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Editorial Review

Diabetic Nephropathy

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Diabetic nephropathy is defined as clinical syndrome characterized by proteinuria, hypertension and progressive renal insufficiency[1]. Symptoms referable to the kidney in diabetics have been recognized for a long time. In 1936 Kimmelstiel and Wilson described the nodular intercapillary lesions developing in the glomeruli of patients with long term diabetes along with clinical syndrome of renal failure, heavy proteinuria and hypertension[2]. Since then kidney disease in diabetics has been known as Kimmelstiel Wilson Syndrome. It is estimated that up to 50% patients with diabetes mellitus will develop renal failure[3-5]. The number of diabetic patients going into ESRD program is increasing[6]. At present diabetic nephropathy is considered the most common cause of end stage renal in United States and western Europe. According to report from United States in 1978 only 6% of the total ESRD patients were diabetics. In 1986 20% and in 1986 29% of the total ESRD patients were suffering from diabetic nephropathy[7-9]. Half of them had type 1 diabetes mellitus. Our experience at Shaikh Zayed Hospital is same. Almost one third of new patients with ESRD are diabetics. More than 90% of these patients have type II diabetes. It is now firmly established that overt diabetic nephropathy is associated with high morbidity and mortality from uremia. Death from renal disease is most common cause of mortality in IDDM. In NIDDM other systemic complications specially cardiovascular are mainly responsible for mortality, still renal failure contributes significantly to mortality and morbidity in these patients[10].

There is marked heterogeneity in the clinical picture seen in long term diabetics. Some diabetic patients even with poor metabolic control may not develop clinical diabetic nephropathy. It is possible that some other factors unrelated to metabolism may be responsible. Possible mechanisms which may play a role in the development of diabetic nephropathy are[11-11].

1. Genetic disposition to hypertension.
2. High level of aldose reductase
3. Low level of glomerular heparin sulfate
4. High growth hormone secretion
5. Hyperfiltration
6. High vascular permeability in general
7. Environmental factors; High protein diet, High sodium intake, nonsmoking etc.
8. Other unknown factors.

The diagnosis of diabetic nephropathy is usually based on clinical evidence. If a young patient with a history of diabetes for a decade shows overt proteinuria greater than 0.5 grams / 24 hours diabetic nephropathy is suspected. The development of the proteinuria is a late event. Changes in structure and function of the kidney occur very early. In fact these are present at diagnosis and on the basis of these functional and structural changes a number of stages in the development of diabetic nephropathy are outlined[14,15].

Stage I: Hyperfunction and hypertrophy stage

This stage is present at diagnosis. Elements of this stage are also apparent with longer duration of diabetes, particularly when diabetes control is imperfect. Kidneys are large and hyperfiltration is present. Glomeruli are hypertrophied. Basement membrane and mesangium are normal. Glomerular filtration rate (GFR) is supernormal, usually about 150 ml/minute. Urinary albumin excretion (UAE) may be increased but is reversible by insulin treatment. Blood pressure is normal and may fall initially during insulin treatment. Main pathophysiologic changes are glomerular expansion and increased intraglomerular pressure.

The determinants of glomerular hypertension have been investigated using micropuncture techniques in diabetic rats renal vasodilatation, increased glomerular plasma flow and raised mean transglomerular hydrostatic pressure gradient have been found. Table 1 outlines the proposed mechanisms resulting in changes in renal hemodynamics[16-17].

Stage II: Silent stage

This stage is found after about 2 years, and lasts up to 15 years of diabetes. A number of patients

continue in this stage throughout their life. UAE is normal, is often increased in stress situations and during exercise and poor metabolic control. There is increasing basement membrane thickness and mesangial expansion. Hyperfiltration is present. GFR is increased usually to same extent as kidney volume. Blood pressure is normal. Pathophysiologic changes are quite variable depending upon metabolic control.

Table 1: Mediators of renal hyperfiltration in IDDM.

Vasoactive hormones.
Increased production of vasodilatory prostaglandins
Impaired responsiveness to thromboxane
Increased renal kalikrein production
Abnormal responsiveness to norepinephrine
Increased level of atrial natriuretic hormone
Abnormal renin-angiotensin system
Insulinopenia and abnormal calcium metabolism
Increased polyol pathway metabolism
Hyperglycemia and extracellular fluid volume expansion.
Increased growth hormone level
Increased glucagon level

Stage III: Incipient diabetic nephropathy or at risk nephropathy

This stage is typically found after 8-12 years. Persistent microalbuminuria is present in this stage. Microalbuminuria defined as urinary albumin excretion rate greater than 20 μg/minute and less than or equal to 200 μg/minute[18]. Urinary albumin excretion increases steadily over the years. Increase rate is about 20% / year on average with a wide range related to blood pressure control[19]. In early stage III UAE is 20-70 μg/minute and GFR is about 160 ml/minute. In late Stage III UAE is 70-200 μg/minute and GFR is about 130 ml/minute. Mean decline GFR is 10-12 ml/m/1.73 M^2 /year[20-21]. Blood pressure starts to increase in this stage. The magnitude of the elevation is in the range of 10 to 15% above values in control subjects[22-24]. Blood pressure is elevated more during exercise. Even a slight elevation in blood pressure appears to be an accelerating factor during the course of diabetic nephropathy. Transcapillary escape rate of albumin is increased. More advanced retinopathy is present[25,26]. Glomerular closer probably starts in this stage. In some patients high intraglomerular pressure is present. It is known that microalbuminuria carries a bad prognosis and intervention before this is important. Without intervention, 80% of these patients will develop overt diabetic nephropathy[18,19]. It has been shown both in experimental animals as well in humans that antihypertensive treatment in this stage can reverse the microalbuminuria[27,28].

Stage IV: Overt nephropathy

Clinical or overt nephropathy is found in up to 50% of IDDM patients after 15-25 years of diabetes. It is characterized by the classical morphological lesions. More and more glomeruli show closure and sclerosis. Advancing mesangial expansion is seen. The remaining glomeruli show hyperfiltration and hypertrophy. Often frank hypertension is present and as the disease progresses hypertension becomes almost ubiquitous. Microalbuminuria develops into clinical proteinuria and the GFR is declining. In early stage GFR is 130-70 ml/min, in intermediate stage it is 70-30 ml/min and in advanced stage GFR is 30-10 ml/min. Fall rate in GFR can often be reduced considerably by effective antihypertensive treatment. A drop in albumin excretion is also seen with reduction of blood pressure. Diabetic retinopathy precedes proteinuria in most patients. By the time renal impairment has developed almost all patients have some retinopathy. Indeed in the absence of retinopathy diagnosis of clinical diabetic nephropathy should be reconsidered.

Stage V: Uremia

This stage is found after 20-30 years of diabetes. It is characterized by generalized glomerular closure and GFR less than 10 ml per minute. Blood pressure is high.

Other diabetic associated renal complications

Urinary Tract Infections

Urinary tract infections (UTI) were reported to be common in diabetic patients. Ten to forty percent of diabetic patients have been found to have chronic pyelonephritis on autopsy in older series[29]. More recent surveys do not show a greater incidence of UTI in diabetic. It is postulated that tubulointerstitial changes attributed to chronic infection in older days are merely a portion of chronic progressive renal disease seen in diabetics[30]. Patients with bladder dysfunction secondary to autonomic neuropathy probably do have increased incidence of urinary tract infections. Such infection can lead to particularly severe

systemic consequences like diabetic ketoacidosis and papillary necrosis. Thus urinary tract infections, particularly pyelonephritis should be treated aggressively in diabetic patients.

Papillary necrosis

Papillary necrosis is a common complication of late diabetic nephropathy. Almost 50% of all cases of papillary necrosis are associated with diabetes mellitus[31]. Urinary tract infection and microcirculation occlusion of papillary circulation may be responsible for infarction of papillae. Clinical features may be hematuria, passage of papillary material, pain, fever and even acute oliguric renal failure. When a patient with history of long standing history of diabetes mellitus develops sudden deterioration of renal function along with hematuria and UTI, possibility of papillary necrosis should be considered. The diagnosis is confirmed by demonstration of "ring sign" demonstrated on intravenous pyelography.

Bladder dysfunction

Bladder dysfunction occurs in diabetic patients due to autonomic neurogenic damage to the sacral innervation of bladder. Reduced sensation of bladder distention, impaired urinary stream with straining and hesitancy, infrequent voiding as well as sensation of incomplete emptying are the usual features. The development of neuropathic bladder in the diabetic patient may hasten the progression of renal failure due to chronic obstruction and more frequent urinary tract infections in these patients[32]. Control of infection, administration of parasympa-thomimetic drugs and external compression to ensure bladder emptying may help. In some patients intermittent or persistent catheterization and eventually surgically procedure may be needed.

Radiocontrast agent induced acute renal failure

Radiographic contrast agents lead to acute renal failure in several situations. Diabetic renal disease is one of the clearest risk factor. A number of studies have shown that the incidence and severity of contrast induced acute renal failure is related to the degree of pre-existing renal disease. The incidence of acute renal failure greater than 90% following contrast studies has been reported when the serum creatinine[33-35] was more than 5 mg per dl. There is no increased risk for diabetic patients with normal renal function. With adequate prehydration and use of small amounts of nonionic dyes, this risk can also be reduced.

Hyperkalemia

Hyperkalemia is found more often in diabetic patients with nephropathy compared to patients who have renal failure due to non diabetic cause. This is due to decreased renin-aldosterone secretion, which is due to

a) Extracellular volume expansion, because of intracellular fluid shift due to hyperglycemia.
b) Hyperglycemia leading to increased glucose/ sodium reabsorption from proximal tubule.
c) Hyporeninemia-Hypoaldosteronism due to loss of renin producing cells

Management of diabetic nephropathy

Once diabetic nephropathy is established, proteinuria is unremitting, and renal function begins to decline. Every attempt should be made to arrest or postpone progression of renal insufficiency. Besides management of hyperglycemia special attention should be given to problems from hypertension and fluid retention that usually occur at an earlier stage of renal failure than other causes of renal disease. Retinopathy should be monitored closely. Photocoagulation should be arranged when indicated. The possibility of urinary tract infection should be checked and treated when present with non-nephrotoxic drugs. Radiocontrast studies should be avoided as much as possible. Bladder emptying should be assessed clinically and by ultrasonography. Serum calcium and phosphorus should be monitored and corrected to avoid metabolic bone disease.

Important experimental and clinical trials have or being conducted to see the effect of different interventions in progression of diabetic nephropathy. Most of these studies are related to glycemic control, antihypertensive treatment, and protein restricted diet.

Glycemic control

Strict glycemic control if maintained from early stages can retard the progression of diabetic nephropathy. If the treatment is begun late, results

are not favorable[19,36-38]. Meticulous glycemic control that is, fasting blood glucose level below 140 mg/dl and postprandial blood glucose below 200 mg/dl and avoiding hypoglycemic episodes, should be achieved. This may require frequent blood glucose monitoring. The requirement for insulin and oral hypoglycemic drugs gradually drops as the renal function deteriorates, due to decreased excretion and metabolism of these agents and poor dietary intake due to anorexia, nausea and vomiting due to uremia or diabetic gastropathy. Insulin requirement may be increased in some patients due to decreased physical activity and increased insulin resistance in uremia. Monitoring urine sugar may not be helpful because of variable renal threshold for glucose and difficulty in getting urine samples in time because of infrequent voiding due to autonomic neuropathy involving bladder.

Antihypertensive treatment

In the presence of microalbuminuria or overt diabetic nephropathy careful monitoring of blood pressure and renal function should be performed. Recent studies have shown that rapid progression of overt diabetic nephropathy is generally related to hypertension and effective antihypertensive treatment can reduce the rate of decline in GFR. A dramatic decline in rate of increase in proteinuria has been observed also. Antihypertensive treatment in earlier stages (II and III) considerably retards the progression of renal disease as manifested by a reduction in rate of increase of microalbuminuria[22,23,28,39,40].

Conventional antihypertensive treatment using cardioselective beta blockers and diuretics without or with addition of vasodilators is effective in most cases. Continuous therapy with angiotensin converting enzyme (ACE) inhibitor has been shown to have glomerular vasodepressor effect in the newly diabetic rats and to largely prevent the subsequent development of a severe, sclerosing glomerular injury. Preliminary studies in humans with diabetic nephropathy also show that ACE inhibitors have antiproteinuric effect and may slow the decline in glomerular filtration rate[41,42]. Proposed mechanisms are;

a) ACE inhibitor could theoretically reduce glomerular capillary pressure in diabetes by preventing an increase in intrarenal angiotensin production without affecting plasma renin level[43]. b) ACE inhibitor also slow degradation of bradikinin and may alter synthesis of prostanoids[44]. c) Normal levels of plasma renin activity in diabetic patients in the presence of extracellular volume expansion is actually inappropriately high and hemodynamic effects of ACE inhibitor in these patients may reflect reduction to appropriate levels of circulating angiotensin II.

The step care approach to drug treatment in diabetic patients with hypertension has been recommended by the Working Group on Hypertension in Diabetes[45] (Fig. 1).

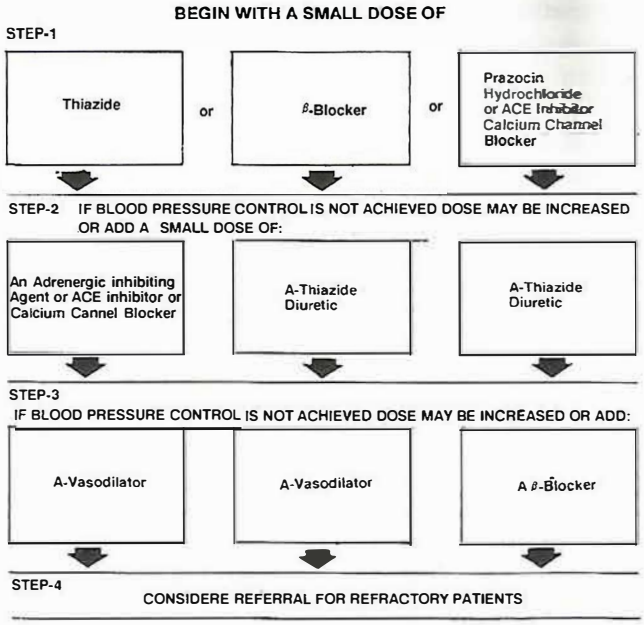

FIG-1: STEP CARE APPROACH TO DRUG TREATMENT IN DIABETIC PATIENTS.

Stepped care approach to drug therapy in diabetic patients with renal hypertension is suggested by the Working Group on Hypertension in Diabetes.

Step 1

Azotemia absent, administer thiazide diuretic;
Azotemia present, administer loop diuretic in devided doses and / or metolazone

Step 2

Administer treatment as in step 1, adding vasodilator, α 1-adrenergic blocker, calcium channel blocker, or angiotensin converting enzyme inhibitor (monitoring of serum potassium and creatinine is indicated)

Step 3

Administer treatment as in step 2, adding cardioselective α 1-adrenergic blocker or another adrenergic inhibiting drug treatment.

Low protein diet

As discussed earlier alteration in glomerular blood flow and glomerular filtration rate may play a role in the initial insult to the kidney as well as disease progression. Dietary protein restriction has been demonstrated to normalize these abnormalities and retard progression of disease in experimental diabetic rats. Limited studies in diabetic patients with nephropathy suggest a similar beneficial effect.

Renal replacement therapy

Renal replacement therapy must be started earlier in diabetic patients with ESRD than nondiabetic patients. As the GFR declines to about 10 ml/minute, rate of progression of almost all the complications especially vascular, increases rapidly. In 1960s dialysis was started when serum creatinine has reached 15 mg/dl. Now serum creatinine levels of 7-9 mg/dl are proposed at which dialysis should first be started[46].

Renal transplantation is advised at even lower levels of serum creatinine namely 5-6 mg per dl[47]. Because of problems of vascular access arteriovenous fistula should be established when serum creatinine is about 3 mg/dl. Renal transplantation is treatment of choice specially in young diabetics without ischemic heart disease. The outcome for renal transplantation has improved during last decade. Using cadaver transplants overall two year survival is over 90% for non-diabetics and 75-80% for diabetics. At present 2 years cumulative survival results of cadaver kidney transplantation, hemodialysis and CAPD are almost similar 66 to 76%. One year survival with CAPD 97% compared to 76% and 83% with cadaver kidney transplants and hemodialysis respectively has been reported. Five year survival with cadaver kidney transplant has been 59% and with hemodialysis 50%. Survival results for living-related donor transplantation are better, being 95% in one year, and 78% in 2, 3, 4, and 5 years.

Diabetic complications, especially vascular disease, account for the poorer results for diabetics. Most deaths are due to cardiovascular disease or sepsis. Blindness often worsened on hemodialysis and visual acuity improved after transplantation in earlier days. With improvement in dialysis techniques similar visual stability has been achieved with in both dialysis and transplanted patients. Amputations are more common after renal transplantation in diabetics. This could be related to corticosteroids use after renal transplant. Age above 60 is an important predictor of relatively poor survival. Cardiac status of the patient before transplant should be evaluated with thallium imaging combined with dipyramidole and if indicated more invasive procedure coronary angiography should be done keeping its nephrotoxicity, cholesterol embolization, and technical problems in mind. Patients with little or no coronary artery stenosis have no great cardiac risk; those with severe stenosis who can be operated should probably have coronary artery bypass surgery before kidney transplantation.

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