DIABETIC NEPHROPATHY-NEWER CONCEPTS IN DIAGNOSIS AND MANAGEMENT

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Diabetes mellitus, with its complications, is now the third leading cause of death in the world: Nearly one third of the mortality in Diabetes (31%) is due to renal diseases. Till recently, the diagnosis of diabetic nephropathy (DN) meant a death sentence, but with more insight into its pathophysiology, and advances in management, the picture is not that gloomy. The onset of DN is conventionally diagnosed when albumin is detected by the usual qualitative tests in urine. But the aim should be to diagnose it at an earlier stage, when the disease is still reversible. Overt continuous proteinuria, hypertension and declining GFR, represent a late stage of the disease.

The natural history of renal involvement in diabetes, which has been better studied in IDDM, follows a characteristic pattern. Thus a series of stages in the development of renal changes in diabetes is recognizable.

Stage ..	(1) Early hypertrophy-hyperfunction
Stage ..	(2) Glomerular lesions without clinical disease.
Stage ...	(3) Incipient diabetic nephropathy.
Stage...	(4) Overt diabetic nephropathy.
Stage ...	(5) End stage renal failure.

1. Early Hypertrophy-Hyperfunction

These structural and functional changes are present in the kidneys, even at the time of diagnosis of diabetes. There is increase in kidney size alongwith increase in glomerular size. The GFR is increased by 20-40% and RPF is normal or slightly increased. Exercise induced microalbuminuria may be present, that reverts with insulin treatment.

2. Renal Lesions Without Clinical Signs

These changes are detectable after 2 years of diabetes, and progress slowly over several. years. There is increase in basement membrane (BM) thickness alongwith mesangial expansion. The GFR is increased by 20 to 30% and RPF may be slightly increased. The blood pressure is normal and there is no

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albuminuria. Only 30 to 40% of patients progress to clinical diabetic nephropathy beyond this stage.

3. Incipient Diabetic Nephropathy

This develops after 10 to 15 years in 30 to 40% of patients. The GFR still remains increased by 20 to 30% but RPF shows an incipient, slow decline. This is the stage of microalbuminuria, with an excretion of 15-300 µg of albumin/min., which increases by 25 µg/min., every year. There is marked increase in proteinuria with exercise. The blood pressure also tends to be raised, especially on exercise. There are evidences to show that strict control of diabetes and hypertension, may revert the changes at this stage.

4. Overt Diabetic Nephropathy

This is seen after 15-20 years of diabetes. The typical histological changes-namely, diffuse glomerulosclerosis, nodular glomerulosclerosis (K.W. lesion), capsular drop, hyaline cap and the afferent and efferent arteriolar changes are all seen at this stage. The GFR starts declining at the rate of 1 ml/ min/month, and this rate of deterioration can be reduced to 0.4 ml/min/month with proper treatment. The RPF declines at the rate of 5m1/min/month. There is albustix positive proteinuria. The blood pressure is usually raised, Early treatment with antihypertensives, especially, selective beta blockers is advisable and helps in slowing the rate of decline.

5. End Stage Renal Failure

This is the final outcome that occurs after 25 to 30 years. There is gross structural damage, with glomerular obsolescence, and the GFR is less than 10 ml/min. The proteinuria may show a decline, due to the fall in GFR but is still high. These changes are no longer reversible.

PATHOGENESIS

The pathogenesis of diabetic microangiopathy which is responsible for the nephropathy is still a ‘riddle wrapped in mystery’. As usual in such a situation, there are quite a few hypotheses. The major hypotheses give importance to hyperglycemia and genetic factors.

1. Hyperglycemia

There is a distinct relationship between lack of insulin, the resultant hyperglycemia and microangiopathy. Many observations support this concept :

(a) Presence and severity of glomerulosclerosis correlate with the duration of diabetes.

(b) Similar lesions are induced in ‘alloxan’ diabetes.

(c) Reversibility of 'alloxan' diabetes lesions with insulin or pancreatic islet cell transplantation.

(d) Glomerular lesions-in kidney transplants in diabetics.

Biochemical changes linking hyperglycaemia to GBM thickening

(a) Increased kidney glucosyltransferase-an enzyme important in the synthesis of GBM material.

(b) Increase in the pool of Uridine - triphosphate, may be secondary to hyper-glycemia-and contributes to renal hypertrophy and hyperfunction.

(c) Increased hydroxylation and glycosylation result in increased hydroxlysine and hydroxlysine disaccharide units in GBM.

(d) There is reduction in negatively charged BM components like heparin sulphate contributing to loss of charge selective barrier.

(e) Glycosylation of the albumin and GBM collagen.

2. Genetic Factors

The emphatic hypothesis of Siperstein states that the microvascular disease is independent of the metabolic disturbances of diabetes, and that it is a seperately inherited disorder, genetically linked to the diabetic state. This hypothesis has created a lot of controversy, and there are strong arguments both for and against it. Points in favour are (i) the nephropathy may manifest even prior to the onset of diabetes. (ii) the demonstration of muscle capillary BM - thickening even in prediabetic states and (iii) the increased susceptibility to microangiopathy in association with HLA B8, B5 and DW3. There are equally sound arguments against the hypothesis, namely : (i) the development of all the changes of DN in related and nonrelated renal allografts transplanted into diabetic patients. (ii) regression of leions, in renal allografts with simultaneous pancreatic transplants.

Minor Hypotheses

1. Changes in plasma proteins with elevation of many acute phase reactants like αl-acid glycoproteins, complement fragments, fibrinogen, creactive protein, haptoglobin etc., contribute to increased plasma viscosity and micro-angiopathy.

2. Reduced RBC deformability and increased RBC aggregation directly impair the microcirculation.

3. Increased levels of glycosylated Hb with increased affinity for O_2 contribute to tissue anoxia.

4. Anoxia leads to endothelial ce1l injury and a proliferative response.

5. Role of platelets : Increased platelet aggregation, reduced fibrinolytic activity and raised levels of von-Willebrand factor contribute to inicrovascular disease.

6. Role of growth hormone and pituitary factors :
   Lundboek has hypothesized a causative role for the raised levels of GH in diabetics. He has shown improvement. in diabetic retinopathy with pituitary ablation and there are reports to show that there is reduction in GBM thickness following hypophysectomy.Dwarfs with deficient GH levels did not have microangiopathy in diabetes.

7. Immunological Factors : The antibodies formed to insulin may form Ag-Ab complexes along the capillaries. The immunopathologic findings of abnormal protein deposition like 1gG and albumin in the glomerular and tubular BM may favour this view. Andersan's study showed that the frequency of high anti-insulin antibody titre was greater in patients with proliferative diabetic retinopathy than in those without diabetic complications.

MANAGEMENT

1. Prevention

At the early stages of supranormal GFR, and asymptomatic proteinuria, the aim should be to accomplish as good a metabolic control as possible, so that the onset of overt nephropathy could be delayed or prevented.

2. Management of Nephrotic syndrome

Many years may elapse (3 to 30 years, with a mean of 13 years) between the diagnosis of diabetes and the appearance of features of renal disease. Once renal disease becomes evident, progression to end stage renal disease ESRD, is usually rapid. The time taken to progress from initial azotemia to uremia (creatinine from 1.5 mg to more than 10.0 mg/dl) may vary in different individuals from 6 months to 60 months. Once functional decline starts, further course in an individual may be projected by plotting the reciprocal of serum creatinine against time in months.

A sudden deterioration may be precipitated by infection, accelerated hypertension, dehydration, congestive heart failure or iatrogenic causes like use of nephrotoxic drugs and contrast nephropathy.

The factors that increase the risk of contrast nephropathy are :

(a) Age more than 50 years.

(b) Duration of diabetes more than 10 years.

(c) Pre-existing renal failure (creatinine more than 3mg%)

(d) Presence of retinopathy; neuropathy or obstruction.

3. Management of uremia

A. Conservative Management

Clearance for clearance, patients with diabetic uremia are sicker than non-diabetics. The emphasis at this stage is on attending to the complications, while the patient and the family are being prepared psychologically, socially and financially, for the eventual dialysis and transplantation.

PROBLEMS OF KEY CONCERN

l. Urinary Tract Infection :

A trivial infection may escalate into papillary necrosis or septicemia. Even asymptomatic bacteriuria deserves full treatment. With normal renal function, either co-trimoxazole or ampicillin for 7 days will be enough. Persistent or recurrent UTI may be suppressed with long term, single dose co-trimoxazole. Incomplete bladder emptying due to neurogenic bladder may be the cause, and deserves attention.

2. Fluid Retention

Proteinuria as massive as 20 grams/day or more, may be seen even in late stages of nephropathy- 'the leaky capillary syndrome'. Patients have features of nephrotic syndrome and fluid retention, Frusemide is useful, in the dose range of 40 to 480 mgm per day. But once creatinine clearance falls below 20 ml/ min, frusesemide alone may not be effective. Adding 'Metolozone' 5 to 20 mg daily, is often helpful. Potassium supplementation is required only if urine output is more than 2 litres/day or when patient is taking digoxin.

2. Hypertension :

In the early stages control of fluid retention is useful. The control of B.P. is important, as it can slow the rate of decline in GFR. Drugs like clonidine, methyldopa, hydralazine, and prazosin are useful. Beta blockers, especially the selective ones could be used wherever possible.

4. Sustaining Euglycemia

Keeping a tight glucose control round the clock, with estimation of blood sugar frequently, helps to stem the tide. Estimation of Hb-A_1C is useful to assess the efficiency of therapy.

5. Protecting Bone Integrity

The hyperphosphatemia, and the reduced active vit. D. synthesis require management with phosphate binders, calcium supplementation, and careful use of active Vit. D 3.

6. Preserving the vision :

The use of panretinal photocoagulation at the earliest sign of proliferative retinopatby helps to prevent the future problem of total blindness.

7. Psychological preparation :

It is important to avoid gloom and depression, and to prepare the patient psychologically for the more demanding future treatment.

TREATMENT OF UREMIA

With the advent of better methods of dialysis, including CAPD, and advances in transplantation techniques and more effective immunosuppressive agents like, cyclosporin-A, there is a lot of enthusiasm of late.

1. Continuous ambulatory peritoneal dialysis , (CAPD)

When for some reason, transplantation is not possible for a patient, CAPD is preferred to hemodialysis (HD) in Western countries, especially for those who do not tolerate HD, who are already blind or have severe CCF. The intraperitoneal administration of insulin, alongwith the dialysate facilitates easier glucose regulation. But the long term success is yet to be proved.

In the absence of facilities for CAPD, at present, we have only one of the two options, namely hemodialysis or transplantation.

Hemodialysis :

This is the only choice for those who do not wish or who are unsuitable for transplantation. The results of long-term dialysis are only equal to that of cadaver grafts (i.e.-40% to 50%). The retinopathy may progress, and the patient's rehabilitation is poor. About 25% of patients, develop an ‘inexorable failure to thrive syndrome’ on HD.

Rena1 Transplantation :

With a live related donor, the 2 year survival rate is more than 80% and the use of donor specific blood transfusion has further improved it to 90%. With cadaveric grafts, the 2 year survival is about 60%, and attempts are being made to improve this, with better methods of immunosuppression. With a successful transplantation, patients get total rehabilitation, the retinopathy gets stabilized,

and neuropathy shows improvement. The problems faced are the risk of infections, steroids complicating glucose control, and the risk of recurring glomerulosclerosis. With the use of cyclosporin and maintenance of euglycemia, this offers the best cure and rehabilitation.

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