Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in most Western societies.

It is also a common cause of ESRD in Nepal.

In most Western countries, DN is the leading cause of ESRD.

According to the US Renal Data System (2012), DN was the most common cause of ESRD.

49% patients admitted for renal replacement therapy (RRT) were diabetics.

More than >90% of patients suffering from Diabetes & ESRD were type 2 diabetes.
PATHOGENESIS OF DIABETIC NEPHROPATHY

- GENETIC FACTORS.
- HEMODYNAMIC CHANGES.
- RENAL HYPERTROPHY.
- MESANGIAL EXPANSION & NODULE FORMATION.
- INFLAMMATION & IMMUNE MECHANISM.

PATHOGENESIS OF DIABETES NEPHROPATHY

- MECHANISM OF PROTEINURIA.
- TUBULOINTERSTITIAL FIBROSIS & TUBULAR ATROPHY.
- HYPERGLYCEMIA & DIABETIC NEPHROPATHY.
  - ADVANCED GLYCATION END PRODUCTS.
  - PROTEIN KINASE C.
  - POLYOL PATHWAY.
- RENIN ANGIOTENSIN & ALDOSTERONE PATHWAY.

PATHOGENESIS OF DIABETIC NEPHROPATHY

- GENETIC FACTORS: The risk of nephropathy is strongly determined by polygenic Factors.
- Approximately 30% to 40% of patients with either type 1 or type 2 diabetes will ultimately develop nephropathy.
- The risk for development of DN is equal in type 1 and type 2 diabetes.

PATHOGENESIS OF DIABETIC NEPHROPATHY

- The prevalence of nephropathy varies according to race & ethnicity.
- Prevalence is relatively high in African Americans, Native Americans, Mexican Americans, Australian aborigines, and urbanized Indo-Asian immigrants in the United Kingdom compared with Caucasians.

PATHOGENESIS OF DIABETIC NEPHROPATHY

- Familial clustering of DN has been reported in both type 1 and type 2 diabetes among both Caucasian and non-Caucasian populations.
- Genome scans for susceptible chromosomal regions for DN has identified several susceptibility loci, for example, on chromosomes 3q, 7p, and 18q.

MECHANISM OF PROTEINURIA

- Net reduction in negatively charged heparin sulfate.
- Podocytopathy:
  - Biopsies in patients with DN have documented a correlation between the degree of proteinuria and podocyte pathology, specifically the width of the foot processes.
  - Low Nephrin (permeability controlling protein).
  - The transcription of nephrin is suppressed by Ang II and restored by inhibitors of RAS.
MECHANISM OF PROTEINURIA CONTD.

- Apoptosis of podocytes (triggered by Angiotensin II and TGF-β).
- Reduced activated protein C (APC). (APC formation inhibits podocyte apoptosis, in Diabetic mice).
- Lack of adiponectin (may further contribute to proteinuria).

PROTEIN KINASE C (PKC) PATHWAY

- Many of the adverse effects of hyperglycemia have been attributed to activation of PKC.
- PKC activity is increased in the retina, aorta, heart, and glomeruli of diabetic animals.
- PKC-β-selective inhibitor ameliorated glomerular hyperfiltration, albuminuria, and renal TGF-β overexpression as well as extracellular matrix accumulation.

ADVANCED GLYCATION ENDPRODUCTS (AGEs) PATHWAY

- Chronic hyperglycemia lead to nonenzymatic glycation of amino acids & proteins (Maillard or browning reaction).
- Over time, these products undergo rearrangement, including cross-linking, to become irreversible AGES. Ultimately, both circulating and tissue proteins as well as lipids and nucleic acids may thus become glycated.
- The concentration of AGES is increased in the sera of DN patients. AGES have also been localized to diabetic glomeruli by immunohistochemistry.

ADVANCED GLYCATION ENDPRODUCTS (AGEs) PATHWAY CONTD.

- AGES bind to a variety of cell types, including macrophages and mesangial cells.
- They mediate a variety of cellular actions, including expression of adhesion molecules, cell hypertrophy, extracellular matrix synthesis, epithelial to mesenchymal transition, and inhibition of NO.
- AGES injected in vivo induce albuminuria and glomerulosclerosis.
- Administration of aminoguanidine, an inhibitor of AGE formation, to animals with diabetes reduces AGE deposition, mesangial matrix expansion, and albuminuria.
Diabetes Nepal

RENIN – ANGIOTENSIN & ALDOSTERONE SYSTEM

- ACEI & ARB Retard the progression of DN.

  Proved by Studies in patients with type 1 and type 2 diabetes.

- Plasma renin activity is low in DN, it is inappropriate in relation to increased extracellular volume and exchangeable sodium, suggesting activation of the RAS.

- Activation of the intrarenal RAS plays a critical role in the development of DN. Proved in Animal experiments.

RENIN – ANGIOTENSIN & ALDOSTERONE SYSTEM CONTD.

- Ang II mediates cell proliferation, hypertrophy, matrix expansion, and cytokine (TGF-β, VEGF) synthesis through its nonhemodynamic effects.

- Aldosterone accelerates progression in renal damage models independent of Ang II. Aldosterone synthesis is stimulated in DN, and it stimulates the synthesis of other proinflammatory and profibrogenic cytokines (MCP-1, TGF-β).

- Other vasoactive agents may also be involved in the pathogenesis of DN, including alteration of systemic or intrarenal production of endothelin, NO, the kallikrein-kinin system, and natriuretic peptides.

To establish the diagnosis of DN, the following tests should be done:

- Measurement of urinary albumin or protein.
- Measurement of serum creatinine concentration and estimation of GFR.
- Measurement of BP.
- Ophthalmologic examination.

The diagnosis of DN is based on the detection of proteinuria.

In addition, most patients will also have hypertension and retinopathy.

To establish the diagnosis of DN, the following tests should be done:

- Measurement of urinary albumin or protein.
- Measurement of serum creatinine concentration and estimation of GFR.
- Measurement of BP.
- Ophthalmologic examination.
The detection of urinary albumin is a specific indicator of DN.

PREVENTION OF DIABETIC NEPHROPATHY

PREVENTION IS BETTER THAN CURE

- Prevention and early detection of nephropathy improve patient outcome.
- General measures for prevention of DN include glycemic control and blood pressure control.
- Treatment of dyslipidemia, modification of diet and lifestyle, including physical activity and weight reduction as appropriate and smoking cessation, can significantly lower the CV risks.

GLYCEMIC CONTROL

- In type 1 diabetic patients, strict glycemic control ↓ the risk for microalbuminuria. DCCT, compared the effects of intensive glucose control with conventional treatment on the development and progression of the long-term complications of type 1 diabetes.
- During a 9-year period, patients receiving intensive therapy (mean HbA1c 7%) had a 35% to 45% lower risk for development of microalbuminuria compared with the control group (mean HbA1c 9%).
- Renoprotection can persist even after a return to less intensive therapy.

Figure 20.2 Diabetes Control and Complications Trial. Intensive glucose control was associated with a decreased risk for the subsequent development of microalbuminuria in type 1 diabetes. (Modified from reference 9.)

Figure 29.19 Urinary albumin excretion rate (UAE). Levels of 24 hour and overnight UAE are diagnostic for microalbuminuria and overt diabetic nephropathy.

Several major studies have demonstrated a lower risk of nephropathy with stricter glycemic control in type 2 diabetes. Kumamoto study found a 60% reduction in the rate of microalbuminuria in relatively young nondiabetic type 2 diabetic patients receiving intensive glycemic treatment (HbA1c 7.1%) compared with conventional treatment (HbA1c 9.4%).

In the U.K. Prospective Diabetes Study (UKPDS) trial, newly diagnosed patients with type 2 diabetes were randomly assigned to intensive management (HbA1c 7.0%) with a sulfonylurea or insulin or to conventional management (HbA1c 7.9%) with diet alone. After 9 years of intensive therapy, relative risk reduction for the development of microalbuminuria was 24%.

Several major studies have demonstrated a lower risk of nephropathy with stricter glycemic control in type 2 diabetes.
**Diabetes Nepal 2013**

**GLYCEMIC CONTROL**

- **Metformin** has been used in low doses in patients with GFR as low as 30 to 60 ml/min. It should not be used at a GFR below 30 ml/min.
- As renal function can deteriorate abruptly, it is better to avoid metformin once serum creatinine concentration rises above 1.5 mg/dl (132 μmol/l) in men and above 1.3 mg/dl (117 μmol/l) in women.
- **Insulin secretagogues** (sulfonylurea and meglitinides) can be associated with hypoglycemia, with occurrence rates reported from 10% to 35%.
- These can be severe and long lasting in those receiving sulfonylureas, requiring hospitalization for treatment.

- **Glycosidase inhibitors** are contraindicated in renal failure.

- **Insulin regimens** are the most commonly used to control glycemia in CKD. The same is true for detemir, but so far no clinical data on its use in CKD patients are available.

- **Insulin secretagogues** can be severe and long lasting in those receiving sulfonylureas, requiring hospitalization for treatment.

- **Insulin regimens** are the most commonly used to control glycemia in CKD. However, the half-life of insulin increases as CKD progresses, so there is a risk for hypoglycemia.

- **Glycosidase inhibitors** are short acting (because they interfere with the absorption of sucrose or starch) so the patients taking these agents need to use dextrose tablets or glucose powder to treat hypoglycemia.

- **Thiazolidinediones** are associated with weight gain [partly due to fluid retention & also due to nonfluid gains. In patients at risk for congestive heart failure, these should be avoided. There is also concern about increased bone fracture rates in patients using thiazolidinediones, which could potentiate CKD-related bone disease.

- **Multi daily injection**, by which insulin doses can be more closely regulated, would be appropriate choice. However, ideal insulin therapies remain undefined in CKD.

**Recommended Drug Treatment of Diabetes at the Various CKD Stages**

<table>
<thead>
<tr>
<th>GFR</th>
<th>Metformin</th>
<th>Meglitin</th>
<th>Sitagliptin, Exenatide</th>
<th>Goepirinid</th>
<th>Glitazons</th>
<th>Repaglinide</th>
<th>Gliptin</th>
<th>Rosiglitazone</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>60m/min</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>30m/min</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Figure 21.4** Recommended drug treatment of diabetes at the various CKD stages. GFR, Glomerular filtration rate; insulin, rapid-acting human insulin.

**Management of Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria/Normal creatinine</td>
<td>Optimize glycemic control (target HbA1c &lt;7%)</td>
</tr>
<tr>
<td>Normoalbuminuria/Hypertension</td>
<td>Consider ACE inhibitor or ARB as antihypertensive agent (target BP &lt;130/80 mm Hg); deny sodium restriction unless +ve for dialysis therapy</td>
</tr>
<tr>
<td>Microalbuminuria/ Hypertension</td>
<td>Start ACE inhibitor or ARB; thiazide dose as tolerated and normalize albuminuria</td>
</tr>
<tr>
<td>Microalbuminuria/ Hypertension</td>
<td>Thiazide ACE inhibitor or APE as tolerated; consider addition of selective aldosterone receptor antagonist (e.g., spironolactone, eplerenone), non-hydration calcium channel blockers (e.g., diltiazem, verapamil), direct renin inhibitors (e.g., aliskiren); dietary sodium restriction +/- loop or thiazide diuretics; treat to normalize albuminuria and BP &lt;130/80 mm Hg</td>
</tr>
</tbody>
</table>
**Management of Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt proteinuria</td>
<td>Continuous management as above with aggressive BP control to minimize cardiovascular risk and consider aspirin therapy, statin therapy, early proteinuria, weight reduction as appropriate</td>
</tr>
<tr>
<td>Declining glomerular filtration rate (GFR)</td>
<td>Provide nutrition counseling regarding sodium, protein, and phosphorus restriction; avoid protein-calorie restriction; prepare for dialysis or transplantation when GFR &lt; 50 ml/min</td>
</tr>
</tbody>
</table>

**TREATMENT OF HYPERTENSION**

- Hypertension is present in about 40% of type 1 and 70% of type 2 diabetic patients with normoalbuminuria.
- Higher blood pressure level is associated with an increased risk for the development of nephropathy; and in patients with established nephropathy, it is associated with more rapid progression and increased risk of kidney failure.
- The NKF, JNC7, & ADA recommend a target blood pressure value of below 130/80 mm Hg in diabetic patients.

**RENIN ANGIOTENSIN ALDOSTERONE BLOCADE IN DN**

- In diabetic patients with established DN, RAS blockade with ACEI or ARBs confers renoprotection that is independent of blood pressure reduction.
- Many studies have demonstrated a beneficial effect of ACE inhibitors and ARBs in retarding progressive renal disease.
- Plasma aldosterone levels are elevated in a subset of patients despite ACE inhibitor and ARB therapy (also known as aldosterone escape or aldosterone breakthrough).
- Aldosterone cause retention sodium and excretion of potassium and magnesium as well as promotes tissue inflammation and fibrosis.

**RAS BLOCADE IN TYPE 1 DIABETES**

- In type 1 diabetics with microalbuminuria, ACE inhibitors reduce the risk of progression to overt nephropathy. In a meta-analysis of 12 placebo-controlled trials in 696 normotensive patients with type 1 diabetes and microalbuminuria treated with ACE inhibitors, the majority for more than 2 years, treatment was associated with a 60% reduction in progression to macroalbuminuria and a threefold increase in regression to normoalbuminuria.

**Table:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CKD Stages</th>
<th>CKD 3 and 4F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic control</td>
<td>≥4.5–7.0 mmol/L</td>
<td>≥7.0–9.0 mmol/L</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>130/80 mm Hg</td>
<td>130/80 mm Hg</td>
</tr>
<tr>
<td>Lipid treatment</td>
<td>LDL cholesterol ≤100 mg/dl</td>
<td>≤100 mg/dl</td>
</tr>
<tr>
<td>Anticoagulation treatment</td>
<td>HbA1c ≤7.0%</td>
<td>≤7.0%</td>
</tr>
<tr>
<td>Vitamin D supplement</td>
<td>≥25(OH)D ≤20 ng/ml</td>
<td>≥20 ng/ml</td>
</tr>
</tbody>
</table>

*Figure 38.1 Management of type 1 diabetes. A similar strategy can be used in patients with type 2 diabetes with increased emphasis on management of cardiovascular risk factors. In considering the manage of type 1 diabetes, the management steps are similar to type 2 diabetes.*
**RAS Blockade in Type 2 Diabetics**

- In type 2 diabetics, there are more data available on the renoprotective effect of ARBs compared with ACE inhibitors. In the stage of microalbuminuria, the IRMA 2 study showed that the ARB irbesartan reduces progression to overt nephropathy by 70% in hypertensive type 2 diabetic patients during a 2-year.
- In the MARVAL trial, the ARB valsartan (90 mg/day) produced a greater reduction in UAE than did amldipine (44% versus 8%) with the same degree of blood pressure reduction, suggesting that the antiproteinuric effect of ARBs is blood pressure independent.

**ACE & ARB Combination**

- ACE inhibitors and ARBs have been used simultaneously for therapeutic synergy in patients with nondiabetic renal disease (COOPERATE trial).
- In both type 1 and type 2 diabetics with nephropathy, results of several earlier small trials suggested that the combination of an ACE & an ARB is more effective in reducing BP and proteinuria than is either drug alone. However, there were no data from these trials on the effect of combined therapy on kidney disease progression.

**Diuretics**

- Despite insufficient controlled evidence, β-blockade with these novel blockers appears to be useful because of the extremely high CV risk in diabetic patients with nephropathy.
- Thus, patients receiving ACE inhibitors or ARBs should be instructed to take a low-sodium diet (e.g., less than 2 g of sodium/d).
- The antiproteinuric effects of RAS blockade are enhanced by sodium restriction.

**Other Antihypertensive Agents Used in DN**

- Nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) have been shown in some studies to have antiproteinuric effects.
- These include diltiazem (44% versus 8%) with the same degree of blood pressure reduction, suggesting that the antiproteinuric effect of ARBs is blood pressure independent.

**Dihydropyridine calcium channel blockers (e.g., nisoldipine, nifedipine, amlodipine) may be used as additional antihypertensive agents, but they have not been shown to reduce albuminuria or to slow the progression of renal disease.

**ACE** & **ARB Combination**

- The recent ONTARGET study, which included diabetic and nondiabetic patients with CV risk, failed to show improved CV outcomes from a combination of an ACE & an ARB.
- Instead, it showed increased renal functional decline, a trend toward an increase in the development of ESRD.
- ACEI & ARBs have also been studied in combination with aldosterone receptor antagonists (e.g., spironolactone, eplerenone) and a direct renin inhibitor (aliskiren); further reductions in proteinuria have been reported with these combinations compared with the ACEI or ARB alone.

**Other Antihypertensive Agents Used in DN**

- Nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil). Dihydropyridine calcium channel blockers (e.g., nisoldipine, nifedipine, amlodipine) may be used as additional antihypertensive agents, but they have not been shown to reduce albuminuria or to slow the progression of renal disease.

**B-blocker**

- Classic β-blockers have adverse metabolic effects and are therefore not recommended in diabetics, but this is no longer true for the modern β-blockers carvedilol and nebivolol.
- Despite insufficient controlled evidence, β-blockade with these novel blockers appears to be useful because of the extremely high CV risk in diabetic patients with nephropathy.
OTHER ANTIHYPERTENSIVE AGENTS USED IN DN

DIRECT RENIN INHIBITION
- Aliskiren is the first orally active direct renin inhibitor approved for treatment of hypertension.
- In the AVOID trial, the addition of aliskiren produced greater reduction in UAE compared with placebo in type 2 diabetic patients with hypertension & nephropathy receiving the maximum recommended dose of losartan (100 mg daily).
- The major side effects of aliskiren are, hyperkalemia, hypotension, & reduced GFR.


TREATMENT OF DYSLIPIDEMIA
- Patients with DN have dyslipidemia, characterized by low levels of HDL cholesterol, high TG levels, & a shift from larger toward smaller LDL cholesterol.
- Dyslipidemia in diabetic patients may contribute to the development of glomerulosclerosis and progressive renal disease.


Elevated TG was independently associated with albuminuria in type 2 diabetic patients (UKPDS).

TREATMENT OF DYSLIPIDEMIA

NON PHARMACOLOGIC INTERVENTION
- Dietary protein restriction may alleviate uremic symptoms in patients at or approaching ESRD.
- Small trials have shown low-protein diet (0.8 g/kg/d) to significantly reduce proteinuria with an increase in plasma albumin in macroalbuminuric type 2 diabetic patients.


Nutritionist counseling is advised for all patients with advanced CKD to avoid protein-calorie malnutrition before renal replacement therapy.

All patients with DN should be given counseling on salt, potassium, and phosphate restriction as well as choice of carbohydrates and fats.
**NON PHARMACOLOGIC INTERVENTION**

**LIFE STYL MODIFICATION**

- Lifestyle modifications such as smoking cessation and weight reduction can provide additive renal benefits and lower the risk of CV events in patients with established DN.

- There is evidence that smoking cessation ameliorates progression of microalbuminuria to macroalbuminuria and improves renal prognosis.


**NEWER TREATMENT DN**

- Peroxisome proliferator-activated receptors (PPAR). Thiazolidinediones (e.g., pioglitazone, rosiglitazone) are PPARγ agonists with insulin-sensitizing actions.

- Pioglitazone in combination with the ARB losartan seems to offer greater renoprotection than does losartan alone in short-term studies.

- There is evidence that smoking cessation ameliorates progression of events in patients with established DN.

- Several other agents, including avosentan (an endothelin A receptor blocker), protein kinase C inhibitors, fenofibrate, pirfenidone, mycophenolate mofetil (MMF), and fish oil, have been evaluated for proteinuric renal disease including DN.
