Abstract

The prevalence of Chronic Kidney Disease (CKD) continues to escalate at an alarming rate and diabetes has become the most common single cause of End-Stage Renal Disease (ESRD) in the world. This is because diabetes, particularly type 2, is increasing in prevalence, and the patients are living longer now. Diabetes is the major cause of end-stage renal disease in the developed world, accounting for 40% to 50% of cases.

Diabetic nephropathy contributes significantly to the economic burden of diabetes. In UK, the cost of diabetic complications in 2011/2012 was estimated at £14 billion, by 2035/2036 this is expected to rise to £22 billion. Worldwide, healthcare costs for diabetic patients are much higher than non-diabetic patients. Also, among diabetic patients the cost of health care is much higher in those with complications (Micro < Macro < Micro + Macrovascular complications) than in those without complications, therefore identifying and controlling diabetes and its complications is essential in reducing the burden of the disease.

In this review we shall explore the pathophysiology, risk factors, staging, screening, management and prognosis of Diabetic Nephropathy in explicit details to make it easily understandable for the Health Care Professionals.

Keywords: Diabetic Nephropathy, Diabetes, Health Care Professionals

Introduction

Diabetic Nephropathy (DN) is the leading cause of ESRD in the UK. In 2012, DN accounted for 26% of cases ESRD [1], and 40% diabetics will develop DN [2].

The features of DN are increasing urinary albumin excretion, rising BP and declining renal function [3]. There are specific pathological changes with five different stages. The key is the level of urinary albumin excretion-microalbuminuria (incipient nephropathy) or macroalbuminuria/proteinuria (overt nephropathy) [4]. As it is an asymptomatic process screening is required [2, 3].

<table>
<thead>
<tr>
<th>ACR-Albumin/Creatinine Ratio (mg/mmol)</th>
<th>Normal</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>&lt;3.5 female</td>
<td>3.5-30 female</td>
<td>&gt;30</td>
</tr>
<tr>
<td></td>
<td>&lt;2.5 male</td>
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<td></td>
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<tr>
<td>24hr collection mg/24hr</td>
<td>&lt;30</td>
<td>30-300</td>
<td>&gt;300</td>
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</tbody>
</table>

Table 1: Levels of UAE (adapted from Holt[5])

In UKPDS, 2% of T2DM with normal UAE progressed to microalbuminuria annually, 2.8% progressed from microalbuminuria to macroalbuminuria (4). At diagnosis 10% will have DN, and 25% in 10 years post diagnosis [4, 6].
In T1DM microalbuminuria usually appears after 5-15 years post diagnosis, with proteinuria/ macroalbuminuria found in 15-40% [2, 5]. Not all will have increasing UAE in T1DM a third will revert to normal [7].

Risk factors include duration of DM, hyperglycaemia, hypertension, ethnicity and genetic factors. The UKPDS and DCCT showed that improved glycaemia reduced progression [4, 8, 9], and in T2DM, controlling hypertension reduces risk [4]. Suppression of RAS is the key to risk reduction [2, 3, 10].

There is increased cardiovascular risk [2, 3]. Compared to normal UAE, microalbuminuria increases CVD risk by 2-3 times. With proteinuria this risk is increased by 10³.

Diabetic nephropathy can be easily screened for and the modification of risk factors can improve the outcome. We will discuss the risk factors, pathogenesis, staging and treatment of this important cause of mortality and morbidity.

Search Strategy
Available studies and abstracts were identified through Pub Med and Medline data bases (From 1998-2019) and Cochrane data bases. Key search terms were diabetes and nephropathy. All available studies and abstracts describing the relationship between diabetes and nephropathy were included. The reference list of review articles was also searched.

Discussion
Epidemiology
Approximately 463 million people worldwide have diabetes and the prevalence is expected to rise to 700 million in the next 20 years [11]. This growing epidemic carries with it an increasing burden of micro and macrovascular complications. Diabetic nephropathy is one of the serious microvascular complications of diabetes [12].

Diabetic nephropathy is defined as eGFR of <60 ml/min/1.73m2 and albumin/creatinine ratio (ACR) of >30 mg/g. It occurs in up to 40% of all patients with diabetes [13] and accounts for >44% of ESRD patients [14]. The prevalence of DN has doubled over the past decade, especially in areas of high prevalence of diabetes like USA, Japan and Europe. About 50% of DN patients will progress to ESRD within 10 years of diagnosis, increasing to 75% in 20 years if no preventive measures are implemented [13].

Diabetic nephropathy contributes significantly to the economic burden of diabetes. In UK, the cost of diabetic complications in 2011/2012 was estimated at £14 billion, by 2035/2036 this is expected to rise to £22 billion. Worldwide, healthcare costs for diabetic patients are much higher than non-diabetic patients. Also, among diabetic patients the cost of health care is much higher in those with complications (Micro < Macro<Micro + Macrovascular complications) than in those without complications, therefore identifying and controlling diabetes and its complications is essential in reducing the burden of the disease [15].

Pathophysiology of diabetic nephropathy [16]
Knowing the exact mechanisms by which diabetic nephropathy develop helps in identifying new treatment modalities.

Diabetic nephropathy occurs due to interplay between hemodynamic and metabolic factors.

Hemodynamic factors
1. Increased systemic and intraglomerular pressure.
2. Activation of vasoactive hormones particularly renin angiotensin system and endothelin. The above 2 steps lead to:
   a) Activation of intracellular second messengers like:
      • Protein kinase C.
      • MAP kinase.
      • Nuclear transcription factors like NF-alpha B.
   b) Growth factors like:
      • Prosclerotic cytokine
      • TGF-B
      • permeability enhancing growth factor
      • vascular endothelial growth factor
      • VEGF

Metabolic factors
Activation of glucose dependent pathways inside the kidney leads to
• Enhanced oxidative stress
• Renal polypol formation
• Accumulation of Advanced glycation end products

Activation of all these pathways result in increased renal albumin permeability and accumulation of extra cellular matrix leading to increased proteinuria, glomerulosclerosis and finally tubulointerstitial fibrosis.
Discussion
These type of tumours are very rare they comprise only 5% of neoplasms and are seen in 0.4-2.6 for every 100,000 cases around the world, the mucoepidermoid tumour affects parotid and minor salivary glands in adults and is mostly seen in women and young adults, most of the cases arise in the parotid gland with this case accounting for only 2-4% of the cases because it was seen in the submandibular gland, this patient is currently under treatment he was performed two surgeries for removal of ganglions located in neck and in the submandibular gland, highest prevalence for this type of tumour is around the fifth decade of life and they can be asymptomatic like in this case with the patient having few to no symptoms. It has a pluripotent cell origin and as we mention can be classified into three stages [3].

References


Risk factors for diabetic nephropathy

Risk factors for diabetic nephropathy include positive family history, hyperglycemia, hypertension, smoking and others.

Genetics and ethnicity

There is a concordance of nephropathy among twins having T1DM [17]. There is five times more chance to develop nephropathy in diabetic siblings of patient with diabetes and nephropathy [18].

Beneficial effects of ACE inhibition on nephropathy showed there are high levels of ACE in patients with nephropathy and diabetes, especially abnormal alleles of ACE gene carriers [19].

ESRD is more common in ethnic groups like African Americans, Mexican Americans and Native Americans [20].

Hyperglycemia

Hyperglycemia and duration of diabetes is a strong risk factor of diabetic nephropathy [19]. In DCCT and other treatment trials showed lowering glucose levels reduces DN [23]. Diabetic nephropathy is not common in patients with HbA1c <7.5-8% [21, 22].

The conversion of glucose to sorbitol by aldose reductase in polyol pathway is also postulated as a contributing factor for microvascular complications in patient with diabetes [18, 24].

Hypertension

Hypertension is an effect and cause of DN. Hypertension causes dilatation of afferent arterioles which leads to intraglomerular hypertension and damage [15]. In diabetes there may be an abnormal renal responsiveness to RAS [25].

Others

Dyslipidaemia is also a contributing factor for DN development. The phenotype of lipid alters with progression of nephropathy [26, 27]. Others risk factors for DN include smoking, preeclampsia, periodontitis, inflammatory markers, growth factors and cytokines, increased level of mannos binding lectin and bone related peptide osteoprotegerin [28-33].
Microalbuminuria / a predictor of clinical complications

Urine albumin ranging from 30 to 300mg in a 24-h urine sample is defined as Microalbuminuria [34, 36, 39].

Microalbuminuria (MA) and clinical complications

T1DM: It is an independent predictor of CV risks in patients above the age of 45 years [35].

T2DM: It is considered to be the harbinger and strongly associated with CV risks and mortality and morbidity [35].

Part of metabolic syndrome is also manifested by the levels of microalbuminuria in association with other components (metabolic like lipids and BP, urate, body habitus and hs-CRP).

Association with SBP and CRP in causing endothelial dysfunction [35, 37]

Elevated SBP is associated with generalized endothelial dysfunction and leaky capillaries are associated with albumin leak in the glomerulus and chronically inflamed endothelium.

<table>
<thead>
<tr>
<th>Table 2: Showing the constellation of findings associated with microalbuminuria [35]</th>
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<tbody>
<tr>
<td>Study Title</td>
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<tr>
<td>IDNT</td>
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<tr>
<td>RENAAAL</td>
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<tr>
<td>MARVAL</td>
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</tbody>
</table>

Table 3: Depicting the clinical trials of Albuminuria and renal outcomes in T2DM [38]
<table>
<thead>
<tr>
<th>Study Title and design with interventions</th>
<th>Gist of outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life study, Losartan studied in interventions</td>
<td>Microalbuminuria is associated with hypertension and CV risks</td>
</tr>
<tr>
<td>TOMS, Treatment of mild HT study, Enalapril</td>
<td>Reduction in microalbuminuria along with BP control</td>
</tr>
<tr>
<td>PREVEND (Prevention of vascular and renal end-stage disease)</td>
<td>Increase e-GFR with Microalbuminuria due to hyperfiltration and reduced GFR with macroalbuminuria</td>
</tr>
<tr>
<td>HOPE</td>
<td>Increased CV risk and events with Microalbuminuria</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>Increased morbidity and mortality due to CV disease</td>
</tr>
<tr>
<td>Copenhagen City Heart Study</td>
<td>Microalbuminuria associated with increased lipids and raised BP with increased mortality</td>
</tr>
</tbody>
</table>

**Table 4:** Showing other studies related to microalbuminuria and CV risk not totally related to diabetes [38, 39]

Framingham Heart Study, HOPE, LIFE, PREVEND, HARVEST, HOOM, MONICA and Copenhagen city heart study emphasized the importance of control of BP and Microalbuminuria (some using RAAS blockade) in reducing the incidence of CV events and associated morbidity and mortality.

**Microalbuminuria can be useful screening method in assessing CV risk in [35]**

1) T2DM patients  
2) >45 years older T1DM  
3) Stage 2 Hypertension in elderly

**Macroalbuminuria/a predictor of clinical complications**

Macroalbuminuria predicts retinopathy, neuropathy and cardiovascular disease.

Gall M et al, in their study showed 13.5% of T2DM had macroalbuminuria. Arterial hypertension was prevalent in 85% and ulcer of foot was seen in 25% [40].

Susan S et al, in a cross-sectional study involving 947 T2DM patients from year 1990 to 1993. DN was prevalent in 75% among macroalbuminuric patients. Among the patients who were suffering from DN, proliferative retinopathy was detected in 49%. The prevalence of neuropathy was also higher, 68% of patients with macroalbuminuria was having neuropathy. Cardiovascular disease was highly prevalent among those with macroalbuminuria, in 58% of the patients. The study showed an independent association between macroalbuminuria and occurrence of cardiovascular disease [41].

**Diabetic nephropathy stages**

**First stage; Early, hyperfunction [42]**

- Characterized by hyperfunction  
- Structural changes; hyperplasia and hypertrophy of nephrons, kidney size increased  
- GFR increased 20-40%  
- Blood pressure within normal  
- Albumin excretion is increased, and by physical activity (provocation test) increased This stage is reversible by blood sugar control (such as insulin treatment)

**Second stage; Glomerular lesion without clinical finding [42]**

- It develops over years.  
- Structural changes; increased thickness of basement membrane  
- GFR increased 20-30% or normal  
- Blood pressure within normal  
- Albumin excretion most of patients are within normal and exercise test abnormal after years  
- This stage is reversible by blood sugar control.
Third Stage; Incipient stage [42]
- Structural changes not well studied.
- GFR still increased
- Blood pressure increased
- Albumin excretion increased 25ug/min each year

Fourth stage; Overt diabetic nephropathy [42]
- Characterized by pronounced proteinuria
- Structural changes; diffuse and nodular glomerulosclerosis and hyalinosis of arteriolar
- GFR decreased
- Albumin excretion /progressive macroproteinuria
- Blood pressure increased
- The antihypertensive treatment retards the progression, aim of BP (140/85-90).

Fifth stage; End stage renal failure [42]
- Characterized by glomerular closure
- GFR <10ml/min
- Blood pressure high
Not reversible by blood sugar control.

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>GFR &gt; or = 90ml/min</th>
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<tbody>
<tr>
<td>Stage 2</td>
<td>GFR 98-60ml/min</td>
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<tr>
<td>Stage 3</td>
<td>GFR 59-30ml/min</td>
</tr>
<tr>
<td>Stage 4</td>
<td>GFR 29-15ml/min</td>
</tr>
<tr>
<td>Stage 5</td>
<td>GFR&lt;15ml/min</td>
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</table>

Table 5: Stages of diabetic nephropathy [43]

Detection of microalbuminuria/ screening

Screening/ diagnosis

T2DM patients should be screened for microalbuminuria at the time of diagnosis [44] as 7% of them will already have developed it [45].

The recommended first screening for T1DM patients is 5 years from diagnosis [44], however if the glycaemic control is poor, it should be performed 1 year after diagnosis [44, 46].

In the absence of microalbuminuria screening should be repeated annually for both T1DM and T2DM patients [44].

The gold standard ADA recommended method is to measure albumin in a spot urine sample (either morning or random one) (41). The results are expressed as urinary albumin concentration (mg/l) or as urinary ACR (mg/g or mg/mmol) [47].

The cut off value of 17mg/l in a random urine specimen has 100% sensitivity and 80% specificity for diagnosing microalbuminuria [48].

The abnormal result must be confirmed in two out of three samples collected over 3 to 6 months period due to variability in daily urine albumin excretion [44].

<table>
<thead>
<tr>
<th>Conditions increasing UAE</th>
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<tbody>
<tr>
<td>Urinary Tract Infections</td>
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<tr>
<td>Haematuria</td>
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<tr>
<td>Acute febrile illness</td>
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<tr>
<td>Vigorous exercise</td>
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<tr>
<td>Short-term pronounced hyperglycaemia</td>
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<tr>
<td>Uncontrolled hypertension</td>
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<tr>
<td>Heart failure</td>
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Table 6: Conditions increasing urine albumin excretion [49]
Prevent nephropathy; optimal glycaemic control, lifestyle, blood pressure and lipids control

Early management of hyperglycemia, hypertension, dyslipidemia and smoking in diabetic patients, is very important to prevent or delay the progression of DN [51].

Lifestyle measures include salt restriction, to stop smoking, exercise and maintaining an ideal weight [52].

Improvement of glycemic control slows the progression and the onset of microalbuminuria in both T1DM and T2DM. The HbA1c target should be < 6.5 % and the greatest benefit comes from early and better control [52].

Uncontrolled BP leads to progression of proteinuria and deterioration of renal function. The recommended target BP is below 130/80 according to NICE guidelines in both T1DM and T2DM. ACEIs or ARBs are the first drugs of choice and both can slow the progression of DN [52].

Target LDL-C < 100 mg/dl and < 70 mg/dl in diabetic patient and diabetic with CVD respectively. Collaborative Atorvastatin Diabetes Study (CARDS) revealed a great reduction of CVD and suggested that all DM patients should be on statins [51].

Management of microalbuminuria [53]

Management of microalbuminuria involves intensive glycaemic control which reduces the progression of the UAE in both T1DM & T2DM patients.

Blood pressure control reduces the progression and development of the albuminuria. Treatment with ACEI or ARB’s play a role by reducing the intraglomerular pressure and decreases the hyperfiltration, delays deterioration of the eGFR along with reduction of the BP. Doses are increased to maximum tolerated and approved dose with continuous monitoring of the creatinine and potassium level. Monitoring for UAE to assess treatment response and disease progression is required.

Other classes of antihypertensive therapy such as the Ca channel blockers, beta blockers and diuretics are used along with ACEI or ARBs for BP control.

Protein diet restriction delays the progression of albuminuria and delays the deterioration of eGFR.

Management of macroalbuminuria [53]

Management of macroscopic albuminuria involves optimization of glucose control, blood pressure, lipids and maintenance of ideal body weight through therapeutic life style modification/ reinforcement together with drug adjustment if needed, to achieve required target. Vaccination for HBV should be anticipated.

Monitoring for eGFR every 6 month for deterioration and complications of Chronic kidney disease complications when eGFR< 60ml/min/1.73m2; Hb, Urea, creatinine, potassium level, HC03-, Ca2+, PO2-, se albumin, and at least yearly parathyroid hormone level, vit D level.

Adjustment for drug dose is required to achieve; target glycaemia, blood pressure, lipid control, smoking cessation therapy when indicated and avoidance of hypotension.

Counseling regarding diet: Advise salt restriction (< 3-5g/d, protein, potassium and phosphate restriction as renal deteriorates. The possibility of renal replacement therapy if renal parameters are worsening, the importance of regular follow-up and nephrologist visit should be addressed.
Avoid medications that may deteriorate renal function or stopping medications that are contraindicated according to the stage of renal failure.

Management of different stages of diabetic nephropathy/ Nephrologist referral

There should be a multidisciplinary approach to managing patients with diabetic nephropathy, focusing not only on slowing progression but also on modifying cardiovascular risk factors [52]. DCCT trial showed that intensive management of diabetes could delay microalbuminuria and slow the progression of microalbuminuria to proteinuria [54].

Stage 1; No proteinuria

- **Lifestyle Modification**
  - Dietary control of CHO and fats and salt restriction.
  - Exercise and stop smoking
  - Glycemic Control: Target HbA1c <7 as improved glycemic control slows the onset of microalbuminuria in both type 1 and type 2 diabetes [55, 56].
  - BP: Maintain BP below 135/85
  - Lipids: Statins if lipid targets are not achieved [57, 58].

Stage 2; Microalbuminuria

- Monitor urinary proteins and 24 hrs creatinine clearance
- Add ACE inhibitors or an ARB. Current guidelines recommend that normotensive patients with microalbuminuria should also be treated with an ACEI [59].

Stage 3; Proteinuria

- All the above plus aim BP <125/75 mmHg and low protein diet

Stage 4; declining kidney function

- Prepare for dialysis or renal transplant

Stage 5; CKD

- Dialysis - Haemo or Peritoneal dialysis
- Transplantation; Kidney or Pancreas-Kidney [60].

Referral to Nephrologist

Referral to a nephrologist should be considered if the GFR is steadily declining or is already below 60 to 70 mL/min/1.73m2 or serum creatinine >150mmol/l [61]. Difficult to control BP, hyperkalemia, or rising creatinine level on an or serum creatinine >150mmol/l steadily requires referral to Nephrologist

**Prognosis of Diabetic nephropathy**

Diabetic nephropathy (DN) causes considerable morbidity and mortality. In the US and Europe, DN is the major cause of end-stage renal disease (ESRD) [63]. Both T1DM and T2DM develop ESRD, but larger proportions affected are those with T2DM, due to the increase in prevalence of T2DM. In T1DM with nephropathy, ESRD accounts for 59-66% of mortality. The growing prevalence of ESRD in Europe seen in type 1 diabetics with proteinuria is 50%, while in Type 2 diabetics it is 3-11%, in a period of 10 years following the start of proteinuria. The prediction of morbidity and mortality in DN is by Proteinuria. The mortality rate was small and constant in those diabetics who had no proteinuria while those diabetics with proteinuria had 40 times increase in death rate. In a study done in Germany, the chances of surviving for 5 years, in older type 2 diabetics was below 10%, and around 40% in young type 1 diabetics [64, 65].

The prognosis of DN in both T1DM and T2DM has been improving due to the targeted approach, timely recognition of DN and managed appropriately according to the stage.

**Conclusion**

Diabetic nephropathy is one of the commonest microvascular complications of diabetes and is associated with other diabetes related microvascular diseases. It affects 20-40% of people with diabetes and is a leading cause of ESRD [53]. Interplay of multiple environmental and genetic factors determines its development and progression, the most important of these is uncontrolled hyperglycaemia and hypertension. The hallmark of DN is the presence of microalbuminuria in the early stages which progresses over a variable period to macroalbuminuria and deterioration of the renal function to ESRD requiring RRT.

Adequate control of blood glucose and hypertension are the mainstay of management in addition to life style interventions similar to those required to manage renal failure due to causes [52].

**Competing interests**

The authors declared no competing interests regarding the publication of the paper.

**Authors Contribution**

Sumon Rahman Chowdhury contributed to the study conception and design, supervised the study, conducted data analysis and wrote the manuscript. Reza Haider Chy and Tasnua Tanzil planned the study and prepared the first draft proposal. Alam Md. Sharif contributed to the data analysis, supervised the study and critically revised the manuscript.

**References**


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