Review Article

A Review on Diabetic Nephropathy Disease: Risk Factors and Complications

Neha Chakraborty[a], Suresh Janadri[*a], Kalpana Pathak[a], Manjuntha PM[a], Prakash T[a]
[a]Department of Pharmacology, Acharya & BM Reddy College of Pharmacy, Bengaluru 560107, Karnataka, India.
***Corresponding author's E-mail:** sureshjanadri@gmail.com

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ABSTRACT

Diabetic nephropathy also known as diabetic kidney disease is the chronic loss of kidney function associated with diabetes mellitus. The leading cause of kidney disease is diabetic nephropathy and affecting about 40% of diabetic patients of type 1 and type 2 diabetes. The incidence rate of the disease is still prevailing due to the limited efficacy and several unpleasant side effects associated with these procedures. Hyperglycemia is considered as a primary initiating factor for end-stage renal infection in diabetic patients, which leads to the increased leakage of albumin over the glomerular filtration barrier. Diabetic nephropathy is characterized by destruction of glomerular filtration barrier, with the accumulation of extra cellular matrix. Hemoglobin A1c, fasting blood glucose and hypertension is also known to be an additional risk factor influencing microangiopathy. The key therapeutic approach for treating or preventing the development and progression of diabetic nephropathy is focuses on regulating the blood glucose level as well as inhibiting the mechanism renin-angiotensin system. This review focuses mainly on the global distribution, pathogenesis, pathological changes and hierarchical glomerular lesions in diabetic nephropathy, global concern of diabetic kidney disease, risk factors, the various complications, stages and treatment of diabetic nephropathy.

Keywords: Diabetic nephropathy, Transforming growth factor-β1, Glucose transporter 1, Tumour necrosis factor-β.

INTRODUCTION

Diabetic nephropathy is described by the breakdown of glomerular filtration barrier, with the accumulation of extra cellular matrix and diabetic nephropathy progression consisting of three phases (i) Glomerular hypertrophy and hyperfiltration, (ii) Inflammation of glomeruli and tubulo interstitial regions (iii) Reduced number of cells by apoptosis and accumulation of extracellular matrix.[1]

Diabetes streptozotocin model is widely used in diabetic disease studies such as diabetic nephropathy, retinopathy, and neuropathy.[2-4] After overnight fasting, diabetes may be induced by a single intraperitoneal (ip) administration of STZ (50mg /kg). Two days after induction, diabetes can be confirmed by measuring blood glucose levels.[5] Transforming growth factor β (TGF-β) signaling is a well-recognized way of developing of diabetic nephropathy.[6,7] TGF-beta 1 is regarded as the most efficient profibrogenic cytokine and stimulates aggregation of extra cellular matrix (ECM),[8] which is widely recognized as one of diabetic nephropathy's most significant pathological features. Allicin, curcumin, skimmin, thymoquinone etc. like natural sources, are having a broad spectrum of physiological activities such as antimicrobial properties, antifungal properties, antioxidant properties, antihypertensive properties, cardio protective properties, anticancer properties, inhibitory immune modulatory function[9] The key therapeutic approach to treating or preventing the diabetes nephropathy growth and enhancement focuses on regulating the level of blood glucose and inhibiting the mechanism of renin-angiotensin. However, the incidence rate of the disease continues to prevail due to the limited effectiveness and several unpleasant side effects associated with this treatment.[10] In type 2 diabetic observational study lansoprazole has produced a significant reduction in glucose probably, due to an increase in endogenous gastrin levels.[11]

Hyperglycemia is viewed as a primary initiating factor in endstage renal infection in diabetic patients, which contributes to the GFB (glomerular filtration barrier) increased albumin leakage.[12] Secondary hyperglycemia to diabetic nephropathy may cause major structural changes in the glomerulus such as the glomerular basement membrane thickening, was causing weakening of glomerular cells in the glomerulus.[13]

Pathological changes of Diabetic Nephropathy

Glomerular lesions are the major and clear pathological improvements in clinical diabetic nephropathy patients' renal biopsies.[14] In general, expansion and glomerular basement membrane thickening diffuse and nodular (GBM).[15] Diffusive mesangial development, this is the earliest in the five years after onset of diabetes started detectable improvement in light microscopy.[16] The [Vv (Mes / glom)] mesangial fractional volume is associated with the albumin excretion rate (AER) and the glomerular filtration rate (GFR) of both type 1[17] and type 2 diabetes.[18]

GBM (glomerular basement membrane) thickening can occur within two time period of eight years of diabetes onset. It is considered as relatively early injury that the electron microscopy can detect and measure.[19] Four hierarchical glomerular lesions in diabetic nephropathy are given below in Table 1.

Table 1: Four hierarchical glomerular lesions in diabetic nephropathy

Class	Description and criteria
I	Mild or nonspecific improvements in light microscopy and confirmed electron microscopy-proven GBM thickening: Glomerular Basement Membrane > 395 nm (female), GBM > 430 nm (male).
II a	Slight mesangial extension in > 25% of the mesangium directly observed; area of mesangial proliferation < capillary cavity zone.
II b	In > 25% of the mesangiumdetected, severe mesangial expansion. Mesangial proliferation area < capillary cavi ty area.
III.	Atleast one convincing (KimmelstielWilsonlesion) nodular sclerosis.
IV.	Advanced glomerulus diabetic sclerosis > 50% of glomeruli.

1. GLOBAL CONCERN OF DIABETES AND DKD (Diabetic Kidney Disease)

Diabetes Atlas of the international diabetes federation reported that there were 366 million people have diabetes globally in 2018 (8.3 percent of young people), and then by 2030 this could be 552 million people.[20] It is estimated that 48 percent of this expansion will prevailing in China and India. The extended pervasiveness of diabetes would unacceptably impact countries with low and middle incomes compared to countries with high incomes. To place the worldwide increment in diabetes in context, the normal yearly development in diabetes incidence the increase will be 2.7% which is 1.7% times the expected yearly growth in the overall population. In the U.S, 11.3% people have lived 20 years or more with diabetes. In the year 2011 (25.6 million individuals) commonness expanding in more established age gatherings (26.9 percent of people of 65 years of age).[21]

Sadly most would not have the option to bear the cost of the expense of renal replacement therapy (RRT) after illness advanced kidney disease to end stage renal diseases (ESRD). The U.S. Renal Data System confirmed diabetes related ESRD rates caused by diabetes in specific nations in 2009: 58% to 60% in Malaysia and Mexico, and over 40% in Thailand, New Zealand, Hong Kong, the Republic of Korea, Japan, Taiwan, the U.S., Israel and the Philippines.[22] In the United States in the year 2009, diabetes represented most occurrence instances of ESRD (154 for every million patients suffering with ESRD) and furthermore originated the vast majority of the common cases (647 for each million patients). Since starting in 1996, there has been a 35% decrease in the age-balanced frequency rate for end stage renal disease brought about by diabetes,[23] a fall of 3.9 percent annually.[24]

It ensures that that while the total number of occurrence of diabetes-induced ESRD is increasing due to the growing number of patients with diabetes, there is a possibility that ESRD will develop if a person is diabetic. In AUS and NZ (ANZDATA) renal registry data, the proportion of diabetic kidney disease patients with RRT rose from 17% in 1980 to 35% in 2009 in new cases of ESRD, but the rate of increase appears to have declined since 2005.[25]

The expense of diabetic kidney disease is significant. Hence, the yearly therapy expense in the year 2009 to 2010 for individuals with ESRD brought about by diabetes in Australia was evaluated to be $73,527 per individual for renal replacement therapy and $12,174 for traditionalist therapy.[26] The full cost of AUS diabetic kidney disease in 2009 to 2010 was $20.5 for people with diabetes in CKD stages one to four and $446.3 million for people with ESRD and diabetes. It is estimated that this cost will double by 2020.[27] To sum up, the diabetes illness has prompted significant increments in quantities of individuals with DKD and ESRD. The expenses for social insurance are huge. Badly, expanded diabetes predominance will influence areas and populaces that might not be able manage these expenses. Pressing consideration is expected to avoid DKD and to forestall movement of DKD. The accompanying segment will break down the ebb and flow the study of disease transmission of diabetic kidney disease in more prominent detail.

2. PATHOGENESIS

Pathogenesis of Resident and non-resident renal cells are activated by hyperglycemia in formation of humoral mediators between, cytokines, including the development factors that are liable for auxiliary modifications, for example, expanded statement of ECM and utilitarian changes, for example, expanded penetrability of glomerular base pressure of membrane or shear. These adjustments are addition to the cause of diabetic nephropathy.[33] The release of glucose into hepatic cells is controlled by GLUT-1, a surface receptor for inhabitant hepatic cells. That in-vitro, high glucose fixation (23 to 30 nm) prompted over articulation of GLUT-1 mRNA and overproduction of GLUT-1 protein in mesangial cells. Likewise, glucose transport expanded in cells. Overabundance 1 is adjusted in its demeanor by TGF β1 truth be told,[28] shown that this development factor was portion and time subordinate. At the point when an enemy of TGF β1 monoclonal counter acting agent was included with in-vitro, GLUT-1 mRNA articulation and d-glucose take up was diminished.

Generally, endogenous TGF β1, developed by mesangial cells refined under high levels of glucose conditions, will enhance the transport of glucose to boost glucose absorption by prompting over articulation of mRNA and

protein, GLUT-1, along these lines, it quickens glucose-incited metabolic variations from the norm in mesangial cells. A further component of growth, PDGF β, is linked with fundamental glomerular level changes.[29]

2.1 Regulation illustrated in-vitro of TGF β1

In adult, mesangial cells containing high proportion of glucose including anti-PDGF β antibody neutralization. Researchers discovered that a high concentration of glucose contributed to a significant and lasting improvement in the expression of PDGF β chain genes whereas the PDGF β receptor mRNA doubled after 6 hours then reduced after 24 hours. TGF β1 mRNA, on the other hand raised after 24 and 48 hours of high glucose incubation. Consequently, they concluded that early activation of platelet derived growth factor (PDGF) loop causes high glucose, which in turn causes a rise in the expression of TGF β1 genes, therefore this modulates the proliferation of human mesangial cells and mesangial matrix growth.[30]

4. RISK FACTORS FOR DIABETIC NEPHROPATHY

4.1 Rise in excretion of urinary albumin

Enhanced excretion of the urine of albumin is a leading risk factor for diabetic nephropathy progression for both type-1 and type-2 diabetes.[31-33] This was the first indication of diabetic nephropathy is mildly enhanced in urinary albumin excretion in several patients, i.e. 30-300 mg/g in a spot urine sample (also called microalbuminuria).[34] Diabetic patients with serious rises in albuminuria in the spot urine, i.e.> 300 mg albumin /g creatinine sample (also known as macroalbuminuria or medical albuminuria), are at especially greater risk of declining renal impairment.[34,35]

4.2 High levels of glucose

Insufficient glycemic control is a major risk factor in the development and progression of diabetic nephropathy. High concentrations of HbA1c in patients with T1D and T2D are associated with an increased risk of nephropathy.[36] Scientific studies have shown a considerable improvement in the prevalence of diabetic nephropathy in both T1D and T2D patients who have obtained improved glycemic control.[37-39] In addition, in the study diabetes control and complication trial / Epidemiology of diabetes complication and treatments (DCCT / EDIC), Patients with mild albuminuria but lower rates of HbA1c had a reduced risk of development to severe albuminuria or ESRD.[37-39] Similar findings were recorded in randomized controlled trials in patients with type-1 and type-2 diabetes.[39] DCCT reduced the risk of developing severe albuminuria or ESRD from moderate albuminuria.

4.3 Certain risk factors for diabetic nephropathy

Long term patients affected from diabetes have an increased risk of developing nephropathy.[34-38,40] Another important independent risk factor for nephropathy is high blood pressure. In addition, lower blood pressure was associated with moderate albuminuria regression to normal albuminuria in patients with T2D.[42] Renin-angiotensin system inhibitors tend to slow diabetic nephropathy progression than other groups of antihypertensive agents, though blood pressure control is related.

4.4 Oxidative stress in diabetic nephropathy

Both oxidative and subclinical pressure seems to function in diabetic nephropathy pathogenesis. A marker of oxidative stress, elevated urinary levels of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG) predict diabetic nephropathy development in T2D patients.[43] High tumor necrosis factor rate. An increased incidence of reduced renal function in T1D or T2D patients is also correlated with with α receptors separately.[42,43] Sadly, research investigating the impact of antioxidants or anti-inflammatory agents to postpone diabetic nephropathy development has provided disappointing results, both in respect of safety and efficacy.

5. COMPLICTIONS IN DIABETIC NEPHROPATHY

5.1 Haemoglobin A1c

One of the key factors affecting microangiopathy is the glucose balance. HbA1c represents the past 2 to 3 months of average blood sugar level and long term hyperglycemia results in protein glycosylation that results in systemic microvascular damage and promotion of microangiopathy and growth.[40] The Diabetes Control and Complications Trail (DCCT) and UKPDS results on type 1 and type 2 diabetes demonstrated the possibility of microvascular diabetic complications can be significantly reduced by strict glycaemic control.[39]

5.2 Blood glucose fastening

Outcomes from the large-scale retrospective study in Poland (POL) showed that Fasting Blood Glucose is one of the major risk factors for patients with type 2 diabetes mellitus; the risk of proteinuria increased 1.15 times for every 1 mmol / L rise in FBG. the clinical characteristics of type 2 diabetes mellitus patients in hospital and T2DM patients in the community In patients with diabetic nephropathy, however, the FBG rate was lower in diabetic nephropathy patients than in non-diabetic nephropathy patients.[41,42] Moreover, we also found that in our study, the FBG level of T2D patients with diabetic nephropathy were higher than that of NDN patients; however the higher the FBG level, the more severe the diabetic nephropathy condition. This disparity was statistically significant between groups. While, the incidence of CAU was much higher when the FBG level reached 11mmol/L than that of other patients. This showed that patients with diabetic nephropathy, however the FBG rate was lower in diabetic nephropathy patients than in non-diabetic nephropathy patients. Diabetic nephropathy patients must concentrate on both HbA1c and FBG rate.

5.3 Hypertension

This study found that the risk is 1.8 times higher of diabetic nephropathy in patients with T2DM and HTN than those

without HTN, which was compatible with some other research. Not only do patients with T2D complicated with HTN have an elevated risk factor for cardiovascular disease and also microangiopathy complications to occur and evolve.[43]

6. THE STAGES OF DIABETIC NEPHROPATHY

Table 2: Types of stages of diabetic nephropathy

Types of Stages	Description
Stage 1: Hyperfiltration Stage	This is associated with increased glomerular filtration rate (GFR) and increased capillary glomerular pressure, because of renal hypertrophy, hyperfiltration is considered to appear.[44]
Stage 2: The silent stage	There is no such thing medically obvious proof of renal failure with no sign of albuminuria, GFR is normal. This process however, is associated with major structural changes, including thickening of basement membrane and mesangial expansion. Only renal morphology studies can predict more kidney damage.[45]
Stage 3: Microalbuminuria Stage	At this point, typically 5 to 15 years after the initial diagnosis of TID, the level of urinary albumin excretion is increased to 20 to 200 µg/ min or 30 to 300 mg/ day in the microalbuminuric range.[46 -48]
Stage 4: Macroalbuminuria stage	Marked by pronounced nephropathy and usually occurs 10 to 15 years after the onset of T1D. This level, if left untreated, is highly predictive of further progress to renal failure.[48]
Stage 5: Impairment of the renal system	The final phase described by uremia and end stage renal disease (ESRD), which can appear in up to 40% of patients with T1D, involves renal function replacement therapy.[48]

7. CURRENT AND FUTURE STRATEGIES FOR PREVENTION AND TREATMENT OF

DIABETIES NEPHROPATHY

A number of current options for treatment to us for the treatment and prevention of diabetic nephropathy development affect inflammatory cytokines through their activities. This statement is supported by the following data on various current and potential therapeutic agents. This has been known clearly that ACEI / Angiotensin Receptor Blockers (ARB) appear superior to other therapies to inhibit and delay advancement of DN.[49-52] It has recently become evident that ACEI /ARB retains anti-inflammatory activity by modulating NF-Kb.[53] Interestingly, enalapril almost completely abolishes local TNF-β expression in experimental model and decreased urinary TNFβ levels, indicating that the progression of the disease may be due to local rather than systemic TNF-β output.[54]

7.1 Prevention and treatment

Normoalbuminuric patient treatment of known health problems such as hypertension, hyperglycemia, smoking and dyslipidemia is the basis for diabetic nephropathy preventive measures. These are also risk factors for coronary heart disease and should be treated thoroughly.

7.1.1 Intensive regulation of blood glucose

Clinical studies have shown consistent rates of A1c < 7% in type 1 and type 2 diabetic patients with a lower risk of clinical and systemic aspects of diabetic nephropathy. In the Diabetes Control and Complications Trial (DCCT), efficient diabetes treatment lessened microalbuminuria prevalence by 39%.[55] It is important to note that patients randomly assigned to strict glycemic control had a long-lasting lowering of 40% in microalbuminuria and hypertension threat 7 to 8 years after the end of DCCT.[56]

7.1.2 Renin-Angiotensin system blockade

There was no interpretation of the role of ACE inhibitors in the early detection of diabetic nephropathy in type 1 diab etes patients. The use of perindopril in normotensive Type 1 diabetic patients over 3 years has inhibited the rise in alb uminuria.[57] ACE therapies and ARBs both reduce the incide nce of diabetic nephropathy in patients with type 2 diabet es.[58,59] Minimize the onset of coronary heart disease.[60]

7.1.3 Diet Intervention

Substituting red meat with chicken in the regular diet lowered UAE by 46% and lowered elevated cholesterol, LDL cholesterol and apolipoprotein B in type 2 diabetes patients in a 4 week report. [61] This was probably associated with the reduced saturated fat content and the higher proportion of polyunsaturated fatty acids present in chicken meat relative to red meat. The beneficial effect on endothelial function of polyunsaturated fatty acids[62] could also reduce UAE. A standard protein diet of chicken as the only meat source can be additional method for treating diabetic patients with microalbuminuric type 2. Long term studies, though, are required as per a meta-analysis.[63]

7.1.4 Dyslipidemia

The primary objective for low density lipoprotein (LDL) cholesterol in general is <100 mg /dl for people with diabetes and <70 mg /dl for coronary heart disease patients.[64] It is still unknown the effect of antilipemic agent lipid reduction on the progression of diabetic nephropathy. So far, no large trials have been conducted to analyze whether dyslipidemia treatment can prevent or decrease the development of diabetic nephropathy. There is some evidence, however, that antilipemic lipid reduction could preserve GFR and decrease proteinuria in diabetic

patients.[65] 40 mg of simvastatin lowered the occurrence of major vascular complication and GFR in the heart protection study, lowered by 25 percent in patients with diabetes, independent of baseline blood glucose levels.[66]

7.2 TREATMENT

To delay the progression of diabetic nephropathy, adequate control of metabolic and hemodynamic abnormalities is needed. For fact, this requires an acceptable decrease for blood glucose and hypertension regulation.

7.2.1 Glycemic control

Effective glycemic management in reducing microvascular diabetic complications is effective DCCT was a study of 1,365 diabetics of type 1 and normoalbuminuria.[67] Less incidences of microalbuminuria and macroalbuminuria were reported in patients randomized to intense glucose control for almost 10 years. Some drugs can confer therapeutic effects regardless of lowering glucose. Inhibitors such as pioglitazone and rosiglitazone display antifibrotic and anti inflammatory effects in the diabetic rats kidneys.[68] The combination perindopril / indapamide have been examined in the 11,140 type 2 diabetics advance trial. Since average take up of 4.3 years, perindopril / indapamide treatment lowered the occurrence of current microalbuminuria and stopped microalbuminuria from advancing to overt nephropathy. Nevertheless, it was not affected by serum creatinine and end stage renal disease. It was also contended that, due to the 5.6/2.2 mmHg difference among both treatment groups, impact on albuminuria was not independent of blood pressure.[69] The Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) study revealed that treatment with ACE inhibitors could slow the progression of type 2 diabetic microalbuminuria with hypertension and baseline normal albuminuria.[70]

7.2.2 Angiotensin receptor blockers (ARB)

1,715 hypertensive Type 2 diabetics with nephropathy were randomly selected throughout the IDNT (Irbesartan Diabetic Nephropathy Trial) to acquire irbesartan, amlodipine, or placebo.[71] Irbesartan decreases the risk of End Stage Renal Disease or serum creatinine increasing by 20 %-23 % compared to amlodipine or placebo. Unlike traditional antihypertensive drugs, 1,513 Type-2 nephropathic diabetics were randomly selected for losartan or control in the RENAAL trial. Losartan increased the risk of doubling the risk of ESRD or serum creatinine by 25 % - 28 % compared to placebo.[72] The outcomes have been independent of the reduction of blood pressure. Such as slightly earlier results of captopril in type 1 diabetes, slightly lower albuminuria residuals levels were connected with lower possibility of end stage renal disease.[73]

7.2.3 Aldosterone antagonists

Aldosterone has been the ultimate aspect of the Renin Angiotensin System (RAS) cascade. Aldosterone enhances fibrosis, inflammation and ROS, as well as disorder of the endothelium, cell growth and multiplication.[74] Spironolactone tends to decrease proteinuria by itself or in combination with an Angiotensin-converting enzyme (ACE) or Angiotensin II receptor blockers (ARB) inhibitor in diabetics of type 1 and type 2.[75] secondly to a decreasing blood pressure impact, it is also probable to provide anti-inflammatory pathways, including monocytes chemo attractant protein (MCP-1). Macrophage migration inhibitory factor (MIF) and macrophage reductions aggregation.[76]

7.2.4 Calcium channel blocker (CCB)

It might also be effective to add nondihydropyridine CCB t o RAS inhibition. In type 2 diabetics, It was shown that ver apamil and diltiazem decreased proteinuria.[77] The impacts of adding together lisinopril or trandolapril with verapamil medication have been additive in decreasing albuminuria and a reduce in GFR.[78] Furthermore, in combination with trandolapril, the BENEDICT-B study of verapamil did not find an extra value in macroalbuminuria progression in hypertensive, form 2 diabetics, unaware of blood pressure reduction[79] in the 24 week. Valsartan has become more effective in 332 type 2 diabetics MARVAL valsartan or amlodipine randomized study (CCB dihydropyridine), in preventing albuminuria than amlodipine, along with remission to normoalbuminuria.[80]

7.2.5 Diuretics

Compared to thiazide, diuretics for nutritional sodium limitation (example) 50 mg hydrochlorothiazide) eliminated albuminuria in type 2 diabetics in conjugation with an ACE inhibitor (lisinopril 40 mg/ day). Nevertheless, the combination is connected with more regular indications of orthostatics. A diuretic loop may be more appropriate for highly developed chronic kidney disease. Diuretics can make ACE inhibitors and ARBs more efficient.[81]

7.2.6 AGE inhibitors

AGE inhibitors minimize the development of AGE, improve degradation or break crosslink with AGE. Aminoguanidine (pimagedine) is the AGE inhibitor technology that works by scavenging intermediates including 3-deoxyglucosone and methyglyoxal.[82] Aminoguanidine in diabetic rats is scientifically attenuating albuminuria, mesangial development including collagen accumulation.[83] Moreover, the placebo controlled action test in 690 serum creatinine diuretics with extreme nephropathy found no difference over time with a 2-4 year drop in proteinuria.[84]

7.2.7 Transplantation

Consistent pancreas / kidney transplantation is a safe therapy for end stage renal disease (ESRD) in type 1 diabetes, one of the most insulin management and reoccurrence of diabetic nephropathy all through the allograft. [85] Patients having chronic kidney disease alone after ten years of pancreatic transplantation showed reduced albuminuria and then regeneration of diabetic nephropathy on serial biopsy lesions, particularly deterioration of membrane thickening of glomerular basement and mesangial matrix accumulation.[86] Few of the

following advantages might be compensated by calcineurin in similar interstitial fibrosis and arteriolar hyalinosis (e.g. cyclosporine). The very same researchers note, however, the ten year tubulointerstitial remodeling improved some interstitial deposition of collagen detected at time period of five years and during these many years, even though vascular improvements were still not damaged.[87]

CONCLUSION

Diabetic nephropathy affects approximately one third of those with diabetes. Improved management has led to reduction in incidence of progression to ESRD in this group. However, cardiovascular mortality is greatly increased in people with overt diabetes nephropathy. The number of people affected by chronic kidney disease due to diabetes will escalate in the coming decades, and this will impose great strains on health delivery and costs, particularly in developing countries. In the last few years, we have witnessed enormous progress in the understanding of the risk factors and mechanisms of diabetic nephropathy, the stages of renal involvement in diabetes, and the treatment strategies to prevent or interrupt the growth of diabetic nephropathy. Early detection of diabetic nephropathy, adoption of multifactorial intervention stargeting the main risk factors (hyperglycemia, hypertension, dyslipidemia, and smoking), and use of agents with a renoprotective effect (ACE inhibitors and/or ARBs) do indeed reduce the progression of renal disease. Treatment of hypertension is a priority. Attention to these procedures will also ensure the reduction of cardiovascular mortality.

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