14

Diabetic Nephropathy; Clinical Characteristics and Treatment Approaches

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1. Introduction

Diabetes mellitus is a major public health problem and its' prevalance is contuniously rising especially in developed or developing countries. According to World Health Organization (WHO) data the prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (1). Despite of improved treatment options for both diabetes mellitus and other associated risk factors, diabetic nephropathy is still a major problem causing increased morbidity and mortality as the increase in total number of diabetic patients finds a reflection in increased prevalence of diabetic patients in end stage renal disease (ESRD) population. There are some studies reporting decreased incidence of diabetic nephropaty in developed countries as a result of better glycemic control and agressive treatment of hypertension with new generation antihypertensives (2). However total number of diabetic nephropathy patients seems to be increasing as a result of increased numbers of diabetic patients and diabetes has become the primary cause of ESRD in the developed countries. Approximately 44% of new patients entering dialysis in the United States are diabetics. In the United States, approximately 20.8 million people, or 7.0% of the population, are estimated to have diabetes, with a growing incidence. Roughly one third of this population, 6.2 million, is estimated to be undiagnosed with type 2 diabetes (3, 4). Similar to these findings prevalence of diabetic nephropahty also increases in in developing countries For example, according to Turkish Society of Nephrology data prevalence of diabetic ESRD patients increased form 7% to 32.5% from 1991 to 2008. A similar trend was also observed for hypertensive nephropathy which raised from 6.3% to 26.8% (5). This hypertensive population is important as according to some previous reports, only one third of essential hypertension patients has normal blood glucose metabolism at diagnosis (6). So it is possible that prevalence of pure diabetic or pure hypertensive nephropathy is lower than predicted but the combination of these two pathological condition is very high in otherwise healthy and ESRD populations.

2. Risk factors

Multiple risk factors for development of diabetic nephropathy were defined. Most important of these seems to be the duration of diabetes mellitus. 20-30% of type I diabetics are supposed to have clinically significant renal involvement (microalbuminuria) after 20 years duration and 15-20% develop ESRD after an additional 10 year (7, 8). These durations are not well defined for type 2 diabetics. 5-25% of these patients might have clinically significant renal failure or even ESRD (1%) at time of diagnosis and approximately 20-30% reach ESRD at 20 years duration (9). The impact of age at time of diabetes diagnosis on development of renal failure is not clear. Among patients with type 2 diabetes, increasing age, along with increasing duration of diabetes was reported to be associated with increased risk for developing albuminuria (10). However some contradicting studies report that, patients who developed diabetes prior to age 20 had a higher risk of progressing to end-stage renal disease (25 versus 5 per 1000 patient years at risk) (11). For type 1 diabetes, the risk of developing ESRD was reported to be very low for patients diagnosed prior to age 5; however at older ages, the relationship of age to progression to ESRD is uncertain (12, 13).

Poor glycemic control is another important risk factor for development of diabetic renal involvement. The Diabetes Control and Complications Trial (DCCT) demonstrated that interventions that improve glycemic control in patients with type 1 diabetes mellitus reduce the risk of development and slow the progression of diabetic microvascular disease, and may also protect against the occurrence of macrovascular disease (14). The United Kingdom Prospective Diabetes Study (UKPDS), a study of over 4000 patients with prolonged follow-up, suggests that strict control also results in a reduced risk of microvascular disease in patients with type 2 diabetes (15).

Hypertension, another important risk factor, is very common in diabetic patients. In fact hypertension is a cause and also a result of diabetic renal disease. Among those with type 1 diabetes, the incidence of hypertension rises from 5% at 10 years, to 33% at 20 years, and 70% at 40 years (16). The blood pressure typically begins to rise within the normal range about three years after the onset of microalbuminuria. Ultimately, the incidence of hypertension is approximately 15 to 25% in all patients with microalbuminuria and 75 to 85% in those with overt diabetic nephropathy (17). On the other hand type 2 diabetic patients have different characteristics. Most of them already have hypertension, even without renal involvement/microalbuminuria at the time of diagnosis (18). Also essential hypertension patients have some glucose metabolism abnormalities including insukin resistance without overt diabetes at time of diagnosis (6).

Obesity and hyperlipidemia might also cause progression of diabetic nephropathy while weight loss and control of hyperlipidemia by using statins might improve renal status (19-22).

Approximately one-half of patients with type 1 diabetes of less than five years duration have an elevated glomerular filtration rate (GFR) that is 25 to 50 percent above normal and this situation was reported to have negative effects on disease progression (23). If GFR is above 150 mL/min risk for developing microalbuminuria significantly increases. In one prospective study, for example, patients with type 1 diabetes and a GFR above 125 mL/min had a risk of developing microalbuminuria within 8 years of approximately 50 percent versus only 5 percent in patients with a lower GFR that was similar to that seen in nondiabetics (23).

Some genetic susceptibilities for developing diabetic renal disease were also reported. Most important of these factors are race, family tendencies and ACE gene polymorphisms (24-28). Considering gene polymorphisms; in patients with type 2 diabetes, the ACE/DD polymorphism was reported to associate with an increased risk for the development of diabetic nephropathy, more severe proteinuria, greater likelihood of progressive renal failure, and mortality on dialysis (26-28).

3. Pathophysiology

Development of diabetic nephropathy depends on different pathogenic processess. Major of these pathyways will be summarized below

a. **Glomerular hyperfiltration:** Studies in experimental animals indicate that dilatation of the afferent (precapillary) glomerular arteriole plays an important role in the hyperfiltration response, by raising both the intraglomerular pressure and renal blood flow (29). Some hormonal factors including insulin-like growth factor I (IGF-1), atrial natriuretic factor and sex hormones were speculated to have effects on hyperfiltration. Most important of these seems to be IGF-1 which induces hyperfiltration, renal vasodilatation and hypertropy in experimental models (30). Increased intracellular sorbitol accumulation, hyperglycemia, glycosylation endproducts and increased sodium reabsorption and tubuloglomerular feedback also has effects on glomerular hyperfiltration
b. **Hyperglycemia and AGEs:** Hyperglycemia is known to have a direct effect on mesangial expansion and injury, a result possibly secondary to increased matrix production or glycosylation of matrix proteins. Glycosylation of tissue proteins also may contribute to the development of diabetic nephropathy. Chronic hyperglycemia causes nonenzymatic glycosylation of free amino acids on circulating or tissue proteins and this process forms reversible early glycosylation products and later irreversible advanced glycosylation end products (AGEs). Circulating AGE levels are increased in particularly diabetics with renal insufficiency, because AGEs are normally excreted in the urine. The net effect is tissue accumulation of AGEs, in part by crosslinking with collagen, which can contribute to the associated renal and microvascular complications (31, 32).
c. **Prorenin:** A recent experimental model has reported a possible pathogenic role for prorenin in the development of diabetic nephropathy in which prolonged prorenin receptor blockade prevented the development of nephropathy without alterin angiotensin II activity (33).
d. **Proinflammatory cytokines and growth factors:** A group of proinflammatory, profibrotic cytokines and growth factors were speculated to have effects on diabetic nephropathy pathogenesis. Most important of these are vascular endothelial growth factor (VEGF), transforming growth factor – beta (TGF-ß). Experimental models reported that VEGF blockade improves albuminuria in diabetic nephropathy (34). Similarly the combination of an anti-TGF-beta antibody and an ACE inhibitor completely normalized proteinuria in experimental diabetic nephropathy models (35).
e. **Proteinuria:** Final result of above mentioned pathogenic factors is proteinuria. Normal protein discharge in urine is lower than 30 mg/day for albumin and 150 mg/day for total protein. Microalbuminuria (30-300 mg/day) is a critical treshold for diabetic nephropathy and after this stage untreated patients usually develop overt proteinuria

(> 300 mg/day microalbuminuria). Proteinuria was reported to induce inflammation, fibrosis, and it is also have direct tubular toxicity which all promote development of diabetic nephropathy

4. Histopathological changes

All components of renal infrastructure can be affected by diabetic nephropathy. Some of these changes are specific for diabetes, some not. Most common and important changes are capillary basal membrane thickening, diffuse glomerulosclerosis and nodular glomerulosclerosis (Kimmelstiel – Wilson nodules). Nodular glomerulosclerosis was described by Kimmelstiel and Wilson in 1936. These nodules are eosinophilic and PAS positive hard masses which are located in the central regions of peripheral glomerular lobules. They appear to be of mesengial origin and when they are pathogomonic for diabetic nephropathy however they are not universal and found only in 10-40% of patients. The diffuse mesengial lesions are more frequent than nodular glomerulosclerosis and present in 50-90% of patients. They include increased mesengial matrix, basala membrane thickening, capillary narrowing, hyalinization and periglomerular fibrosis. Afferent and efferent arteriolar hyalnization is highly specific for diabetic nephropathy, on the other hand only afferent arteriol involvement is a finding of hypertensive nephrosclerosis.

5. Clinical manifestations and natural history

Clinical stages of type 1 diabetes mellitus renal involvement is summarized in Table-1. These stages are also accepted for type 2 diabetic patients however they might not always follow these steps (36). ESRD is not the only major consequence of diabetic nephropathy but patients have increased risk of cardiovascular disease , morbidity and mortality even in the early stages of nephropathy. Microalbuminuria (30-300 mg/day albuminuria) is the first clinical sign of diabetic nephropathy and this situation is highly associated with other complications of diabetes like cardiovascular disease and retinopathy. 24 hour urine or spot urine albumin / creatinine ratios should be used for microalbuminuria follow-up. Overt proteinuria is defined as >300 mg/day albuminuria and at this stage total protei,n loss in urine might exceed 1g/day. 5-7 years after development of overt proteinuria these patients usually develop ESRD.

6. Diagnosis and differential diagnosis

Proteinuria developing in a diabetic patient is an important marker for diabetic nephropathy however in case of atypical presentation renal biopsy might be indicated. A typical diabetic nephropathy presentation is a type 1 diabetes history for at least 10 years, presence of retinopathy, previous microalbuminuria, no macroscopic hematuria and microscopically inactive urinary sediment. Type 2 diabetic patients might not have this kind of a clinic and as previously mentioned 5-25% of these patients might have clinically significant renal failure or even ESRD (1%) at time of diabetes diagnosis (9). In case of atypical presentation a renal biopsy is usually indicated. Possible atypical presentations are as follows; short diabetes duration (> 10 yrs for type 1 diabetics), no previous retinopathy, overt proteinuria without previous microalbuminuria, macroscoic hematuria, red cell or leucocyte casts, presence of systemic manifestations of any other disease that also can

involve kidneys like collagen tissue disorders, amyloidosis etc, rapid decline in renal function without significant proteinuria. Long diabetes duration, previous retinopathy and microalbuminuria might not always be present in type 2 diabetics so in these patients presence of glomerulonephritis clinical features or any other systemic disease with possible renal involvement are biopsy indications.

Stage	Duration of diabetes mellitus	GFR and renal perfusion	Urine findings	Serum findings	Clinical findings	Morpho-logical findings
1. Nephro-megaly and hyper-filtration stage	At diagnosis	Increased	Reversible albuminuria	No significant finding	Increased renal size	Glomerular hypertrophy
2. Latent stage	2-5 years	Normal/Increased	No significant finding	No significant finding	No significant finding	Increased basal membrane thickness
3. Incident diabetic nephropathy stage	5-15 years	Normal/Increased	Microalbuminuria (30-300 mg/day)	No significant finding	Hypertension	Increased basal membrane thickness and mesengial expansion
4. Overt diabetic nephropathy stage	10-25 years	Decreasing progressively	Overt proteinuria	Increased creatinine	Hypertension and significant nephropathy	Diffuse/nodular glomerulosclerosis
5. End stage renal disease stage	15-30 years	Decreased	Overt proteinuria	Uremia	Hypertension and significant nephropathy	Glomerulosclerosis

Table 1.

Diabetic patients are also prone to some renal diseases or complications which might need to be differentialy diagnosed. Almost every form of glomerular diseases were reported in diabetic nephropathy patients however membranous nephropathy is the most common one. Papillary necrosis, renovascular diseases (arterial or venous), bladder autonomic neuropathy, acute or chronic pyelonephritis, radiocontrast nephropathy and renal tuberculosis should always be kept in mind while evaluating a diabetic patient with renal findings.

7. Treatment and prevention of diabetic nephropathy

Strict glycemic control decreases development of diabetic nephropathy in both type 1 and 2 diabetics. Intensive insulin therapy partially reverse the glomerular hypertrophy and hyperfiltration, delay the development of microalbuminuria, reduce the onset or progression of diabetic nephropathy compared to less intensive therapy, stabilize or decrease protein excretion in patients with microalbuminuria (14, 15, 37, 38). Intensive glycemic not only slow or even prevent development of diabetic nephropathy but also decrease morbidit and mortality ferom other diabetic complications. However the less prominent benefit from strict glycemic control in overt diabetic nephropathy indicates that factors other than hyperglycemia contributes to the glomerular injury. Reducing the intraglomerular pressure with dietary protein restriction or antihypertensive therapy with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) can minimize progression of or even prevent glomerular disease in the absence of glycemic control. There is now clear evidence that antihypertensive therapy (particularly with RAS blockers) and perhaps protein restriction can reduce the rate of progression in patients with type 1 diabetes and overt nephropathy.

Hypertension increases rate of diabetic nephropathy progression. DCCT and UKPDS trialsdemonstrated that strict blood pressure control decreases microalbuminburia and macroalbuminuria development by 29% and 39% respectively in 6 years follow-up period (14, 15). WHO and JNC advises to keep blood pressure below 130/80 mmHg in diabetic patients. In JNC-VII quideline even a lower level (125/75 mmHg) was proposed for prevention and/or slowing diabetic nephropathy progression (39). ACEI preference in diabetic patients is also recommended in these quidelines. ACEI not only decrease intraglomerular pressure (so decrease proteinuria) by their hemodynamic effects but also decrease glomeruler size and fibrotik process. ACEI were also reported to increase negative charge of basal membrane and so decrease proteinuria. ARBs could also be used alone or in combination with ACEI for increasing nephroprotection (40, 41). Nondihydropyridine class calcium antagonists (NDHCB) are also recommended as a combination with RAS blockers. In BENEDICT trial it was demonstrated that ACEI-NDHCB combination might delay development of microalbuminuria in hypertensive diabetic patients without proteinuria (42). Salt intake should be restricted (< 70 mEq/day) for a beter antirpoteinuric effect as salt seems to blunt effects of both RAS blockers and NDHCB (43, 44). Aldosterone antagonists were also reported to reduce proteinuria when used alone, and to have an additive effect on proteinuria when used in combination with an ACE inhibitor or an ARB in both type 1 and type 2 diabetes (36, 45). Further blood pressure reduction may partially explain the beneficial effect, although an anti-inflammatory mechanism has also been proposed (46). However hyperkalemia in combination treatment ACEI/ARB and aldosterone antagonists) is a significant problem especially in advanced diabetic nephropathy.

Low protein diet decreases hyperfiltration in early stages of diabetic nephropathy and also could slow down GFR loss. However very low protein diets (< 0.6/g/kg/day) could cause malnutrition which is an important mortality risk factor in ESRD population so 0.8 g/kg/day protein diets and essential amino acid supplementations are usually recommended (47).

Hyperlipidemia should also be screened in diabetic patients and must be treated with statins or fibrats if needed. Diabetic patients without hypertension but under simvastatin treatment were reported to have a 25% decrease in microalbuminuria levels (48).

8. Renal replacement treatment in diabetic esrd patients

Diabetic patients usually need renal replacement therapy (RRT) in earlier stages of renal failure. It was reported that nondiabetic patients start receiving RRT when GFR falls below 10 ml/min but on the other hand diabetics need RRT with higher GFR (15-20 ml/min) levels (49). These patients are prone to hypervolemia and lung edema due to accompanying cardiac problems and malnutrition due to proteinuria and dietary restrictions. Diabetic patients developing diuretic resistant edema might need ultrafiltration and start RRT even with higher GFR values.

Patient survival in diabetics on maintenance dialysis is lower than that seen in nondiabetics with end-stage renal failure due to chronic glomerular disease or hypertension (50). As noted in the 2005 USRDS database, only approximately 25 percent of patients with diabetes survived five years after initiation of dialysis and cardiovascular disease is the most common cause of death, accounting for more than one-half of cases (50).

Renal transplantation is a choice of RRT in diabetic ESRD patients however five year survival is clearly lower than other ESRD patients ranging from 75% to 83% (51). Despite of this poor outcome, transplantation still result in decreased extrarenal vascular diseaseand better quality of life compared with either hemodialysis or peritoneal dialysis (51).

Making choice of dialysis modality in diabetic patients is similar with nondiabetic patients. Comorbid conditions, home situation, independence and motivation of the patient, ability to tolerate volume shifts, patients' desire, status of the vasculature and/or abdomen should be evaluated for each patient. The relative effect of hemodialysis and CAPD on survival in diabetic patients is uncertain. Initial reports suggested that CAPD was associated with a better outcome (52). However data from the USRDS case-mix study suggest that mortality may actually be increased in diabetic patients receiving CAPD (53). A subsequent very large study attempted to assess the impact of multiple risk factors, including diabetes, on survival after initiation of either hemodialysis or peritoneal dialysis. Utilizing data from 398,940 patients who initiated dialysis between the years 1995 to 2000 (54). Mortality risk was significantly higher on hemodialysis than PD among younger diabetics with no comorbidity. By comparison, hemodialysis was associated with a lower mortality risk in older diabetics with either no comorbidity or a baseline comorbidity.

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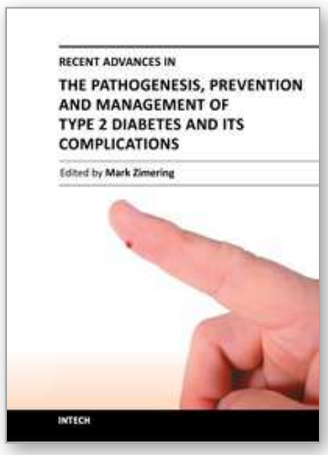

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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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