

## DIABETIC NEPHROPATHY - PATHOPHYSIOLOGY AND MANAGEMENT

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### INTRODUCTION

Diabetic nephropathy (DN) is a generic term referring to any deleterious effect on the kidney structure or function caused by diabetes mellitus. Clinically it is defined as the presence of persistent proteinuria, more than 0.5 gram over 24 hours, in a diabetic patient, usually along with retinopathy, hypertension and declining glomerular filtration rate (GFR), in the absence of urinary tract infection heart failure, or other renal disease.

Diabetic nephropathy is one of the commonest and the most important microvascular complications of diabetes mellitus. Diabetes mellitus has become an increasingly important cause, of end stage renal disease (ESRD) requiring renal replacement therapy and constitutes one third to half of the patients undergoing dialysis. In view of increasing prevalence of DM, it is likely that diabetic related ESRD will also be in the rise, unless prevented.

### PATHOPHYSIOLOGY

Diabetic nephropathy progress through various phases. The clinical course and natural history is, however, best defined in type 1 diabetes mellitus.

An early physiological abnormality is glomerular hyperfiltration associated with glomerular hypertension.<sup>1</sup> GFR is found to increase by 20 - 40% in diabetes mellitus.

This is followed by a period of silent phase. In this phase, though, there is normal urinary albumin excretion, key pathophysiologic event in DN, basement membrane damage, starts.<sup>3</sup>

The next stage is the appearance of micro-albuminuria. The microalbuminuria can be regarded as part of more generalised vascular permeability of diabetic microvascular disease. It has been suggested that the early increased in

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protein excretion is likely to be the consequence of alteration of glomerular haemodynamics. However, subsequently loss of fixed negative electrical charge on the membrane due to decreased concentration of anionic heparin sulphate results in loss of albumin through urine.<sup>4</sup> The stage of microalbuminuria is critical time in the evolution of diabetic renal disease. If adequate therapeutic intervention is not taken in this point progressive decline of renal function occur.

A clinically asymptomatic period follows and leads to macroalbuminuria (albuminuria >300 mg in 24 hrs). Once overt nephropathy has developed renal function declines at significant but variable rate of 2 - 20 ml/min/yr. leading to ESRD in 7-15 years period. > In type 2 diabetic mellitus, the stages of DN differ in initial stages. These differences have been evaluated recently.<sup>5</sup> At the time of diagnosis of type 2 diabetes mellitus, rate of hyper-filtration is half than that seen in type 1 diabetes mellitus, microalbuminuria is already present in 15% of the patients and may be associated with hypertension. In the silent phase (stage 2), apart from basement membrane thickening and mesangial expansion, vascular and tubulointerstitial changes are common. Presence of microalbuminuria in stage 3, is strong indicator of cardiovascular disease, where in type 1 diabetes, microalbuminuria is an indicator of renal prognosis. The later stages are similar in both the type of diabetes.

### Risk Factors for the development of DN

There is no straightforward casual relation between hyperglycemia and renal disease. The renal involvement is seen in 35-50% diabetic patients. The majority of diabetic patients do not develop renal failure, although, some histological damage is universal. The factors, which are important in bearing pathogenesis of DN, are;

**a) Genetic:** Genetic influence on the development

of DN is strongly supported by the study in Pima Indians.<sup>6</sup> Seaquest et al<sup>7</sup> has pointed out that diabetic sibling from parents with diabetes and renal disease are five .times more likely to suffer from diabetic nephropathy than diabetic sibling of diabetic parents without renal disease. Studies in thte Pima Indians by petit et.al<sup>6</sup> observed that proteinuria developed in 14% diabetic offspring when neither parent had proteinuria and 46% if both the parent had proteinuria. Brazilian study has shown the risk to be 3.75 fold.<sup>8</sup>

**b) Hyperglycemia:** Hyperglycemic milieu is essential in the development of DN. It is uncommon in patient with HbA1C consistently less than 7.5-8%.<sup>9</sup> Glomerular hyperfiltration occurs under moderate hyperglycemia. Severe hyperglycemia (14-16 mmol/l), on the other hand in associated with normal or reduced GFR.<sup>2</sup> Direct glucotoxic effects leading to increase synthesis & accumulation connective tissue and alteration in endothelial cell function and structure are observed in experimental studies.<sup>10</sup> Hyperglycemia dependent metabolic pathways also play role in development of DN-

- Nonenzymatic glycosylation leads to formation of advance glycosylation end products (AGEs). These AGEs changes the tertiary structure of protein, and also changes the functions of various proteins, cytokines, hormones, and extracellular matrix. In a study the AGE content in the arterial wall collagen was found to be four fold higher in diabetic patient than nondiabetic.<sup>11</sup>
- Polyol pathway: In presence of hyperglycemia sorbitol production via polyol pathway is increased. This is more so on tissue where glucose uptake is insulin independent. It is postulated that increase in sorbitol production alongwith reduced myoinisitol concentration will upset osmoregulation in renal cells and leads to DM.<sup>12</sup> However, clinical trials using aldose reductase inhibitor fails to reduce

microalbuminuria in humans, though research in these fields are still ongoing.

- Other metabolic pathways that are postulated to be involved in the genesis of DN are increased protein kinase C and growth factor activity,<sup>13</sup> Endothelial dysfunction, abnormal lipid metabolism<sup>14</sup> etc.

**C) Hypertension:** Haemodynamic factor is very important in the development of diabetic nephropathy. Systemic hypertension leads to afferent arteriolar dilatation contributing to intraglomerular hypertension, hyperfiltration and haemodynamically mediated damage of glomeruli.<sup>15</sup> There may be abnormal renal response to angiotensin system in the diabetic kidney.<sup>16</sup> Patient with proteinuria and hypertension suffers from rapid deterioration of renal function if not treated aggressively.

**c) Smoking:** Smoking has been linked to increase in the incidence and progression of diabetic nephropathy.<sup>17,18</sup> Mehlar P et al,<sup>19</sup> in their study has shown that smoker diabetics have 1.6 high risk of nephropathy.

**d) Obesity:** Although obesity has been categorised as risk factor for DN, the exact role of obesity is not clear.<sup>5</sup>

**e) Homocysteine:** Homocysteine is increased in diabetes patients. This is more so in type 2 diabetes mellitus than type 1 diabetes. Homocysteine is associated with endothelial cell dysfunction in type 1 DM<sup>17</sup> and with neuropathy and nephropathy in type 2 diabetes.<sup>18</sup> There is also strong positive association between urinary albumin excretion and plasma homocysteine level.<sup>20</sup>

**f) Serum lipid:** A large multicentre trial has revealed the serum cholesterol was independent predictor of loss of renal function.<sup>21</sup> Apolipoprotein B has also been found to be associated with declining GFR.<sup>22</sup>

## MANAGEMENT

ESRD, due to diabetes mellitus has higher dialysis associated mortality than similar non-diabetic patient. They also suffer from higher morbidity.<sup>23</sup> Therefore focus is to prevent development of diabetic nephropathy. Once overt nephropathy is present, however, progression of renal deterioration cannot be halted, only slowed. Once macroalbuminuria appears, the cumulative incidence of ESRD was reported to be 70% over 15 years in Caucasian and Pima Indian. This may more in certain ethnic group.<sup>19,24</sup> Therefore the stress is laid upon screening and management of modifiable risk factors.

**Blood pressure control:** Hypertension is found in half of the diabetic population. Presence of nephropathy in patients with diabetes and hypertension result in almost 40 fold increase in mortality.<sup>25</sup> Parvin et al has demonstrated that with effective control of blood pressure albumin excretion rate can be reduced to 50% and decline of GFR can be slowed to 0.29/ml/min/month from 0.9 ml/min/month.<sup>26</sup> Various studies have shown that higher the mean arterial pressure greater is the renal loss in both non-diabetic and diabetic patient.<sup>22,27</sup>

Recently there is consensus on recommended target blood pressure of 130/80 mmHg for patient with diabetes and hypertension.<sup>27</sup> As urinary albumin excretion is the predictor of the rate of decline in GFR,<sup>28</sup> it is logical that an antihypertensive chosen to treat diabetic nephropathy must be able to reduce microalbuminuria. Few antihypertensive with this property are angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor antagonist, non-dihydropyridine calcium channel blocker and cardioselective B-Blocker (carvedilol). Analysis of UKPDS,<sup>28</sup> HOPE,<sup>29</sup> Danish study<sup>30</sup> captopril study revealed that ACEI inhibitors

reduce cardiovascular mortality apart from its renoprotective effects. Moreover ACEI has been found to have inhibitory effects on mesangial cell proliferation, interstitial fibroblast, glomerular growth and improvement in glomerular membrane size.<sup>31</sup> The limiting factors in use of ACEI inhibitor are; markedly raised serum creatinine, bilateral renal artery stenosis, hyperreninemic states, hyperkalemia etc.

The use of non-dihydropyridine subclass of calcium channel blockers including diltiazem and verapamil is more strongly associated with vasodilatation of afferent arteriole than efferent arteriole. They are also shown to decrease albuminuria. There are reports that combination of ACEI and calcium channel blocker in low dose combination achieves greater reduction of protein excretion and decline in GFR.<sup>32</sup>

**Glycemic control:** Diabetic nephropathy is uncommon in patient with HbA1C constantly below 7.5%.<sup>9</sup> In the Diabetic Control Complication trial (DCCT), there was 39% reduction in the incidence of microalbuminuria in primary prevention group and there was decreased in the progression from microalbuminuria to macroalbuminuria by 54% in the secondary prevention group.<sup>33</sup> In the United Kingdom Prospective Diabetes Study<sup>34</sup> newly diagnosed 367 diabetic patients were divided into intensive treatment group (HbA1C: 7%) and conventional group (HbA1C: 7.9%). there was 34% decrease in the risk of development of microalbuminuria and relative risk of developing macroalbuminuria was also decreased. The relative risk of doubling serum creatinine was also decreased in 12-yr. follow up in small group. Study from Japan has revealed that intensive treatment with insulin decreased the frequency of development of microalbuminuria by 57% and macroalbuminuria by 70%.<sup>35</sup> The increasing results of regression of diabetic

nephropathy in eight patients with type 1 DM who received pancreatic transplantation<sup>36</sup> open up a new vista that it could be reversible process.

The recommended optimum preprandial, bed time and HbA1C by American Diabetic Association are 80-120mg, 100-140mg/dl and HbA1C <7% respectively. It is the strict control rather than the methods of control that matters.<sup>37</sup>

**Diet in diabetic Nephropathy:** Dietary protein restriction has been questioned on the basis of disappointing result of Modification of Diet in Renal Disease study.<sup>38</sup> However the demerits of the study being heterogeneity of renal diseases and small number of type 1 diabetes. Metanalysis has shown that low protein diet (0.69 g/Kg/day ) is beneficial in terms of declining in GFR both in diabetic and non diabetic patients.<sup>39</sup> The current recommendation of protein is 0.6g/kg/day to 0.8g/kg/day. Since the rate of hepatic synthesis of albumin is maximised in proteinuric patient, a low protein diet has no effect on serum albumin. However, protein restriction needs to be avoided in hypercatabolic and malnourished patient.

**Treatment of dyslipidemia:** Dyslipidemia is known risk factor for atherosclerosis. Hyperlipidemia and their role on diabetic nephropathy is not clear, though, it has been implicated to cause glomerular injury. Large controlled studies are needed to confirm their role in renal disease. Till then the current guideline in treatment of Coronary Heart Disease may be followed.<sup>40</sup>

**Other modalities:** Smoking worsens hypertension and albuminuria. Therefore, smoking cessation is imperative. Other renal disease prevention measures like prompt treatment of urinary tract infection, avoidance of renal toxic drugs, dehydration etc are also applicable to diabetic nephropathy.

## FUTURE PERSPECTIVE

Impaired endothelial dependent vascular responses has been observed in patients with diabetes mellitus irrespective of albuminuria. This endothelial dysfunction is implicated to be due to raised homocysteine level.<sup>20,41,42</sup> If increased homocysteine is casually related to endothelial dysfunction, that in turn, responsible for diabetic nephropathy, low dose vitamins (folic acid, B12, B6) therapy can be part of multifactorial approach in preventing progression of diabetic nephropathy.

Some researchers have focused on loss of heparin sulfate and negative charge of glomerular basement membrane. Heparin injection is to restore heparin sulfate, oral glycosaminoglycans, danaparoid sodium has shown some beneficial result in initial studies.<sup>43</sup>

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