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A review basic on diabetic nephropathy

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Abstract
Diabetic nephropathy is one of the common complications of diabetes mellitus that has become the leading cause of end stage renal failure in many developed countries. In general, 1 of 3 diabetic patients is developing diabetic nephropathy. High blood pressure, high cholesterol and smoking are increasing the risk of development of diabetic nephropathy. Glomerular basement membrane thickening and mesangial expansion are the main morphological features of the diabetic nephropathy. The main objective of this review is to discuss about the pathophysiology, screening and diagnosis, risk factor and management.

Keywords: Diabetic, nephropathy, homoeopathy

Introduction
Diabetes mellitus is a leading epidemic of the present world. It is considered the leading cause of death among end-stage renal disease (ESRD) patients. The complications associated with diabetes mellitus have boosted the number of deaths in the last years. These complications are the result of long lasting effects of diabetes mellitus on the glomerular microvasculature of the kidney [1]. Diabetic nephropathy (DN) develops in patients with several years' medical history of diabetes and renal failure. However, research shows that patients with type 1 diabetes progress early to ESRD as compared to those with type 2 diabetes mellitus. Diabetic nephropathy is more prevalent in ethnic minorities as compared to other groups in society. There are new and different treatment options available since medical science has progressed due to increased research efforts. Unfortunately, there is no permanent cure [2, 3]. The aim of this article is to explore the research of therapeutic strategies currently in use by medical practitioners in order to increase understanding of diabetic nephropathy [4].

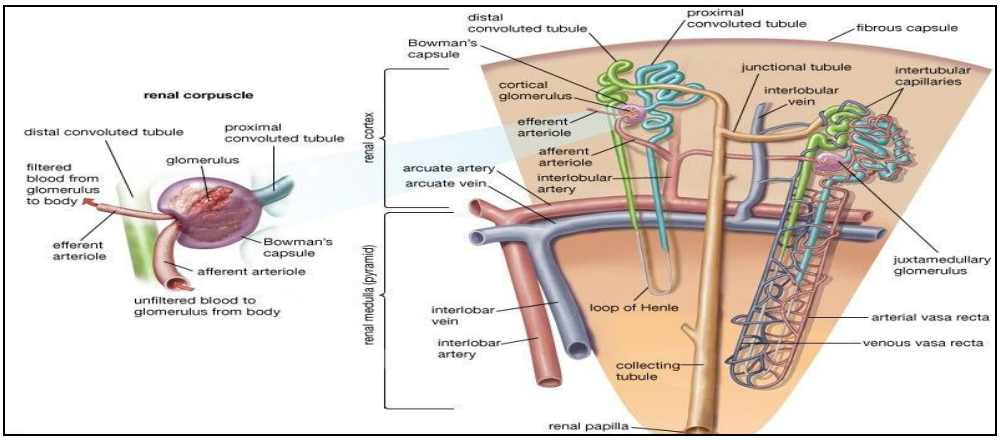

Fig 1: Anatomy of Nephron

Features of Diabetic Nephropathy
Glomerular Basement Membrane Thickening**:** Glomerular basement membrane (GBM) thickening is a characteristic early change in type 1 diabetes mellitus and type 2 diabetes mellitus and occurs with duration of disease [5, 6]. Glomerular basement membrane thickening is a consequence of Extracellular matrix (ECM) accumulation, with increased deposition of normal ECM components such as collagen, laminin, and fibronectin. Such accumulations could result from either increased production of these proteins or their decreased

degradation, or both [7, 8]. Glomerular basement membrane thickening might already be present in type 1 diabetes mellitus patients, who are normoalbuminuric [9].

Mesangial Expansion: Mesangial cells are found in a part of the kidney called the glomerulus involved in filtration in the urine. Water, waste, and excess nutrients are filtered from the blood through the capillary walls into the surrounding Bowman's capsule. The mesangial cells are found between the capillaries and help regulate the filtration process while providing support for the glomerular structure and they are involved in the kidney's response to injury and disease. Intra glomerular mesangial cells have an irregular shape and are related to smooth muscle cells. They do have similar proteins such as myosin and actin, and have the ability to contract.

Pathophysiology

Diabetes nephropathy is a clinical syndrome characterised by the insistent albuminuria that should be confirmed on at least two occasions separated by 3-6 months, by continuous decline in the glomerular filtration rate (GFR), and by increased arterial blood pressure. Diabetes nephropathy is characterised by different events [10]. The characteristic occurrence is thickening of the glomerular basement membrane (GBM). After renal damage, the thickening of the basement membrane starts, which leads to pathologic modifications in mesangial and vascular cells [11-13]. It includes formation of AGEs, accumulation of polyols, and activation of protein kinase C. It leads to activation of the inflammatory pathway playing a significant role in the damage of GBM.

Secondly, the renal hemodynamic anomaly is similar in both types of diabetes. An initial physiologic abnormality is glomerular hyperfiltration related to intra glomerular hypertension [14-16]. This is complemented by the onset of Microalbuminuria. Microalbuminuria is considered the first sign indicating the onset of diabetic nephropathy.

The exact pattern observed in the pathophysiology of diabetic nephropathy is:

- Hyperglycaemia
- Thickening of GBM
- Glomerular hyper filtration
- Impaired endothelial integrity
- Onset of Microalbuminuria
- Impairment of nitric oxide transport
- Loss of afferent/efferent auto regulatory control
- Continued loss of glomerular filtration capabilities

A clinically asymptomatic point of failure follows with development of Microalbuminuria (30 mg albumin per day) to Microalbuminuria (>300 mg albumin per day). Once overt nephropathy (Microalbuminuria) has established, renal function falls at a significant but alterable rate (decline in GFR of 220 ml/min/ year). The rate of decline depends on type of diabetes, genetic predisposition, glycaemic control and, very significantly, blood pressure. Hypertension is the single most essential cause of the evolution and opinion of successful intermediation in diabetic nephropathy. Later stages may also be supplemented by clinically significant albuminuria, oedema, and nephrotic syndrome. Ultimately, the distinguishing clinical picture of renal failure develops. It is thought that the development of nephropathy occurs in similar fashion in both types of diabetes.

Natural clinical course of diabetic kidney disease:

The natural history of diabetic nephropathy is divided into five stages

Stage 1

Renal pathology develops at the onset of diabetes. The growth of the kidney increases by several centimetres. By the time of diagnosis, the GFR and urinary albumin excretion (UAE) have been increased. It can be controlled at this level by onset of insulin.

Stage 2

The second phase typically lasts for 5-15 years after diagnosis of diabetes. The characteristics of the second phase include:

- GFR remains elevated due to hyperfiltration.
- Kidneys remain hypertrophied and UAE rate stays normal.

Stage 3

The characteristics of stage three are:

- Microalbuminuria is present. It occurs in 30-50% of patients after diabetes onset, 80% of whom go on to develop overt nephropathy over 10-15 years.
- GFR remains elevated or returns to normal range
- Blood pressure starts to rise in 60% of patients

Histological changes progression is as seen in stage two.

Stage 4

This stage is also known as clinical nephropathy or overt nephropathy. The characteristic histological features of stage four are formation of the Kimmelstiel-Wilson nodule (focal glomerular sclerosis) and macroproteinuria. It can progress to nephrotic in 30% of patients or may decline in 80% depending on deterioration of GFR [17].

Stage 5

As the GFR continues to decline, ESRD may develop. Diabetes nephropathy is considered the most common cause of ESRD because of associated autoimmune neuropathy and cardiac disease [17].

The stages of chronic kidney disease (CKD) are mainly based on measured or estimated GFR. There are five stages but kidney function is normal in stage 1 and minimally reduced in stage 2.

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>300 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

Fig 2: Natural history of diabetes nephropathy

Screening and Diagnosis

Screening for diabetic nephropathy must be initiated at the time of diagnosis in patients with type 2 diabetes, since 7% of them already have Microalbuminuria at that time. For patients with type 1 diabetes, the first screening has been recommended at 5 years after diagnosis. However, the prevalence of Microalbuminuria before 5 years in this group can reach 18%, especially in patients with poor glycemic and lipid control and high normal blood pressure levels. Furthermore, puberty is an independent risk factor for Microalbuminuria. Therefore, in type 1 diabetes, screening for Microalbuminuria might be performed 1 year after diabetes diagnosis, especially in patients with poor metabolic control and after the onset of puberty. If Microalbuminuria is absent, the screening must be repeated annually for both type 1 and 2 diabetic patient.

The first step in the screening and diagnosis of diabetic nephropathy is to measure albumin in a spot urine sample, collected either as the first urine in the morning or at random, for example, at the medical visit. This method is accurate, easy to perform, and recommended by American Diabetes Association guidelines. Twenty-four– hour and timed urine collections are cumbersome and prone to errors related to collecting samples or recording of time. The results of albumin measurements in spot collections may be expressed as urinary albumin concentration (mg/l) or as urinary albuminto-creatinine ratio (mg/g or mg/mmol). Although expressing the results as albumin concentration might be influenced by dilution/concentration of the urine sample, this option is still accurate and cheaper than expression as albumin to creatinine ratio. The cutoff value of 17 mg/l in a random urine specimen had a sensitivity of 100% and a specificity of 80% for the diagnosis of Microalbuminuria when 24 h timed urine collection was the reference standard. This value is similar to the cutoff value of 20 mg/l recommended by the European Diabetes Policy Group. All abnormal tests must be confirmed in two out of three samples collected over a 3- to 6-month period, due to the known day-to-day variability in UAE. Screening should not be performed in the presence of conditions that increase UAE, such as urinary tract infection, hematuria, acute febrile illness, vigorous exercise, short term pronounced hyperglycemia, uncontrolled hypertension, and heart failure. Samples must be refrigerated if they are to be used the same day or the next day, and one freeze is acceptable before measurements. Immunoassays routinely used for albumin measurements present adequate diagnostic sensitivity for detection of diabetic nephropathy. However, it was recently demonstrated that conventional immunochemical-based assays did not detect an unreactive fraction of albuminuria, underestimating UAE. High performance liquid chromatography measures total albumin, including immunoreactive and immunoreactive forms, and may allow early detection of incipient diabetic nephropathy[18].

Risk Factors

Increased urinary albumin excretion is a major risk factor for the progression of diabetic nephropathy in both type 1 diabetes (T1D) and type 2 diabetes mellitus. In most patients, the first sign of diabetic nephropathy is moderately increased urinary albumin excretion, i.e. 30-300 mg/g creatinine in a spot urine sample (also termed Microalbuminuria). Patients who develop severely increased albuminuria, i.e. >300 mg albumin/g creatinine in a spot urine sample (also called Macroalbuminuria or clinical albuminuria), are at particularly high risk for developing a decline in renal function. However, a substantial proportion (up to 40%) of patients with moderate albuminuria returns to normoalbuminuric. Moreover, up to 50% of patients with type 1 diabetes mellitus or type 2 diabetes mellitus experience a decline in glomerular filtration rate (GFR), despite the presence of only moderate albuminuria or even normoalbuminuric. Therefore, elevated urinary albumin excretion (UAE) is not a necessary prerequisite for the development of diabetic nephropathy. This finding has consequences for the diagnosis of the disease, namely that GFR should be assessed in addition to UAE. Moreover, elevated UAE is associated with increased cardiovascular risk, but it is controversial whether reducing it translates to a lower incidence of cardiovascular events [19].

Elevated glucose levels

Inadequate glycemic control is a pivotal risk factor for the development and progression of diabetic nephropathy. In

patients with both type 1 diabetes mellitus and type 2 diabetes mellitus, high HbA1c levels are associated with an increased risk for developing nephropathy. Observational studies reported a clear decrease in the incidence of diabetic nephropathy in both patients with type 1 diabetes mellitus and type 2 diabetes mellitus who achieved better glycemic control. Indeed, in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, patients with moderate albuminuria, but lower HbA1c levels, had a lower risk for progressing to severe albuminuria or ESRD. Randomized controlled studies in patients with type 1 diabetes mellitus and type 2 diabetes mellitus reported similar findings. In DCCT, intensive glycemic control reduced the risk of progression from moderate albuminuria to severe albuminuria or ESRD. Moreover, strict glycemic control reduces the risk of progression from severe albuminuria to reduced GFR or ESRD. However, it is unclear whether the different antidiabetic agents are all similarly effective in delaying the progression of diabetic nephropathy. This remains to be elucidated.

Other risk factors

Patients with a longer duration of diabetes have a higher risk for developing nephropathy. Elevated blood pressure is another important independent risk factor for nephropathy. In the DCCT/EDIC study, lower blood pressure was associated with reduced risk for progression from moderate albuminuria to severe albuminuria or ESRD. Moreover, in patients with type 2 diabetes mellitus, lower blood pressure was associated with regression from moderate albuminuria to normoalbuminuric. Inhibitors of the rennin angiotensin system appear to delay the progression of diabetic nephropathy more than other classes of antihypertensive agents, while the reduction in blood pressure is similar. Dyslipidemia also appears to play a role in the pathogenesis of diabetic nephropathy. In the DCCT/EDIC study, lower low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels were associated with reduced risk for progression from moderate albuminuria to severe albuminuria or ESRD. In patients with type 2 diabetes mellitus, elevated total cholesterol (TC) levels are also associated with increased risk for the development of both moderately and severely increased UAE. In addition, low levels of TC and TG are associated with regression from moderate albuminuria to normoalbuminuria in type 2 diabetes mellitus. The interventional studies with stains mentioned above also provide evidence for a role of dyslipidemia as a risk factor for diabetic nephropathy by showing that lowering LDL-C levels is associated with delayed progression of the disease.

Management

Annual screening for Microalbuminuria is recommended for patients with T2DM from the time of diagnosis as the duration of their diabetes will be unknown. For patients with type 1 diabetes mellitus, annual Microalbuminuria screening is recommended from five years after diagnosis. BP treatment targets vary in different guidelines but we suggest targets of 125/75 mmHg for those with proteinuria over 1 g/24hr and 130/80 mmHg for those with less than 1 g/24hr. A reduction in protein excretion to below 0.5–1.0 g/24hr is recommended, although this can be difficult to achieve in practice. National Institute for Health and Clinical Excellence (NICE) management of type 1 diabetes mellitus guidelines identify management of lifestyle, glycaemic control, BP, albuminuria and dyslipidaemia as priorities for treatment [20].

Glycaemic control

Excellent glycaemic control can prevent the onset of Microalbuminuria, reverse glomerular hypertrophy and hyperfiltration, and stabilise or decrease proteinuria in those with established diabetes nephropathy. Intensive therapy to near-normal glycaemia can reduce the onset or progression of diabetes nephropathy even in those with previous poor glycaemic control. Methods for HbA1c measurement are affected by renal failure, leading to falsely elevated levels. However, in those patients with advanced CKD other factors contribute to decrease in measured HbA1c, leading to an underestimate of glycaemic control, for example reduced red blood cell life span, recent transfusion, iron deficiency, accelerated erythropoiesis due to administration of erythropoietin and metabolic acidosis. CKD is associated with insulin resistance, but the half-life of insulin increases as renal failure progresses and patients may need a reduction in total insulin dose, particularly those with reduced appetite associated with uraemia. Oral hypoglycaemic drug therapy can also be challenging in diabetic patients with advanced CKD. Metformin is used with caution in people with CKD because of the associated risk of lactic acidosis. A dose reduction of 50% is suggested for those with an eGFR below nephropathy, an ACEI or ARB should be considered and uptitrated to achieve blood pressure and proteinuria targets. Repeating a renal function test is advised one week after introduction or dose escalation; a creatinine rise less than 30% and a potassium level below 6 mmol/l may be accepted. Patients should be told to stop these drugs during any episodes of dehydration, intercurrent illness or exposure to radio contrast.

Conclusion

In the last few years, 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 the progression of diabetic nephropathy. Early detection of diabetic nephropathy, adoption of multifactorial interventions targeting the main risk factors (hyperglycemia, hypertension, dyslipidemia, and smoking), and use of agents with a reno-protective effect (ACE inhibitors and/or ARBs) do indeed reduce the progression of renal disease. Diabetes nephropathy remains the leading cause of ESRD in developed countries, and its occurrence seems to be aggregate in the developing countries. The cost of treating this situation, mainly when patients require renal replacement therapy is huge in order to attain the healthy people 2020 goal. Multifactorial tactic directing strict control of blood sugar, lipids and blood pressure and use of ACEIs and ARBs in proteinuric patients will be preferable. Moreover in addition, low cost community based program to increase physical activity and avoid unhealthy lifestyle. This will leads to decline in the incidence of diabetes in the population.

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