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DIABETIC NEPHROPATHY: PRINCIPLES OF DIAGNOSIS AND TREATMENT

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Abstract:
Diabetes mellitus is one of those diseases whose ratio is increasing at a very rapid rate worldwide. It is one of the leading causes of death in patients having end stage renal diseases. Diabetes mellitus comes up with various complications which are difficult to handle. These complications are associated with effects of Diabetes on the glomerular microvasculature of the kidneys. Patients who have a history of several years of renal disease and diabetes, they are more likely to develop Diabetic Nephropathy.
Since medical science has progressed, many new diagnosis and treatment options are available, but unfortunately there isn't any permanent cure. The purpose of this paper is to throw light on various therapeutic strategies that are currently used by doctors to increase the understanding of DN and to help patients fight against it.
The study was carried out randomly in different hospitals of Lahore and general data was collected to study in detail the occurrence, diagnosis and treatment which is carried out for diabetic nephropathy.

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INTRODUCTION:

Diabetic nephropathy is randomly increasing every year. [1] It is one of the most commonly known complication in diabetes patients that leads to multifaceted issues, not easy to handle. According to a survey, its expected increasing ration in the coming 10 years is 25%. [2] However, the current ratio of diabetic nephropathy is different and variable as it totally depends upon the causes of its occurrence. Multiple factors contribute towards DN occurrence. [3] Therefore, various screening programs may contribute in the initial documentation of patients who are stake of developing this disease. [4]

Different causes can play crucial role in the development of DN, they can be multiple or singular. These include diet, lifestyle, stress, depression, genetic variability and other relevant health systems. [5] If a comparison is made among Asian and Westen diabetic population, then it was found that the Asian population is more prone to diabetic nephropathy owing to the presence of macroalbuminuria or microalbuminuria. [6]

Pathophysiology

Diabetic Nephropathy is a clinical syndrome. It is characterized by the continuous decline in the filtration rate of glomerulus, increased arterial blood pressure and insistent albuminuria, which should be confirmed with occasional checkup with a difference of 3 to 6 months. A number of different events characterize diabetic nephropathy. For instance, the thickening of the basement membrane of the glomerulus is counted in this account. Pathological modifications in mesangial and vascular cells began when the thickening of the basement membrane starts after renal damage. accumulation of polyols, formation of AGEs and protein kinase activation are included in this modification. [7,8] This process also activates the inflammatory pathway which plays an important role in damaging GBM. [9]

The pattern which is observed in pathophysiology of DN includes the following points:

- Hyperglycaermia
- Thickening of GBM
- Glomerular hyper filtration
- Impaired endothelial integrity
- Occurrence of microalbuminuria
- Issues in nitric oxide transport
- Loss of auto afferent- efferent regulatory control
- Loss of filtration capabilities of glomerulus

A clinical trial of patients shows asymptomatic point of failure that follows the development of >300 mg albumin per day (macroalbuminuria) to 30 mg albumin per day (microalbuminuria). Once when nephropathy also known as microalbuminuria is developed then renal functions began to fall at a rapid rate. The rate of functional failures depends entirely upon the type of diabetes, glycemic control, genetic predisposition and blood pressure. The blood pressure is very significant factor in this. Later stages might involve oedema, nephritic syndrome and albuminuria. It is thought that both types of diabetes equally participate in nephropathy development.

Stages of Diabetic Nephropathy

Commonly, DN is divided into five stages:

Stage 1: At the onset of diabetes, renal pathology develops. The size of kidneys increases to several centimeters. Till when it is diagnosed, the filtration rate of the glomerulus and urinary albumin excretion have been increased. This issue can be controlled with the use of insulin at this stage 1.

Stage 2: After the diagnosis of diabetes, the second stage can last for 5 to 15 years, depending upon the circumstances in which patient is living. Second phase includes the following circumstances:

1. Owing to hyperfiltration GFR remains elevated
2. UAE rate stays normal and kidneys remain hypertrophied

Stage 3: Progression of histological changes, found in stage 2, occurs. In stage 3, 30- 50% patients have microalbuminuria after diabetes onset and 80% of them develop overt nephropathy within 10 to 15 years. Blood pressure began to rise in 60% of patients and GFR remains elevated, or in some cases returns to normal range.

Stage 4: Clinical nephropathy or overt nephropathy is in stage 4. Formation of the Kimmelstiel- Wilson nodule which is focal glomerular sclerosis and macroproteinuria occurs. This issue can decrease in 80% of patients depending upon the deterioration of GFR and can increase in rest 30% of patients.

Stage 5: In this stage, End Stage Renal Disease (ESRD) may develop as the GFR continues to decline. Diabetic nephropathy is known as the most common cause of renal failure because it is associated with cardiac diseases and autoimmune neuropathy as well.

Screening and Diagnosis

It is imperative to record the medical history of patients with diabetes, especially focusing on hypertension and cardiovascular diseases. Urine analysis, erect blood pressure record and history of supine must be carried out.

Screening for microalbuminuria in diabetic patients is a must thing. Albumin is measured at the initial stages to observe and examine the presence of DN. For total protein excretion and creatinine clearance

measurement in urine, a 4 hour urine collection and examination is helpful.

The transient increase in UAE (Uterine Artery Embolization) can occur due to uncontrolled fever, hyperglycemia, hypertension, congestive heart failure, urinary tract infection or any physical exertion. Therefore, it is recommended by the specialists to carefully and repeatedly examine the microalbuminuria levels in the urine following 3 to 6 months. The values of different levels of microalbuminuria, which define the specific risks associated with it are given below:

1. Normal urine 300 mg
2. Microalbuminuria 30-300 mg
3. Overt proteinuria >300 mg
4. Nephritic syndrome >300 mg

The assessment of albumin/creatinine ration also known as ACR can be carried out in a random spot urine samples or in early morning demonstration. An ACR with a value of 2.5 is considered as the cut off level for microalbuminuria.

Once proteinuria is developed in the patient, further tests are carried out to find the reason behind it other than diabetes. This condition is particularly important in Diabetes Type 1. Evaluation for hepatitis B and C, lupus nephritis, myolema, human immunodeficiency virus and use of non-steroidal anti-inflammatory drugs, is carried out. Some studies have revealed that patients are at higher risk for glomerulopathies who have Type 2 diabetes. In them, diagnosis is done via renal biopsy.

The above mentioned levels and issues are clarified in trials using angiotensin-II receptor blockers (ARBs) for Diabetes Type 2 and angiotensin-converting-enzyme inhibitors (ACE inhibitors) for Diabetes Types 1. These agents also aid in delaying the End Stage Renal Diseases in patients who have already developed nephropathy. When comparison was made of these agents with anti-hypertensive agents, the results showed that the former's renoprotective effects were independent of the blood pressure control (hypertension).

In patients with stage 4 nephhropathy, it is highly recommended to maintain blood pressure at target levels to 125/7 mmHg. This control of blood pressure will slow down the damage and progression of disease, but will not prevent it.

Different examinations that are crucial to carried out in patients with Diabetic Nephropathy are given below:

Categories	Examination
Urine culture	Complete examination
	Exclude infection
Urine microscopy	Examine for red cell cast in glomerulonephritis
	Anti-DNA antibodies
Complement level	Exclusion of autoimmune disease
	Rheumatoid factor
Renal ultrasound	Exclude obstructive renal disease
	Assess renal anatomy and size
Igs; Protein electrophoretic strip	Exclude multiple myeloma

Management of the Disease

A lot of research has been done on Diabetic Nephropathy by professionals, medical students and doctors. Various treatments and delaying methods have been identified to help patients fight against this disease. The treatment of DN can only be specified and addressed on the basis of the clinical stage of this disease process. But, above this all if the causes and factors that lead to DN can be minimized at the beginning, then there are high chances of no disease development to very late and slow development of disease in patients.

The simplest way to prevent DN is its early diagnosis and management using common preventive methods, including blood pressure and glucose level control. Dyslipidemia can be treated by modifying lifestyle such as including physical activities, weight reduction, no sedentary activities, healthy eating habits and stress free environment. Smoking is one of those factors, that causes various cvardiovascular diseases, its cessation can be significant in prevention of CVD and lung issues. Studies have shown that cessation of smoking has positive impacts upon renal prognosis and ameliorates progression of microalbuminuria to macroalbuminuria. [10]

Firm glycemic levels in patients with Diabetes Type 1 can reduce the occurrence of microalbuminuria, and evidences have proved that intensive insulin regimes can prevent the progression of patients from microalbuminuria to overt nephropathy. [11]

Following are some specific goals in prevention of Diabetic Nephropathy:

1. Control of blood pressure to target levels of 120- 125/ 70 mmHg
2. Avoidance of use of nephrotoxic drugs like aminoglycosides, NSAIDs (Nonsteroidal Anti-inflammatory Drugs)
3. Proper tracking of family history, early diagnosis and management of diabetes

Potential Treatments

A lot of research is going on to help patients having DN and to minimize its progression. Following are some latest treatments in this regard;

1. Treatment with high doses of thiamines and its derivative benfotiamine have shown the reduction of the rate of microalbuminuria in Diabetic Nephropathic patients. The reason observed was the activation of protein kinase C, oxidative stress and protein glycation.
2. It was observed that protein kinase C beta inhibitor played significant role in normalizing glomerular filtration rate, decreasing albumin excretion rate and ameliorates glomerular lesions
3. Most DN patients have dyslipidemia which can contribute to the development of glomerulosclerosis and progressive renal disease. Treatment with statins in Diabetic Type 2 patients that non dialysis dependent showed significant cardiovascular benefit. In them, the target goal is for LDL cholesterol below 100 mg/dl for normal diabetic DN and patients and it is below 70 mg/dl for pDN patients with CVD
4. Antihypertensive agents like diuretic, calcium channel blockers, beta blockers and direct rennin inhibitors have shown in studies that they demonstrate antiproteinuria effects

CONCLUSION:

The mortality ratio of Diabetic Nephropathy patients is exrtremely high. For instance, in comparison to general population, mortality rate of Type 1 Diabetic patients is 20 times greater and the risk can be magnified further by 25 times for those having proteinuria. Mortality is examined to be of 2 years for 30% of pateitns with ESDR. Many patients die at stage 4 before they reaches ESDR level, it is usually owing to the development of CVD along with many other complications.

In the recent years, great progress has made to understand the complications, diagnosis and treatment of Diabetic Nephropathy, stages of renal involvement in diabetes and preventive measurements. Early detection, multifactorial adoption of interventions to target various risks at the same time like hypertension, hyperglycemia, smoking and dyslipidemia, and use of many drugs with renoprotective effect can significantly lower the progression of renal disease and mortality rate. Treatment of blood pressure (hypertension) is a spriority and on top of the list. By taking care of these factors, cardiovascular diseases can also be prevented and patient can live for long a balanced life.

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