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DIABETIC NEPHROPATHY: CAUSES AND PATHOLOGY

[1]Dr Aniqa Khan,[2]Dr Zill e Rehman, [3]Dr Waheed Sardar

[1]MBBS,Quaid e Azam Medical College,Bahawalpur.

[2]MBBS,Akhtar Saeed Medical And Dental College,Lahore.

[3]MBBS,Sahiwal Medical College,Sahiwal.

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Abstract:

Diabetic nephropathy is a type of chronic kidney disease that adversely affects the functioning of kidneys like fluid and salt balance, blood pressure, and excretion. The body's capacity of producing normal insulin levels in the blood is also affected. It is categorized into stages: microalbuminuria and macroalbuminuria. Patients in the upper normal range of albumin levels are prone to both these stages of albuminuria as they also had high blood pressure, while those in lower to the normal albumin range are not likely to fall under these categorize. The level of albumin, observed in samples collected in three to six months define either the patient has diabetic nephropathy or not. The morphological altered glomerular filtration rate and hyalinization of afferent and efferent arterioles of glomerulus also depict the presence of diabetic nephropathy. Dark urine, nausea, fatigue, vomiting, and swollen joints are some prominent symptoms of diabetic nephropathy which are not usually visible at the beginning of this disorder. Diabetes puts immense stress upon kidneys and as a result, the body starts to lose protein through urine and inappropriate blood filtration continues.

In this article, a brief overview of diabetic nephropathy along with its causes and symptoms are touched to give a holistic view and throw some light upon the important features of this disease.

Corresponding author:

Dr. Aniqa Khan,

MBBS,Quaid e Azam Medical College,Bahawalpur.

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INTRODUCTION:

Diabetic nephropathy is one of the leading causes of chronic renal disease and cardiovascular mortality. Diabetes is something that not only affects its source organ but also adversely impacts almost all the internal body organs, thus increasing the mortality rate if remains unchecked. DN is screened and defined by the presence of excessive protein levels in the urine. [1,2]

Early-stage, microalbuminuria is characterized by the presence of small albumin levels in the urine, while advanced levels lead to macroalbuminuria or proteinuria condition. In most cases decreased glomerular filtration (GFR) and proteinuria parallelly occur. [3, 4] However, these levels might vary from case to case as about 10% of Type 2 Diabetes Mellitus patients have low GFR without micro or macroalbuminuria. [5, 6]

Ethnicity, age, medical history, genetics, and lifestyle are some key features that play a critical role in defining the occurrence rate. A study also revealed that renal replacement therapy and ESRD treatment also increases the DN rate in diabetic patients of all age groups. Nevertheless, by controlling glucose levels, increased use of angiotensin, putative blood pressure improvement, and changes in lifestyle can significantly contribute to lowering the risk of DN.

Impacts of Diabetes upon Kidneys

The human body has a natural filtrate system, in the form of the kidneys. The main function of the kidneys is to filter waste products and excess water from the blood so that they can be excreted out of the body in the form of urine. Beside this filtration, kidneys also play an imperative role in maintaining healthy salt- fluid balance, and normal blood pressure. These functions are carried out by a system consisting up of tubules and blood vessels known as nephron. Tiny blood vessels preside in nephron called capillaries along with tiny urine collecting tubes. The main structure in the nephron is a special group of blood vessels called the glomerulus, which is the main filrating site.

High blood glucose levels can negatively interfere with glomerulus functioning. When the glucose level rises, the filtration rate is affected, kidneys don't work effectively and protein began to leak from the blood into the urine. Scarring of glomerulus also called glomerulosclerosis also occurs due to high glucose levels, and as the scarring gets worse kidneys to stop functioning and waste products no longer are filtered out from the blood. When maximum glomerulus damage occurs, kidney failure happens. Diabetic patients often have high blood pressure issues, and this issue can further contribute to kidney damage.

Stages of Diabetic Nephropathy

Diabetic nephropathy is classified into following three stages on the basis of albumin level present in the urine

Stages	**Urine with Marked Time (μg/mg)**	**24 Hours-Urine (mg/ 24h)**	**Random Urine Sample**	
			Albumin concentration (mg/l)**	**Albumin/creatinine ratio (mg/g)***
Normoalbuminuria	< 20	< 30	< 17	< 29.5
Microalbuminuria	20 – 198	30 – 298	17 a 173	30 – 298
Macroalbuminuria	≥ 200	≥ 299.5	≥ 173.5	≥ 300

Special Conditions

Diabetic patients can also have various other kidney diseases at the beginning. History, physical examination, laboratory evaluation, and kidney imaging are involved in the differential diagnosis. Renal biopsy is restricted to only specific situations. The assumption of having DN in patients with micro or macroalbuminuria having DM for the long term, e.g. >10 years, is usually correct. However, in type 2 diabetic patients, the duration of DM isn't confirmed and retinopathy could be absent. In short, a faster decline of GFR, short DM, absent retinopathy, and albuminuria increment are some factors that lead to suspected non-diabetic renal disease. [7, 8]

Risk Factors and Causes

The two main risk factors and causes associated with DN are arterial hypertension and hyperglycemia. DN can develop in 40% of patients who have elevated BP and hyperglycemia for the long term. Once DN results, other factors also contribute to the progress of the disease and advance the stages. [9]

The causes and the main progression risk factors of diabetic nephropathy are given below:

- **Arterial Hypertension**

Arterial hypertension is probably the best-known cause and relevant factor linked with the development and progression of diabetic nephropathy. UKPDS analysis has shown that every with every 10mmHg systolic blood pressure reduction, risk factor reduction by 30% in

microvascular complication occurs. Patients with systolic BP less than 120mmHg are at the smallest risk level. [10]

- **Hyperglycemia**

Both in type 1 and 2 DM, hyperglycemia is a significant risk factor for the development of microalbuminuria and then DN. A decline of 37% in microvascular endpoints was observed with a reduction of 1% glycated hemoglobin A1c. Metabolic control becomes complicated when conditions like micro and macroalbuminuria are present, as high glucose levels have deleterious impacts upon GFR. [11]

- **Dyslipidemia**

In type 2 diabetes mellitus, elevated serum cholesterol level is troublesome for the development of diabetic nephropathy. It is also found that high serum triglycerides, low-density lipoproteins, and cholesterol are linked with micro and macroalbuminuria. All these conditions negatively perpetrate processes like weakening of blood vessels, increasing blood pressure, accumulating fat in tissues, and much more. Thus, dyslipidemia adversely becomes the cause of DN along with many cardiovascular disorders. [12]

- **Proteinuria**

Macroalbuminuria is also known as proteinuria, is itself one of the causes of diabetic nephropathy. The greatest risk of end-stage renal disease is associated with proteinuria >2 g/24 h. inflammatory cascades are activated which damages the glomerular when albumin is leaked at higher levels. [13]

- **Glomerular Hyperfiltration**

About one-third of type 2 diabetes mellitus patients have elevated values of GFR and this condition can theoretically cause diabetic nephropathy. When GFR values began to rise, its efficiency declines, the rate of waste filtration is abruptly damaged and ultimately the overall glomerular structure is damaged. [14]

Pathology

Diabetic nephropathy in type 1 DM patients is characterized initially by a thickening of the tubular basal membrane and glomerular along with the progressive reduction of GFR and mesangial expansions. Hyalinization of the efferent and afferent glomerular arterioles, diffusion of mesangial expansion forming roundish fibrillar zones and palisade nuclei are all prominent pathological features of DN. [15] Moreover, as loss of renal functioning is progressed by critical lesions in form of mesangial expansion, progression to ESRD is caused by damage to glomerular junction and tubules.

Damage to podocytes is also seen to be linked with the glomerulosclerosis process. [16] In a study it was stated that a small podocyte number per glomerulus is a great indicator and predictor of increased UAE and clinical DN progression. Besides, podocyte synthesizes a protein called nephrine, it is considered important for the glomerular barrier stability, has its expression in DN reduction. Examination of patients administered with ACE inhibitors expressed nephrine at levels similar to those of patients with DM without diabetic nephropathy. [17]

Renal lesions in type 2 DM patients are complicated as compared to patients with type 1 DM. In type 2 DM, these lesions can cause proteinuria in almost 10 to 30% of subjects with or without arteriolar alterations, tubulointerstitial alterations, or diffuse glomerulosclerosis. The tubulopathy is possibly related to changes in age, atherosclerosis, hyperglycemia, and arterial hypertension. The severity of lesions, especially in type 2 DM are greatly linked with the progression of diabetic nephropathy and the increased velocity of GFR loss. [18]

Treatment

The principles of prevention and treatment of diabetic nephropathy are the same. However, each factor and cause will play a different role at a different rate in each stage of the disease. Stage definition is extremely important before beginning the treatment for the outcomes of interest. [19]

Recent meta-analyses have shown that in stages like proteinuria, progression to ESDR, or GFR decline, both ACE inhibitors and angiotensin receptor blockers (ARBs) seem to be effective. These aid in reducing creatinine doubling rate and proteinuria. [20] Perhaps, the best treatment is the multiple risk factor interventional approach, as it included controlling and checking various factors simultaneously at the same time to reduce the DN progression, cardiovascular risk, and mortality.

In patients with normo or microalbuminuria, the target is to intervene at hyperglycemia, arterial hypertension, smoking, and dyslipidemia. The clear management data are absent, but these risk factors also cause CVD, so aggressive treatment is a must thing. [21]

Clinical trials depict that intense hyperglycemic treatment decreased the risk of DN development in both types of patients with DM, either type 1 or type 2. However, the intensity of therapy may vary from type to type. This treatment demonstrated a minor protective effect against the progression of albuminuria, but no effect was observed in serum creatinine values. [22]

Treatment of hypertension leads to a significant risk reduction in microvascular events and CVD. A reduction from 154 to 144 mm Hg in UKPDS n

systolic BP reduced the microalbuminuria risk by 29%. Blood pressure targets for patients are different without DM and different for patients with DM (130/80 mm Hg). [23] Hypertension Optimal Treatment (HOT) study has shown a decline of 50% CVD risk in diabetic patients by reducing BP from 85 to 81 mm Hg, but this condition isn't helpful in non-diabetic patients. [24] In the microalbuminuria condition, positive outcomes were received despite the age number, with appropriate hypertension treatment. [25]

To achieve the target of BP 130/80 mm Hg in diabetic and 125/75 mm Hg in patients with proteinuria >1.0 g/24 h and increased serum creatinine, administration of 3 to 4 antihypertensive agents are usually important. The choice of antihypertensive agents is important to reach the BP goals. However, owing to the renoprotective effect of ARBs and ACE inhibitors, these antihypertensive agents should be administered with a diuretic. [26]

CONCLUSION:

Diabetic nephropathy is a chronic complication of diabetes with a growing mortality rate. Therefore, it is imperative to have a clear and better understanding of its risk factors, causes, and the way it can be prevented. Early management of risk factors can greatly reduce the progression of the disease. The multifactorial approach is usually opted like controlling hypertension, hyperglycemia, dyslipidemia, and smoking to effectively treat this issue. The use of renoprotective agents like the renin-angiotensin-aldosterone system are also in trend to delay the progression of kidney diseases in DM patients.

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