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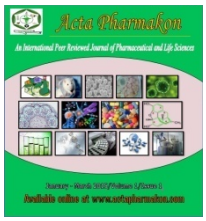

Review Article

Diabetic Nephropathy: A Review

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ABSTRACT

Diabetes is one of the major cause of renal disease. It is characterized by albuminuria, which is usually accompanied by hypertension, progressive rise in proteinuria (albuminuria >0.5 g/24 h), and decline in renal function. Different stages of diabetic nephropathy are summarized in this review accordingly of recent studies. The risk factors such as hyperglycaemia, hypertension, microalbuminuria, ethnicity, gender and family history, duration of diabetes, smoking, and genetic susceptibility and the major pathways *i.e* Polyol pathway, Advanced glycation end-products (AGEs) pathway, Protein kinase C (PKC) pathway, Reactive oxygen intermediate pathway are involved in the pathogenesis of diabetic nephropathy. To delay the progression of DN to ESRD various treatment measures are also summarized here.

1. INTRODUCTION

Diabetic nephropathy is a clinical syndrome characterized by the occurrence of persistent micro albuminuria in concomitance with insulin- or non–insulin dependent diabetes. This nephropathy has a long natural history in type 1 diabetes. Initially, the patient shows hyper filtration, represented by high values of GFR, approximately doubling of the normal value, and occasional occurrence of micro albuminuria. The duration of these abnormal laboratory data is approximately 5 year. Later, during a course of approximately 20 year, the patient shows a gradual decline of the GFR and persistence of micro albuminuria that comes before mild and subsequently moderate proteinuria. The final step of the natural history of the disease is characterized by severe proteinuria with or without nephrotic syndrome and chronic renal insufficiency that declines to End stage renal disease. The gradual impairment of the above laboratory findings is caused by structural alterations at the renal level, which at the beginning consist of a gradual and progressive accumulation of extracellular matrix (ECM) in the

mesangium and glomerular basement membrane. Later, the formation of mesangial nodules represents the characteristic lesions of the Kimmelsteil-Wilson nephropathy with additional extensive tubule interstitial lesions. [1]

Stages of diabetic nephropathy:

Stage I: Hypertrophic hyper filtration. In this stage, GFR is either normal or increased. Stage I lasts approximately five years from the onset of the disease. The size of the kidneys is increased by approximately 20% and renal plasma flow is increased by 10%-15%, while albuminuria and blood pressure remain within the normal range. [2-3]

Stage II: The quiet stage. This stage starts approximately two years after the onset of the disease and is characterized by kidney damage with basement membrane thickening and meningeal proliferation. There are still no clinical signs of the disease. GFR returns to normal values. Many patients remain in this stage until the end of their life. [2-3]

Stage III: The micro albuminuria stage (albumin 30-300 mg/dU) or initial nephropathy. This is the first clinically detectable sign of glomerular damage. It usually occurs five to ten years after the onset of the disease. Blood pressure may be increased or normal. Approximately 40% of patients reach this stage. [2-3]

Stage IV: Chronic kidney failure (CKF) is the irreversible stage. Proteinuria develops (albumin>300 mg/dU), GFR decreases below 60 ml/min/1.73 m2, and blood pressure increases above normal values. [2-3]

Stage V: Terminal kidney failure (TKF) (GFR<15 mL/min/1.73 m2). Approximately 50% of the patients with TKF require kidney replacement therapy (peritoneal dialysis, hemodialysis, kidney transplantation). [2-3]

In the initial stages of diabetic nephropathy, increased kidney size and changed Doppler indicators may be the early morphological signs of renal damage, while proteinuria and GFR are the best indicators of the degree of the damage. [2-3]

Risk Factors for Diabetic Nephropathy

Diabetic nephropathy is an important micro vascular complication of long standing non-insulin dependent diabetes mellitus (NIDDM) as well as insulin dependent diabetes mellitus (IDDM) associated with considerable morbidity and mortality.[4] Various genetic, metabolic, and hemodynamic factors that appear to be important in the pathogenesis of DN are hyperglycemia, hypertension, microalbuminuria, ethnicity, gender and family history, duration of diabetes, smoking, and genetic susceptibility. [5] There are several risk factors for the development of diabetic nephropathy. They can be divided into those that cannot be altered (genetic factors, age, and race) and those that can and must be changed (hyperglycemia, hypertension, dyslipidemia and GFR. [6]

Pathogenesis of Diabetic Nephropathy

Oxidative stress plays a pivotal role in the development of diabetes complications, both microvascular and cardiovascular. [7] The pathogenesis and progression of diabetic nephropathy are likely to be as a result of interactions between metabolic and hemodynamic pathways, which are often disturbed in the setting of diabetes. It occurs as a result of an interaction between hemodynamic and metabolic factors. Hemodynamic factors that contribute to the development of diabetic nephropathy include

increased systemic and intra glomerular pressure, as well as activation of vasoactive hormone pathways including the renin angiotensin system and endothelin. The metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels, and also in the myocardium this increased superoxide production causes the activation of four major pathways involved in the pathogenesis of complications:

- Polyol pathway
- Advanced glycation end-products (AGEs) pathway
- Protein kinase C (PKC) pathway
- Reactive oxygen intermediate pathway

Treatment of diabetic Nephropathy

- Glycaemic control
- Blood pressure control
- Smoking cessation
- Protein restriction
- Cholesterol reduction (possibly)

Glycaemic control

Poor glycaemic control leads to accumulation of advanced glycosylation end products in tissues; hence DN is four times more common in IDDM patients with poor glycaemic control. The onset of microalbuminuria correlates closely with Glycaemic control, with a gradual rise in rate as the glycosylated haemoglobin level increases from 6.1% to 8.1% and a sharp rise occurring above 8.1%. [9]

Blood pressure control

In type 1 diabetics, blood pressure rises with the development of microalbuminuria. With the onset of overt proteinuria, hypertension is usually present and worsens as the nephropathy progresses. [10] Tight blood pressure control is the primary goal in the management of hypertension in diabetics. This may be achieved with any antihypertensive agent. [11]

Antihypertensive agents used in diabetic nephropathy

ACE inhibitors have a strong track record in slowing disease progression in type 1 and type 2 diabetics. In the 1990s, captopril demonstrated the ability of ACE inhibitors in reducing the progression of albuminuria and decline in renal function in type 1 diabetics, independent of blood pressure lowering. ACEIs or ARBs may be considered as first line therapy for treatment of hypertension in diabetics in the absence of contraindications. [12]

Hypoglycemic agents in diabetic nephropathy

Chronic renal disease is associated with decreased clearance of many oral hypoglycemic agents and their metabolites, prolonging the duration of exposure to the drug and its metabolites, more so in patients with moderate to severe renal disease. [13] Safety profile of few drugs used in renal disease is given in Table 1.

- ACEIs/ARBs should be used with caution in patients with bilateral renal artery stenosis or renal artery stenosis of a single functioning kidney. [14]
- Diuretics may potentiate the hypotensive and anti-proteinuric effect of ACEIs/ARBs. Potassium sparing diuretics may worsen hyperkalaemia when combined with ACEI/ARB in the presence of renal failure. [15]

Smoking cessation

Cigarette smoking in diabetes has been confirmed to develop large amount of free radicals and pro-oxidant molecules, exerting an adverse influence

on endothelial cells through an inhibitory effect on components of the L-arginine-nitric oxide pathway. [16]

Protein restriction

In diabetic nephropathy, damage to the kidneys occurs as a consequence of hyperglycaemia, which induces damage of blood vessels leading to several phenomena, including impaired blood flow. Features include increased excretion of protein in the urine, increased blood pressure and declining kidney function. [17] Restriction of dietary protein is beneficial in prevention of progression of diabetic nephropathy in type 1 diabetes. [18] The current UK recommendations suggest the amount of protein consumed should not exceed 1 g/kg/day. [19]

Table 1: Hypoglycemic agents in diabetic nephropathy

S. No.	Class of Drug	Safety profile in renal disease	Remarks
1.	1st generation sulphonylureas	Unsafe	Risk of prolonged hypoglycemia.
2.	2nd generation sulphonylureas	Glipizide safe	Glipizide is preferred but others to be avoided.
3.		Rest unsafe	Risk of hypoglycemia.
4.	α - glucosidase inhibitors	Unsafe	Possible hepatotoxicity.
5.	Biguanides	Unsafe	Risk of lactic acidosis.
6.	Thiazolidinediones	Safe	Volume retention may occur especially with insulin.
7.	Meglitinides	Repaglinide safe	Short half life and minimal renal excretion of repaglinide.
		Nateglinide not completely safe.	Significant risk of hypoglycemia.
8.	DPP-4 inhibitors	Relatively safe	Dose adjustment is needed for moderate to severe renal disease.
9.	Amylin analogs	Safe	No dose adjustment is needed for moderate to severe renal disease.

Cholesterol reduction

In diabetics: (a) therapeutic lifestyle changes should be instituted if LDL cholesterol is > 2.6 moll/l (b) drug therapy should be considered if LDL-cholesterol is > 3.4 mmol/l. All diabetics should be encouraged to go on a therapeutic lifestyle change comprising increased physical activity, reduction in intake of saturated fat and cholesterol, as well as achievement of ideal bodyweight.[20] Therapy with lipid lowering drugs, especially with statins, has been shown to reduce cardiovascular morbidity and mortality in diabetics. [21]

2. CONCLUSION

The single most normal reason for ESRD in the United States today is diabetic nephropathy, and the rate in type 2 diabetes seems, by all accounts, to be expanding. A few variables most likely add to the renal harm, including hyperglycemia and other metabolic by-results of lifted glucose, hypertension (both systemic and intrarenal), and a hereditary inclination in a few patients.

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