Chapter from the book *Diabetic Nephropathy*

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Study of Diabetic Hypertensive Nephropathy in the Local Population of Pakistan

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1. Introduction
Diabetes mellitus is a metabolic disorder that is characterized by high blood sugar and it is because of either problem in insulin secretion (type 1-β cell destruction) or either because of combination of insulin resistance or improper insulin secretion to compensate (type 2). (Riaz, S. 2009)

2. Mechanism of action
Despite ingestion of dietary carbohydrates, serum glucose level remain relatively steady throughout the day. This requires the concerted actions of several different tissues. Pancreatic β-cells, for example, secrete insulin in response to the elevation in glucose that occur after eating. Insulin promotes glucose disposal in adipose tissue and muscle, and also prevents the liver from producing more glucose by suppressing glycogenolysis and gluconeogenesis. In the fasting state, low insulin levels combined with elevated counter-regulatory hormones such as glucagon, adrenaline and corticosteroids promote hepatic glucose production. Recently, evidence has emerged that the brain coordinates many of these effects as well, through direct and indirect glucose sensing and neural outputs to peripheral organs.

Diabetes results from the dysregulation of multiple glucoregulatory hormones that normally acto to maintain glucose homeostasis. For example any defect in insulin production lead to improper regulation of glucose in the blood and result in diabetes. Similarly in patients with type1 and type 2 diabetes, post prandial glucagon secretion is abnormally elevated. This inappropriate secretion of glucagon leads to excess hepatic glucose production and is important contributer to postprandial hyperglycemia in patients with diabetes.

3. Insulin resistance
Deficient insulin action results from inadequate insulin secretion or decrease the tissue response. Insulin resistance is define as lack of sufficient insulin receptors, in target tissue, defect in intracellular transport of glucose and or an altered insulin secondary pattern that is dys-synchronization between pancreatic β cell release of insulin and the body's insulin requirement. (Defronzo, R.A., 1992)
4. Prevalence of diabetes

As the prevalence of diabetes is exponentially increasing in many parts of the world. It is estimated by WHO that until 2025 there will be 300 million diabetics from which 75% will be from developing countries.

In terms of number of people with diabetes mellitus by the year 2025 USA will be most leading country while Pakistan will be at forth country in the list after China and USA. (Jawaid, S. A., 2002). According to a new publication released by World Health Organization (WHO) and International Diabetes Federation (IDF) 3.2 million deaths occur because of diabetes. (Launch of "Diabetes action Now" 5 May 2004 Geneva) And it is six leading cause of death by disease world wide.

There are several factors that contribute in increasing the prevalence of diabetes they include:

Fig. 1. Glucose homeostasis
• Increase population growth
• Aging
• Urbanization
• Increasing prevalence of obesity
• Increasing prevalence of physical inactivity. (King, H., and Rewers, M., 1993.)

5. Etiologic classification of diabetes mellitus

The World Health Organization (WHO) Expert Committee on diabetes in 1980 and later WHO study group on diabetes mellitus approve the recommendation of National Diabetes Data Group (NDDG). (Report of a WHO Study Group 1985) They divide diabetes mellitus into 4 different types:

1. Insulin dependant diabetes mellitus (IDDM)
2. Non-insulin dependant diabetes mellitus (NIDDM)
3. Gestational diabetes mellitus (GDM)
4. Other types

5.1 Type 1 diabetes

5.1.1 Immune mediated diabetes

This is also called as insulin dependant diabetes or juvenile onset diabetes. In this type autoimmunity cause the destruction of β-cells of pancreas. Marker for immune mediated diabetes include islet cell autoantibodies (ICAs), autoantibodies to insulin (IAA), autoantibodies to glutamic acid decarboxylase (GAD65) and autoantibodies to tyrosine phosphatase 1A-2 and 1A-2β. For survival these patients are insulin dependant.

5.1.2 Idiopathic diabetes

In this case there is no known reason and these patients have mostly African or Asian origin. This is strongly inherited but not HLA associated. They are also insulin dependant.

5.2 Type 2 diabetes

This is also known as non-insulin dependant diabetes mellitus or adult onset diabetes. For survival of these patients insulin is not necessary. In these patients obesity is a major cause of insulin resistance while increase age and physical inactivity are also important factors. Ketoacidosis occur because of stress of other infection. it has strong genetic predisposition (Riaz, S. 2009).

5.3 Other specific types of diabetes

5.3.1 Genetic defect of β cell

This is also called as maturity onset diabetes of young (MODY), as it appears before age 25 years and it is characterized by defect in β cell function. In some families inability to convert proinsulin to insulin while in some cases mature insulin molecule production.
5.3.2 Genetic defect in insulin action

Metabolic abnormalities cause the mutations in insulin receptor. For example in type A insulin resistance, leprechaunism, Rabson, Mendenhall syndrome are two pediatric syndromes that have mutation in insulin receptor and have extreme insulin resistance.

5.3.3 Disease of exocrine pancreas

Injury to pancreas can cause diabetes and it include pancreatitis, trauma, infection, pancreatectomy and pancreatic carcinoma

Endocrinopathy

Excess amount of some hormone like growth hormone, cortisol, glucagon, apinephrine can cause diabetes as they are antagonist insulin action.

Drug or chemical induce diabetes

Impairinsulin secretion or insulin resistance also cause by some drugs. For example vacor (rat poison), pentamidine, nicotinic acid, glucocorticoids, thyroid hormones, diazoxide, $\beta$ adrenergic agonists, dilantin, $\alpha$ interferon and other.

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**Fig. 2. Etiologic classification of diabetes mellitus**

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Infection

Some viruses cause the β cell destruction. They include congenital rubella, coxsackie virus B, cytomegalovirus, adenovirus and mumps.

Uncommon

Two conditions are known for it.

1. in stiffman syndrome glutamic acid decarboxylase autoantibodies are produced.
2. antiinsulin receptor antibodies bind with insulin receptor and these antibodies are present in some autoimmune disease and systemic lupus erythematosus.

5.3.4 Other genetic syndrome

Incidence of diabetes mellitus also increase with many genetic syndromes. For example Down syndrome, Turner's syndrome, Kline-felter's syndrome, Wolfram's syndrome, Huntington's chorea, Porphyria etc. Autopsy shows the absence of β cells.

5.4 Gestational diabetes mellitus

Impair glucose tolerance normally occur in third trimester of pregnancy. (O'Sullivan and Mahan 1964) Complications of gestational diabetes mellitus increase risk of cesarean delivery and chronic hypertension.

6. Long term complications of diabetes

Long term complications of diabetes include the:

- retinopathy (potential loss of vision)
- nephropathy (renal failure)
- peripheral neuropathy (risk of foot ulcer)
- autonomic neuropathy cause gastrointestinal, genitourinary and cardiovascular symptoms
- periodontal disease(disease of bone and tissue supporting teeth)
- and sexual dysfunction. (Report of the Expert Committee on the Diagnosis and classification of Diabetes Mellitus)

6.1 Nephropathy

Nephropathy is a damage or disease of the kidney. It may be because of several factors and diabetes is one of the major factor of nephropathy.

6.2 Diabetes and nephropathy

Diabetes nephropathy is microvascular complication that associate with diabetes it slowly deteriorate the kidney and lead to end stage renal disease that is chronic and irreversible. Diabetic nephropathy need for chronic dialysis or a kidney transplant.

Since recovery is irreversible so early detection is effective prevention tool. (American diabetes association diabetic nephropathy diabetic care 2002; 25 (supplement)
6.3 Symptoms of diabetic hypertensive nephropathy

Diabetic hypertensive nephropathy is characterized by

- polyuria (frequent urination)
- polydipsia and polyphagia (excess thirst and food intake)
- weight loss
- blurred vision
- and susceptibility to infection
- Biochemical changes in diabetic patients
- Glycation of macromolecules and tissue proteins
- Risk of cardiovascular peripheral vascular and cerebrovascular disease
- Abnormalities of lipoproteins metabolism (hypertension)
- Psychosocial dysfunction also produce because of social impact of diabetes.

(Report of the Expert Committee on the Diagnosis and classification of Diabetes Mellitus)

6.4 Prevalence of diabetic hypertensive nephropathy

40% of type 1 and 20% type 2 diabetic patients develop the nephropathy. While prevalence of hypertension in type 2 diabetic patients is estimated at 50% with one estimated as high as 74%. (Riaz, S et al. 2009)

6.5 Sources of urinary proteins

The total urinary protein excreted

- 48% was contained in sediments
- 49% was soluble
- and the remaining 3% was in exosomes(Zhou, H., 2006)

6.5.1 Soluble proteins

6.5.1.1 Glomerular filtration of plasma proteins

From glomerular filtration urinary soluble proteins are derived. In proximal tube most of the proteins and peptides are scavenged by highly specialized apical uptake process and this process involves receptor like recognition of peptide molecules. (Christensen, E. I., and Birn, H. 2001; Christensen, E. I. 2002). So in final urine the mount of soluble proteins changes with change concentration in blood plasma, change in glomerular filtration and change in proximal tubule scavenging system.

Based on mechanism change in excretion rate of protein indicative of systemic disease, globular disease or tubular disease.

6.5.1.2 Epithelial cell secretion of soluble proteins

Some proteolytically cleaved membrane bound proteins also present in urine. One of them is Tamm-Horsfall protein. It is most abundant protein in urine and if it is not removed its presence interfere with detection of other proteins.
6.5.2 Solid phase components

Solid phase components consist of sediments that can be precipitated at low centrifugation. It mainly consist of epithelial cells. They are important for diagnostic information because increase number of these cells indicates the renal disease.

6.5.3 Exosomes

Exosomes are derived from glomerular podocytes, renal tubule cells from proximal and distal nephron segments and transitional epithelial cell lining the urinary drainage system. Exosome are the internal vesicles of multivascular bodies and transfer to extracellular fluid by fusion of outer membrane of multivesicular bodies with plasma membrane. (Pisitkun, T., 2004)

6.6 Urinary protein marker for diabetic nephropathy

Urinary protein profiling can reveal changes in excretion rates of specific proteins that can have predictive value in the clinical arena, for example

- In the early diagnosis of disease
- In classification of disease with regard to likely therapeutic responses
- In assessment of prognosis
- and in monitoring response to therapy

6.7 Up-regulated urinary proteins in diabetic nephropathy

6.7.1 Albumin and non-immunoreactive albumin

The molecular weight of albumin is 71,658 KDa. Clinically, diabetic nephropathy can be diagnosed when albumin is detected in the urine (albumin excretion 30–300 mg/day). The presence of albumin in the urine is considered predictive of the subsequent development and clinical progression of diabetic nephropathy. (The Microalbuminuria Collaborative Study Group) Microalbuminuria is not specific for diabetic nephropathy, since albumin can also be detected in some other pathological conditions and the prevalence of microalbuminuria in the general population is rather high. Finally, microalbuminuria is a poor predictor of diabetic nephropathy. (Riaz, S et al., 2010)

6.7.2 α1B-Glycoprotein

The molecular weight of α1B-Glycoprotein is 54,239 KDa. It is homologous to the immunoglobulin supergene family and contains five Ig-like V type (immunoglobulin-like) domains. α1B-glycoprotein binds heme and transports it to the liver for breakdown and iron recovery, after which the free hemo pexin returns to the circulation. α1B-Glycoprotein has possible role in the autoimmunity involved in nephropathy. Its levels have been described to be higher in type 2 diabetes, its relationship with C-reactive protein is lost in both type 1 and type 2 diabetes, and its levels are independently determined by triacylglycerol and the diabetic state (Van Campenhout, A., et al 2006). This molecule can potentially act as a toxic protease, leading in the rat to proteinuria and glomerular alterations (Bakker, W.W., et al 2005). Although there were no direct references to its possible effects in humans with
diabetes or nephropathy, because diabetes is an inflammatory condition associated with iron abnormalities, it can be postulated that α1B-Glycoprotein is altered in diabetes.

6.7.3 Zinc-α2-glycoprotein

The molecular weight of Zinc-α2-glycoprotein is 34,223 KDa. This protein stimulates lipid degradation in adipocytes and may also bind polyunsaturated fatty acids. Zinc-α2-glycoprotein was the second most abundant urinary protein in diabetic nephropathy. An earlier study of type 2 diabetes described zinc-α2-glycoprotein and three other proteins, α1-acid glycoprotein, α1- microglobulin, and IgG, as specific markers for diabetic nephropathy (Jain, S., et al 2005).

6.7.4 α2-HSglycoprotein precursor (fetuin A)

The molecular weight of α2-HSglycoprotein is 39,300KDa. α2-HSglycoprotein precursor is an inflammation-related calcium regulatory glycoprotein that acts as a systemic calcification inhibitor. Both chronic inflammation and uremia may contribute to exhausting fetuin A release in the late stages of kidney disease. Deficiencies of calcification inhibitors such as fetuin A are relevant to uncontrolled vascular calcification and may offer potential for future therapeutic approaches (Ketteler, M., 2005).

6.7.5 Vitamin D binding protein (VDBP)

The molecular weight of vitamin D binding protein is 52,964KDa. Vitamin D binding protein is a multifunctional protein found in body fluids and on the surface of many cell types. In plasma, it carries vitamin D sterols and prevents polymerization of actin by binding its monomers. VDBP also associates with membrane bound immunoglobulin on the surface of B lymphocytes and with IgG Fc receptors on the membranes of T lymphocytes, suggesting its possible role in the immunopathogenesis and progression of the disease. Vitamin D binding protein was also found in the vitreous in diabetic macular edema, along with pigment epithelium-derived factor, apoA-4, apoA-1, trip-11, and plasma retinol-binding protein (RBP). These chemical mediators in the posterior vitreous may play a role in the pathogenesis of diabetic macular edema (Ouchi, M., et al 2005).

6.7.6 Calgranulin B

The molecular weight of calgranulin is 13,234KDa. Calgranulin B is expressed by macrophages in inflamed tissues and is an inhibitor of protein kinases. Differences in the isoforms and abundance of several urine proteins, including calgranulin B, inter-α-trypsin inhibitor, prothrombin fragment 1, and CD59, were known to be associated with stone formation (Bergsland, K. J., et al 2006). There have been no previous reports on their association with diabetes or other renal diseases. A1AT is an inhibitor of serine proteases, and its primary target is elastase, but it also has a moderate affinity for plasmin and thrombin. The serum levels of A1AT and a α1-acid glycoprotein, as well as their glycosylated protein fractions, were reported to be significantly greater in sera from patients with diabetic nephropathy compared with healthy adults. Marked linear deposition of these proteins in the glomerular or dermal vascular walls was also observed in the same patients (Inoue, W., 1989), linking them to diabetic nephropathy. Whereas the
association between A1AT deficiency and glomerulonephritis has been reported only sporadically. (Os, I., et al 1997).

6.7.7 Type IV collagen

The molecular weight of Type IV collagen is 500,000. Type IV collagen is the major component of the glomerular extracellular matrix and the level of type IV collagen in the urine might reflect the rate of matrix turnover in diseased kidneys. Findings indicate that type IV collagen has a specificity for diabetes nephropathy that albumin itself has not, but since urinary collagen IV is detectable only when microalbuminuria is already present. (Tomino, Y., et al., 2001)

6.7.8 Podocytes and nephrin

Podocytes are key structural elements of the glomerular filtration barrier. Podocytes and podocyte-specific proteins can be potentially interesting urinary markers for the early diagnosis of an alteration of the glomerulus. (Dalla Vestra, M., et al 2003) Indeed, urinary podocytes have been detected only in the urine of diabetic patients with micro- and macroalbuminuria, whereas they were absent in healthy controls, type 2 diabetes patients without microalbuminuria or patients suffering from chronic renal failure. (Nakamura, T., et al 2000). Nephrin is one of the many podocyte-specific proteins that have been described in the last few years. nephrin was totally absent in the urine of non-diabetic patients.

6.7.9 Advanced glycation end products

Advanced glycation end products (AGEs) are a heterogeneous group of proteins and lipids to which sugar residues are covalently bound during physio-pathological processes.

Kidneys are thought to be one of the key organs for the clearance of AGEs. In type 2 diabetes serum low molecular weight advance glycation end products are usually higher than non-diabetic. (Turk, N., et al., 2004)

6.7.10 Betaig-h3

The molecular weight of intact Betaig-h3 is 68KDa. Betaig-h3 is an extracellular matrix protein that is induced by transforming growth factor beta, a growth factor implicated in the pathogenesis of diabetic nephropathy. Ha et al. (Ha, S. W., et al., 2004) first showed that the betaig-h3 to creatinine ratio is significantly higher in type 2 diabetes patients than in control subjects. In another study, (Cha, D. R., et al., 2005) it was also observed that the urinary level of betaig-h3 is higher in diabetic patients (betaig-h3/creatinine ratio: 25.02 ± 8.84) than in healthy individuals (18.67 ± 6.56).

6.7.11 L1 cell adhesion molecule (CD171)

L1 cell adhesion molecule (CD171) is a potential new marker for tubular injury. It is expressed in human acute kidney injury and excreted in urine. In normal kidney L1 is located in basolateral membrane in all epithelial cells of collecting duct except for intercalated cells. In acute tubular necrosis, L1 lost its polarized distribution and induce in thick ascending limb and distal tubule cells.
6.7.12 Tamm-Horsfall protein

The molecular weight of Tamm-Horsfall protein is 95KDa. It is produced by ascending limb of loop of Henle. It is most prevalent protein and excretion rate is 25-40mg/day. (Cvoriscevic, D., et al., 1985). In renal disease as number of tubules decrease excretion of this protein also accordingly decrease.

6.8 Downregulated urinary proteins in diabetic nephropathy

6.8.1 Transthyretin (prealbumin)

The molecular weight of transthyretin is 15,877KDa. Transthyretin (prealbumin) is a thyroid hormone-binding protein, which transports a small part of thyroxine from the bloodstream to the brain. About 40% of plasma transthyretin circulates in a tight complex with plasma RBP. Transthyretin was reported as a better and suitable marker for nutrition assessment in patients with chronic renal failure (Saito, K., et al., 2004). Elevated plasma RBP in insulin-resistant humans with obesity and type-2 diabetes was known to induce hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase and impairs insulin signaling in muscle (Yang, Q., et al., 2005). It is possible that low RBP-4 in diabetic nephropathy increases insulin sensitivity and causes spontaneous hypoglycemia, because low RBP-4 is potentially hypoglycemic. (Riaz, S et al., 2010)

6.8.2 AMBP proteins

The molecular weight of AMBP is 38,974KDa. AMBP contains both α1-microglobulin and inter-α-trypsin inhibitor light chain (bikunin). Bikunin is an important anti-inflammatory substance to modulate inflammatory events. Decreases level of this protein affect immunocompetence in diabetic renal disease remains unstudied. The other component of AMBP protein, α1-microglobulin, in urine was directly related to progressive albuminuria in Chinese, Malays, and Asian Indians with type 2 diabetes (Hong, C. Y., et al 2003). This is in contrast to the decreasing levels of this protein observed in our study. Urinary α1-microglobulin indicates proximal tubular dysfunction and could be a useful biomarker for the early detection of nephropathy in diabetic subjects in addition to albuminuria, which indicates glomerular dysfunction.

6.8.3 ApoA-I

The molecular weight of ApoA-I is 30,759KDa. ApoA-I acting as a cofactor for the lecithin cholesterol acyltransferase, participates in the reverse transport of cholesterol from tissues to the liver for excretion. ApoA1, as well as apoB/A1, was included among several nontraditional cardiovascular risk factors in the progression to pediatric metabolic syndrome (Retnakaran, R., et al., 2006), but there have been no reported references to its association with diabetes or nephropathy. (Riaz, S et al., 2010)

6.8.4 Adiponectin

The molecular weight of adiponectin is 28KDa. Adiponectin is an adipocyte-secreted cytokine (adipokine) of human plasma. Decreased adiponectin plasma levels are linked to obesity, insulin resistance and type 2 diabetes. Koshimura et al. found, in the urine of type 2
diabetes patients with macroalbuminuria, a 30 kDa protein immunoreactive towards an anti-adiponectin monoclonal antibody. (Koshimura, J., et al 2004) Urinary adiponectin may result from the elevation of the serum concentration and enhanced filtration through the damaged kidney. Similar findings were more recently obtained, showing that both serum and urinary adiponectin concentrations are elevated in type 2 diabetes patients with nephropathy, as compared to patients with microalbuminuria alone. (Fujita, H., et al., 2006)

7. Hypertensive nephropathy

This is a condition in which kidney damage occur due to chronic blood pressure. In diabetic patients major risk factor for cardiovascular morbidity and mortality is hypertension. (Hypertension in Diabetes Study (HDS) 1993; Hansson, L., et al 1998) Diabetic nephropathy develop in 40% of patients with type 1 diabetes (Krolewski, A. S., et al., 1985) and 35% of patients with type 2 diabetes (Mehler, P. S., 1997) rigorous treatment of hypertension slow the rate of decrease in renal function and improve mortality (Parving, H. H., et al., 1987; Parving, H., and Hommel, E., 1989).

7.1 Diabetes and hypertension

Blood pressure, serum lipids and several cardiovascular factors are affected by central adiposity and insulin resistance. (Niaura, R., et al., 2000) Diabetes mellitus and hypertension both are associated with high urinary albumin excretion. In type 2 diabetes patients the presence of microalbuminuria is often a better predictor of cardiovascular disease than of diabetic nephropathy. (Molitch, M. E., et al., 2004) Microalbuminuria is also important marker of atheromatous and potential of coronary heart disease in diabetic patients. (Donnelly, R., 2002) Recommended target blood pressure in all diabetics is ≤130/80 and urinary albumin excretion >200mg/l the goal is 125-130/75-80. (Augustine, J., Donald, G., diabetic nephropathy 2003).

7.2 Treatment of nephropathy

Currently ACE inhibitors or ARBs are used for preventing progression of microalbuminurea to macroalbuminurea and advance stages of nephropathy. These drugs have a large amount of adverse effects such as extreme hypotension, hyperkalemia and dry cough which has in certain cases becomes sever enough to stimulate tuberculous cough resulting in wrongful antituberculous treatment being prescribed to the patient. In such a scenario it is important that another biomarker other than microalbuminurea be found for diabetic hypertensive nephropathy which would reveal the development of incipient diabetic nephropathy and a specific drug be designed for that biomarker which would have a fewer side effects as it would be biomarker specific. (Martin- Gallan, et al., 2003).

Type 2 diabetic patients, and same age and sex-matched normal healthy controls were recruited from the Sheikh Zayed Hospital, Lahore, Pakistan. Total Urine and urinary proteins were estimated and analyzed initially by different protein assays and 1-D SDS polyacrylamide gel electrophoresis. The samples were purified further by passing through the high abundance protein removal and desalting columns. These serum and urine samples from control and diabetic groups before or after thiamine therapy were further analysed by 2-D liquid chromatographic system in which samples were initially fractionated by
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<td>PI</td>
<td>Function</td>
<td>Up or down regulated</td>
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<td>Ig k chain C region</td>
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Table 1. Urinary protein identified in type 2 diabetic patients with macroalbuminuria (Riaz, S. 2009, 2010, 2011)
chromatofocusing and the selected fractions were further analysed by reverse-phase high performance liquid chromatography. The proteins which showed variation between test and control samples were identified by mass spectrometry MALDI TOF/TOF and LC MS analysis. All the samples belonging to the control and diabetic groups were then analyzed by ELISA and estimated the levels of some proteins which were found to vary. (Samreen Riaz, 2009, 2010, 2011)

8. References

Augustine, J., Donald, G., diabetic nephropathy (2003). The Cleveland Clinic, Department of nephrology and Hypertension, The Cleveland Health Foundation, United States.


the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 351:1755-1762.

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Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features:

- Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy
- Provides novel information on various pharmacological interventions of diabetic nephropathy

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