechanism. Diabetic nephropathy is characterized by ECM (Extra cellular matrix) accumulation in the glomerular mesangium and tubulointerstitium. Advanced glycation end products (AGEs) have been documented to play an important role in the pathogenesis of diabetic nephropathy by stimulating cytokine and growth factor synthesis leading to ECM accumulation.

This underlined that, advanced glycation end products play a key role in progression of diabetic nephropathy. This review will certainly endow the information about the precise role of advanced glycation end products in diabetic nephropathy and finally contribute in the up gradation of the knowledge about nephropathy related diseases. Finally, the finding of this review will give impetus for future investigation to study novel therapies on diabetic nephropathy, which will be in public-interest. The Advanced glycation end products (AGEs) inhibitors intake may be beneficial role in control of diabetic nephropathy and open vista for treatment in clinical setting.

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