REVIEW ARTICLE

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Diabetic Nephropathy

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Diabetic nephropathy is one of the microvascular complications of diabetes. The pathophysiology involves an interaction between metabolic and hemodynamic factors. Metabolic factors include advanced glycation, increased formation of polyols and activation of protein kinase C (PKC). Hemodynamic factors include systemic hypertension, intraglomerular hypertension and the role of vasoactive hormones, such as angiotensin II. Clinical course progresses from microalbuminuria to overt proteinuria and then to renal failure. The disease cannot be cured, but can be prevented or limited in progression. The most important measures to be taken are maintenance of normoglycemia and normal blood pressure and protein diet restriction. Antihypertensive therapy has a major role in slowing the progression of diabetic nephropathy. Renal replacement therapy is available and the best method is kidney transplantation, if not contraindicated.

Nephropathy is a major cause of morbidity and mortality in diabetes mellitus and is the leading cause of end-stage renal disease (ESRD)[1]. Proteinuria was first recognised in diabetes mellitus in the late 18th century and 40 years later Bright[2] postulated that this form of renal disease was specific to diabetes. The disorder, diabetic nephropathy was further clarified by Kimmelsteil and Wilson[3] in 1930s when they described the classic lesions of nodular glomerulosclerosis associated with proteinuria and hypertension.

Later, it had become apparent that nephropathy is a common complication of diabetes. Persistent albuminuria (200 µg/min) is the hall mark of diabetic nephropathy, which can be diagnosed clinically if the following additional criteria are fulfilled: presence of diabetic retinopathy and no clinical or laboratory evidence of kidney or urinary tract disease other than glomerulosclerosis[4]. This clinical definition of diabetic nephropathy is valid in both insulin-dependent diabetes mellitus (IDDM) and non-insulin dependent-diabetes mellitus (NIDDM)[5]. Earlier studies suggested that 25% to 45% of patients with IDDM have overt nephropathy[6]. It is becoming an increasingly important clinical problem in NIDDM. Indeed, because the prevalence of NIDDM is many fold higher than IDDM, this form of diabetes now contributes to at least 50% of patients with diabetes in end-stage renal-failure programmes. Quality of life is markedly impaired in patients maintained on dialysis. Although successful transplantation may improve quality of life, immunosuppression and organ rejection often result in additional complications[7]. Now the recent advances in medicine can effectively delay deterioration of diabetic nephropathy to ESRD.

NATURAL HISTORY

The natural history of diabetic nephropathy is different in IDDM and NIDDM[8]. The older age at onset and predisposition to accelerated cardiac disease in NIDDM may lead to death before renal disease supervenes. In contrast, the younger age at presentation and the relatively later onset of cardiovascular disease in IDDM result in a greater proportion of IDDM patients, who

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survive long enough to develop nephropathy. The classification of nephropathy by Mogensen[9] into several distinct stages can be used for both forms of diabetes. They are as follows:

Stage 1:

Initial changes such as hyperfiltration, glomerular hypertrophy, renomegaly and increased capillary luminal area are observed.

Stage 2:

This involves hyperfiltration and is associated with subtle morphological changes including thickening of the glomerular basement membrane, glomerular hypertrophy, mesangial expansion, modest expansion of the tubulointerstitium and arteriosclerosis. All these features progress with increase in diabetes duration.

Stage 3:

This stage is known as microalbuminuria, or incipient diabetic nephropathy, defined as urinary albumin-excretion rate of 20-200 μg/min[10]. In the microalbuminuric phase significant glomerular injury can be seen on renal biopsy samples[11]. In case of IDDM patients, if microalbuminuria is observed within the first 10 years, it leads to overt proteinuria. If it is developed after 10 years of IDDM, only 50% may develop proteinuria[12].

Stage 4:

This is the stage of overt diabetic nephropathy or macroproteinuria[10]. This stage is found after 15-18 y of diabetes mellitus (either IDDM or NIDDM). The main features of this stage are, albustix-positive proteinuria, fall in glomerular filtration rate (GFR) and rise in creatinine level.

Stage 5:

This is the end stage. The characteristic features are low GFR, low creatinine clearance and renal failure.

RISK FACTORS

Although several factors have been associated with an increased risk of developing diabetic nephropathy, no single factor is yet predictive in the individual patient.

Hyperglycemia:

Hyperglycemia may result in diabetic nephropathy by several pathogenetic mechanisms. Hyperglycemia may activate cytokines, such as transforming growth factor β, which, in turn, may contribute to both the increased number of glomerular cells and enhanced collagen synthesis seen in nephropathy. Hyperglycemia also may lead to renal damage by causing renal hyperfusion, increased sorbitol production, and glycosylation of circulating albumin which may be deposited in the kidney[7].

Hypertension:

Some studies noted that there is a statistically significant increase in the sodium-lithium counter transport mechanism in IDDM patients with nephropathy[13,14] and their parents[15] compared with that in matched IDDM patients without nephropathy and their parents. Sodium-potassium exchanger in skeletal muscles and adipocytes is stimulated in presence of increased insulin. This causes increased intracellular sodium and increase in cellular pH resulting in enhanced reactivity of vascular smooth muscles of to vasoconstrictor effects of various mediators and propensity to cellular proliferation[16]. Hypertension frequently occurs during the course of diabetic nephropathy and may accelerate the progression of the disease[17].

Glomerular hyperfiltration:

Patients with glomerular hyperfiltration appear to be at increased risk of diabetic nephropathy, particularly if the GFR exceeds 150 ml/min. Several factors may induce this hyperfiltration, including hyperglycemia, growth hormone, glucagon, insulin like growth factor I, and increased protein intake.

Genetic factors:

Evidence suggests that genetic susceptibility influences the development of diabetic nephropathy. Polymorphism of genes relevant to renin angiotensin system, such as angiotensin converting enzyme (ACE) and angiotensin type-I receptor have been assessed. Polymorphisms of the ACE gene have been suggested to be linked to diabetic nephropathy by some investigations[18].

Race:

Race appears to influence the susceptibility to nephropathy in NIDDM, with a lower incidence in white patients and a higher incidence in Native-American, African-American, Mexican-American and Asian patients.

Smoking:

Diabetic nephropathy is three or four times more

common in patients who smoke[19]. Although the exact mechanism is not understood, it is suspected that smoking may increase carboxyhemoglobin, which impairs oxygen delivery. Smoking may cause further ischemia in tissues such as retina and glomeruli that are already ischemic in diabetic patients, and thereby accelerate progression of diabetic nephropathy.

CLINICAL DIAGNOSIS

Diagnosis of diabetic nephropathy should be established early. When proteinuria develops in a diabetic patient, it is due to nephropathy in over 90% cases[2]. If the typical clinical course is observed, few confirmatory tests are required. If not renal biopsy is needed. At present, albustix is the best clinical screening test for nephropathy. Some of the diagnostic tests include, albustix, midstream urine examination, serum complement levels, renal ultrasound and renal biopsy. If radiological contrast investigations are needed, great care must be taken to avoid dehydration as acute renal failure may be precipitated especially if renal artery stenosis is present.

PATHOPHYSIOLOGY

It is likely that pathophysiology of diabetic nephropathy involves an interplay of metabolic and hemodynamic pathways in the renal microcirculation in diabetes[20] (fig. 1). Relevant metabolic factors include, glucose-dependent pathways such as activated glycation, increased formation of polyols and activation of protein kinase C (PKC). Hemodynamic factors include, systemic hypertension, intraglomerular hypertension and vasoactive hormones such as angiotensin II.

The chronic effects of elevated blood glucose in inducing tissue injury may occur via the generation of advanced glycated proteins (AGE). Circulating AGEs have strong linking with collagen, *in vitro*. These alter extracellular matrix and are responsible for mesangial expansion and glomerular base membrane thickening. AGEs have strong specific binding receptors on the endothelial cells which lead to increased vascular permeability, increased monocyte influx and increased adhesion molecule expression. All these lead to vascular injury.

Another glucose-dependent pathway known as the polyol pathway has been implicated in the pathogenesis of diabetic nephropathy[21]. The activity of the PKC has been reported to be increased in various diabetic tissues

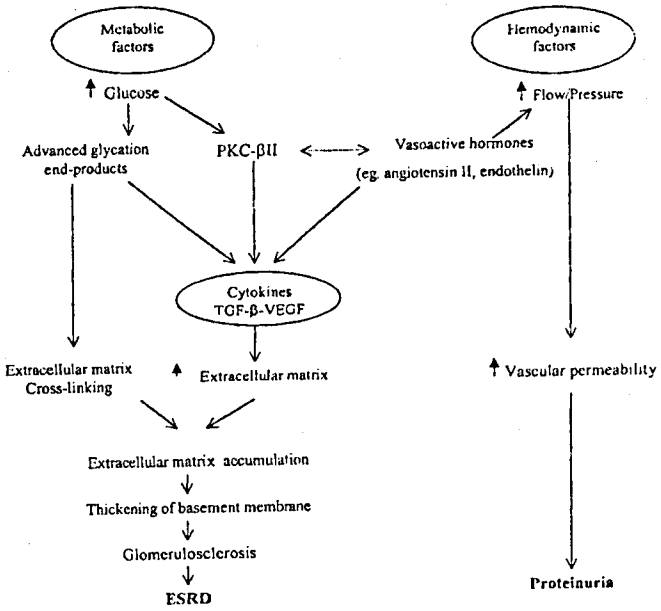

Fig. 1: Pathogenesis of Diabetic Nephropathy

PKC = protein kinase C, TGFb = transforming growth factor β, VEGF = vascular endothelial growth factor.

including the glomerulus. LY 333531, an orally active inhibitor of β-II isoform of PKC has been developed which prevented hyperfiltration and albuminuria in diabetic rats[22].

Diabetic nephropathy is commonly associated with systemic hypertension. The renal hemodynamic changes (increased intraglomerular pressure) may be partly related to the actions of vasoactive hormones such as angiotensin II and endothelin. Renin angiotensin system (RAS) mediated injury may occur via stimulation of a number of scleroting mediators and there is evidence that hyperglycemia acts synergistically with angiotensin-II to promote cellular injury. Although various RAS candidate genes for development of diabetic nephropathy have been examined, controversy remains with the involvement of ACE gene polymorphisms[23]. Recent studies have suggested that the major effects of ACE inhibitors on albuminuria and glomerular ultrastructural injury are related to their capability to inhibit angiotensin-II formation[24]. It has postulated that the prosclerotic cytokine, transforming growth factor (TGF)-β, AGE, angiotensin II and endothelin, all play a pivotal part in the development of diabetic nephropathy[20]. *In vivo* studies have confirmed that agents which block angiotensin II or AGE formation are associated not only with reduced expression of TGF-β and matrix proteins such as type-IV collagen, but also

lead to less renal and vascular injury[25,26]. Other cytokines, such as vascular endothelial growth factor, which are present in the kidneys are also under investigation for their role in diabetic nephropathy[27].

Diabetic nephropathy involves not only renal functional abnormalities but also pathological changes, the major one being extracellular matrix accumulation and basement membrane thickening. Specific inhibitors of the various pathways have led to the development of new approaches to the treatment of diabetic nephropathy.

COMPLICATIONS IN DIABETIC NEPHROPATHY

Cardiac disease:

Coronary artery disease and left ventricular hypertrophy are the two major defects of diabetic nephropathy. Several studies examined coronary arteriograms in patients reaching ESRF showing that between 25% and 40% have severe coronary disease[28,29]; 17% are known to have had myocardial infarcts while over 50% have abnormal electrocardiograms[30]. These abnormalities are twice as common as in non-diabetic ones.

Peripheral vascular disease:

Digital gangrene of fingers and toes is a particular problem, while arterial calcification is commoner, affecting even small peripheral arteries[30,31].

Stroke:

Cerebrovascular disease is a significant problem. Disabling strokes occurred in 10% of NIDDM and 2% of IDDM patients with established renal failure and affect about 5% of patients after transplantation[29].

Mortality:

The increased mortality from myocardial infarction has been shown to occur predominantly in nephropathic patients. Amongst young patients, about 25% die from myocardial infarction before reaching end-stage renal failure (ESRF)[32,33], while the majority of other NIDDM patients with nephropathy die from this cause rather than renal failure. After transplantation, myocardial infarction is responsible for 30-50% of deaths, while early deaths (1-2 y) are divided between coronary deaths and infection, late deaths (2-15 y) are mostly from heart disease[34].

Neuropathy:

Grenfell and Watkins[30] reported that more than half of the patients with advanced nephropathy had symptoms of autonomic neuropathy: impotence, postural hypotension and diarrhoea. The complications also include foot ulcers, sepsis and digital gangrene[35].

THERAPEUTIC INTERVENTIONS

The major therapeutic interventions that have been investigated include near normal blood glucose control, antihypertensive treatment and restriction of dietary proteins.

Glycemic Control:

Several studies including the Diabetes Control and Complications Trial[36] have indicated that intensified glycemic control retards the rate of development of both microalbuminuria and overt proteinuria in patients with IDDM with normal albuminuria. Recent studies showed the same benefit for patients with NIDDM[37]. Pilot studies with aldose reductase inhibitors and aminoguanidine to reduce the accumulation of sorbitol and advanced glycosylation end-products, respectively, suggest that these agents may retard the progression of diabetic nephropathy[7]. Isshiki and co-workers examined the effect of troglitazone on functional and biochemical parameters of glomeruli in streptozotocin-induced diabetic rats[38]. These results may identify thiazolidinedione (TZD) compounds as possible new therapeutic agents for diabetic nephropathy that prevent glomerular dysfunction through the inhibition of diacylglycerol (DAG)-PKC-extracellular signal regulated kinase (ERK) pathway.

Antihypertensive Therapy:

It has a major role in slowing the progression of diabetic nephropathy. Antihypertensive therapy at the stage of persistent proteinuria or established nephropathy shows the linear fall of GFR[39,40]. Antihypertensive treatment include, sodium restriction, diuretics, cardioselective beta blockers (atenolol), calcium channel blockers and ACE inhibitors.

Meta-analysis has documented that ACE inhibitors are superior to β-blockers, diuretics and calcium channel blockers in reducing urinary albumin excretion in normotensive and hypertensive IDDM and NIDDM patients[41]. Anderson and co-workers [42,43] have demonstrated that antihypertensive therapy slows the development of diabetic glomerulopathy but that ACE inhibitors afford superior long-term protection compared with triple therapy with reserpine, hydralazine and hydrochlorothiazide or a Ca^{2+} channel blocker (nifedipine). While substantial

evidence exists for renal protective effects of ACE inhibitors in patients with IDDM, the role of renin-angiotensin system blockade in NIDDM is less clear[44]. Administration of ACE inhibitor ramipril prevented tubulointerstitial injury and the over expression of TGF-beta 1 and alpha 1 (IV) collagen mRNA in rats with experimental diabetes[25].

Dietary Protein Restriction:

Short term studies in normoalbuminuric and microalbuminuric IDDM patients have shown that low protein diet (0.6 to 0.8 g/kg/d) reduced urinary albumin excretion and hyperfiltration, independently of changes on glucose control and blood pressure[45,46]. Two small studies have suggested that a low protein diet in the range of 0.6 mg/kg per day may slow the progression of diabetic nephropathy[47]. However large, long term prospective study is needed to establish the safety, efficacy and compliance with protein restriction in diabetic nephropathy.

Other Interventions:

Biesenbach *et al.*, studied the influence of cigarette smoking on the progression of clinical diabetic nephropathy and concluded that smoking promotes the progression of diabetic nephropathy in patients with NIDDM just as it is known in IDDM patients[48]. Reducing low-density lipoprotein should at least help to decrease the risk of extrarenal vascular disease and may potentially retard progression of diabetic nephropathy.

MANAGEMENT

The management of diabetic patient with ESRD is challenging because the damage brought by diabetes is rarely confined to the kidneys. Currently, there are three therapeutic choices for ESRD diabetic patients: transplantation (kidney only or kidney and pancreas), continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis.

Transplantation:

Kidney transplantation is the optimal treatment for diabetic patients with ESRD. Because kidney transplantation will not alter the course of diabetic complications, such as macrovascular disease or retinopathy, simultaneous pancreas-kidney transplantation effectively prevents recurrence[49] and has been explored as a method of arresting the other complications of diabetes. Currently pancreas transplantation is viewed as an adjunct to kidney transplantation in diabetic patients with established nephropathy.

Continuous Ambulatory Peritoneal Dialysis (CAPD):

In some centers, CAPD is considered the procedure of choice for the treatment of ESRD in diabetic patients[50]. Because the dialysis is continuous, there is more even correction of fluid overload and uremia, with better control of volume-dependent hypertension. The drawbacks of CAPD often restrict its use among diabetics:adequate vision and manual dexterity are necessary to perform CAPD. Previously it was reported that the survival of patients treated with CARD was 60% (better than that of hemodialysis)[51].

Hemodialysis:

Most ESRD diabetics in United States (70%) are treated with hemodialysis[52]. Hypotension during dialysis is common in patients with autonomic neuropathy and may be severe. Like other treatment modalities, hemodialysis does not affect the natural history of the other macrovascular and microvascular complications and retinopathy often progresses on dialysis, which emphasizes the need for frequent ophthalmologic follow-up and treatment.

CONCLUSIONS

Vascular disease needs to be detected and treated at all stages during the care of patients with nephropathy. At the very least, all patients need assessment by electrocardiography and more invasive methods are now needed. The major risk factors, hypertension and hyperglycemia must be properly treated at an early stage, smoking should be discouraged and the treatment of hyperlipidemia is considered.

It is hoped that in the future these impediments will be overcome with more efficient and comprehensive screening of the diabetic population, identification of appropriate genetic or biochemical markers of risk, more extensive use of the available treatments and the advent of new therapeutic approaches that are more effective in the prevention and management of this condition.

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