Renal Disease in Diabetes

Dr Parul Nigam

Staff Specialist, Endocrinology

The Townsville Hospital

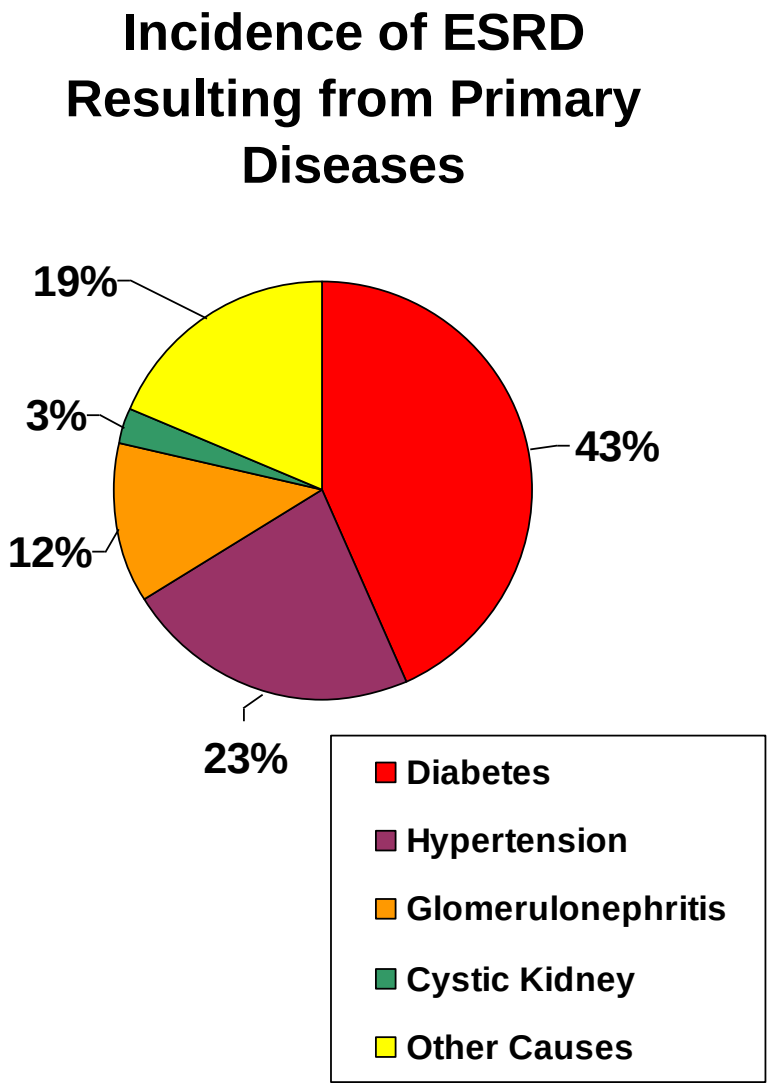
Mater Health Services, Townsville

Why is it important

- Major cause of early death in DM
- Major cause of amputation
- RRT (dialysis) is arduous for the patient and expensive
- Nephropathy is largely avoidable (or can be delayed)

Diabetic Nephropathy

- Over 40% of new cases of end-stage renal disease (ESRD) are attributed to diabetes.



Definition

Diabetic nephropathy is a clinical syndrome characterized by the following:

- Persistent albuminuria (>300 mg/d or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure

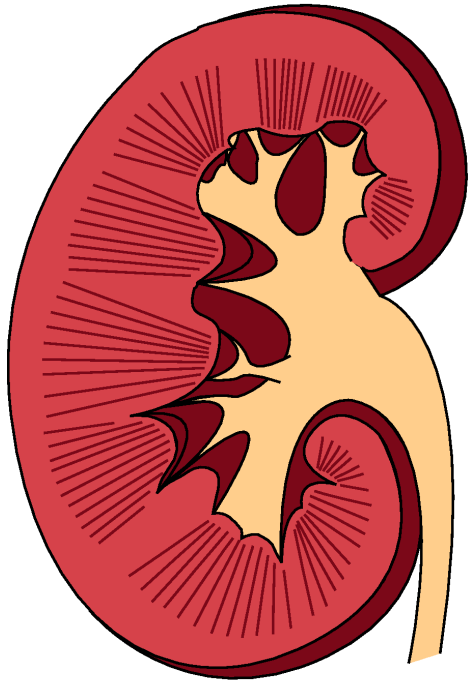
	Rate of Decline in Glomerular Filtration Rate (mL/min/year)	
	Type I	Type II
Normoalbuminuria	1.2 - 3.6	0.96
Microalbuminuria	1.2 - 3.6	2.4
Overt Nephropathy	9.6 -12	5.4 - 7.2

Five Phases of Kidney Disease

Stage 1: Hyperfiltration, or an increase in glomerular filtration rate (GFR) occurs. Kidneys increase in size.

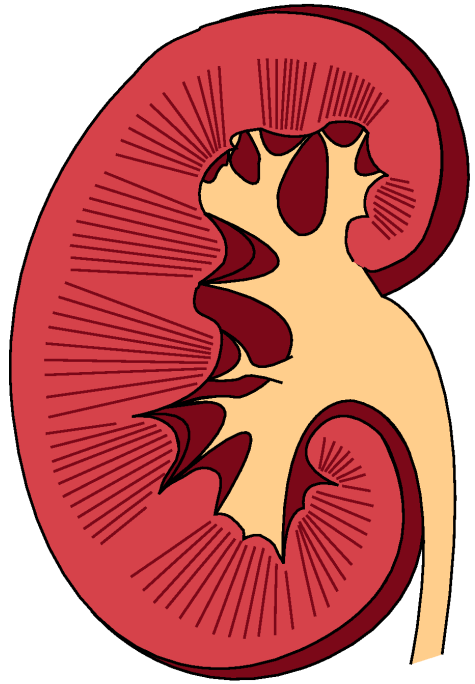
Stage 2: Glomeruli begin to show damage and microalbuminurea occurs.

Stage 3: Albumin excretion rate (AER) exceeds 200 micrograms/minute, blood Creatinine and urea rise. Blood pressure may rise during this stage.



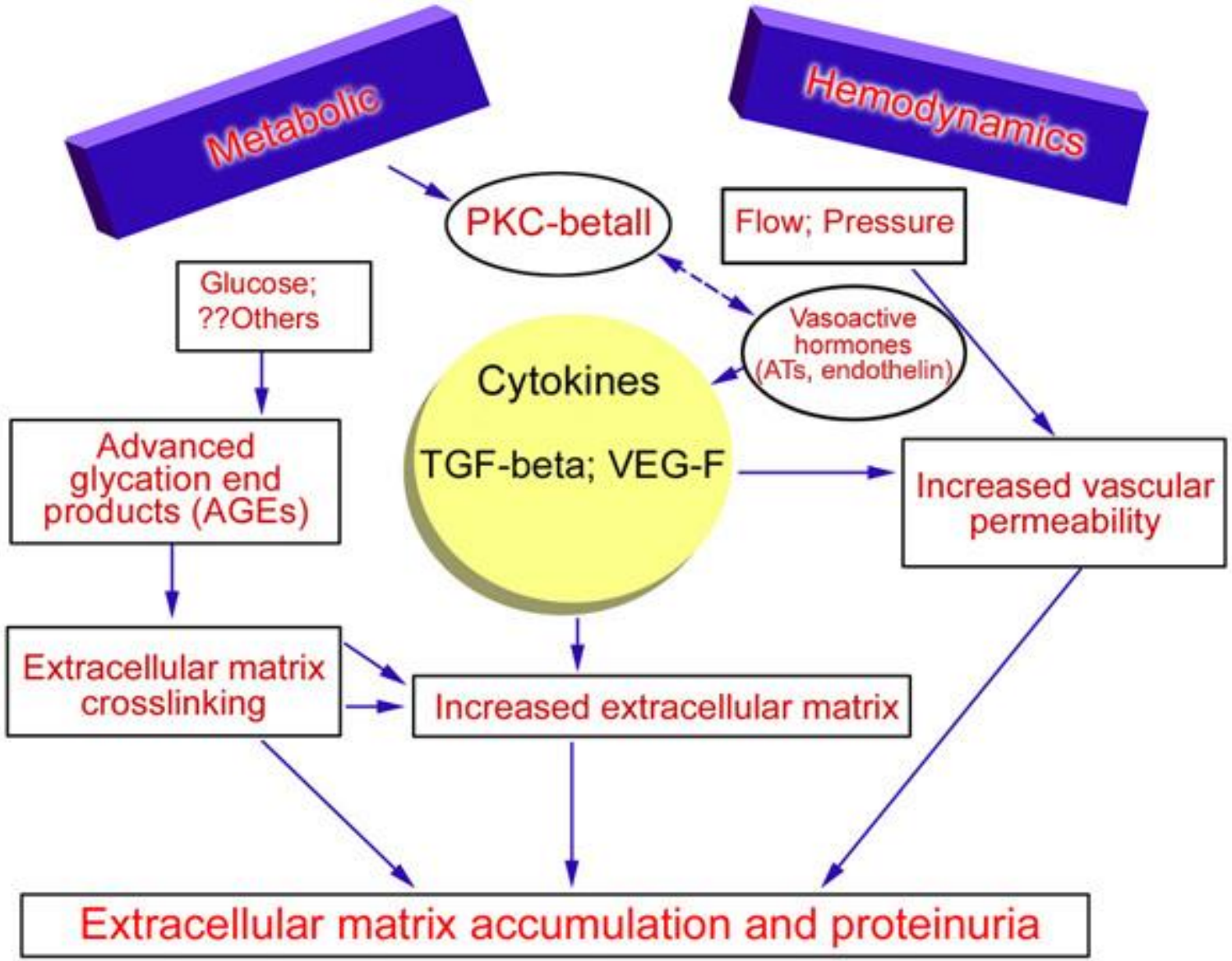
Five Phases of Kidney Disease (con't.)

Stage 4: GFR < 75 ml/min, large amounts of protein pass into the urine, and high blood pressure almost always occurs. Creatinine and urea in the blood rise further.

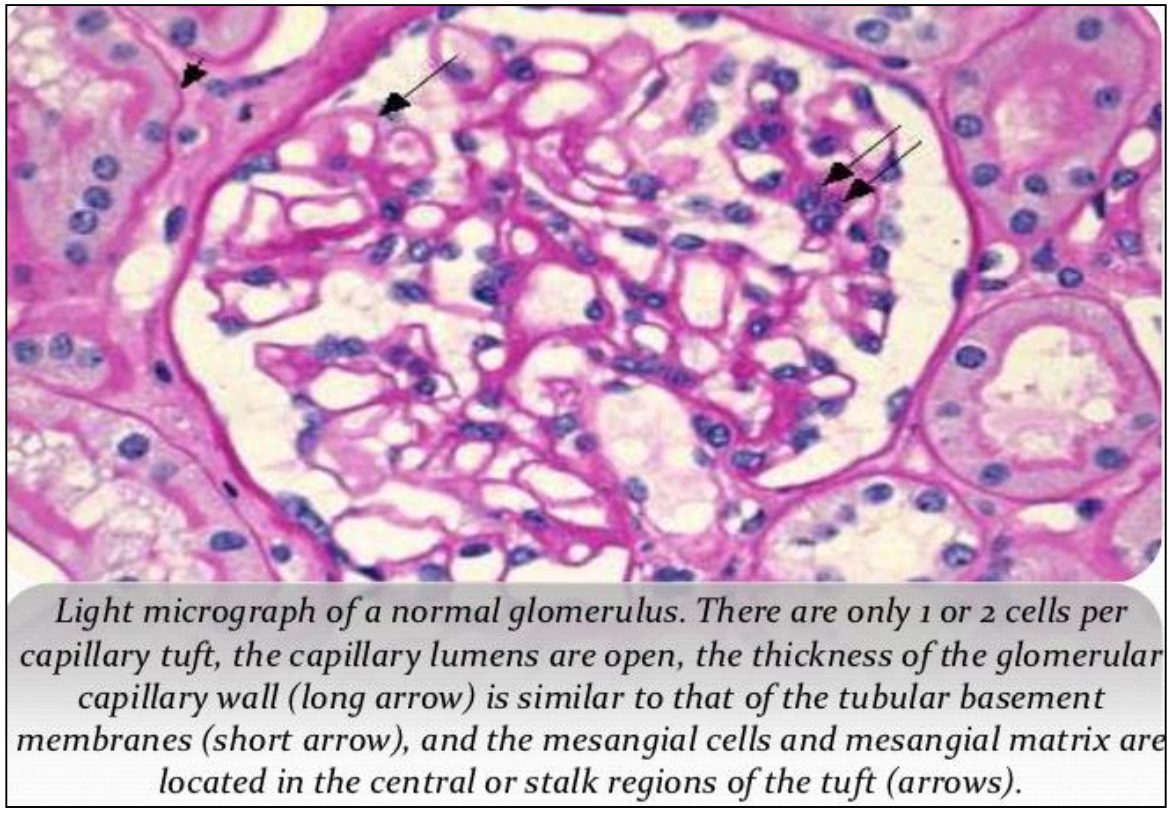


Stage 5: Kidney failure, or end stage renal disease (ESRD). GFR is less than 10 ml/min.

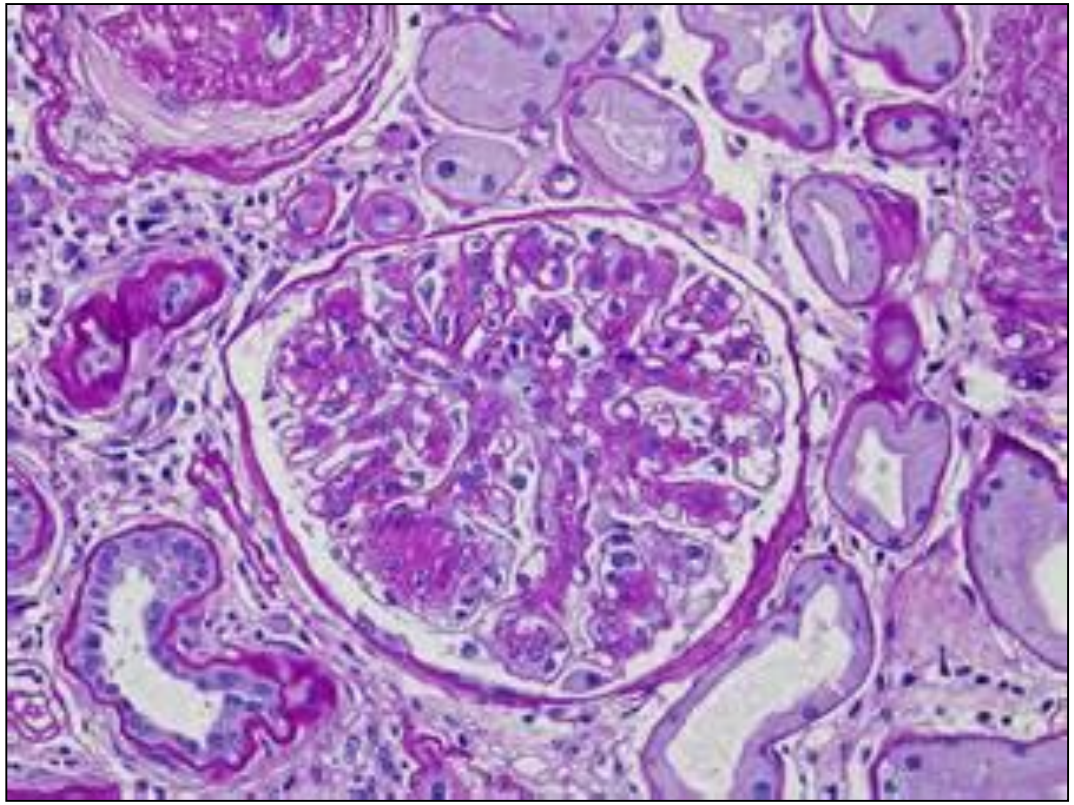
The average length of time to progress from Stage 1 to Stage 4 kidney disease is 17 years for a person with type 1 diabetes. The average length of time to progress to Stage 5, kidney failure, is 23 years.


Metabolic
Hemodynamics
PKC-betaII
Flow; Pressure
Glucose;
??Others
Vasoactive
hormones
(ATs, endothelin)
Cytokines
TGF-beta; VEG-F
Advanced
glycation end
products (AGEs)
Increased vascular
permeability
Extracellular matrix
crosslinking
Increased extracellular matrix
Extracellular matrix accumulation and proteinuria

Normal Kidney



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

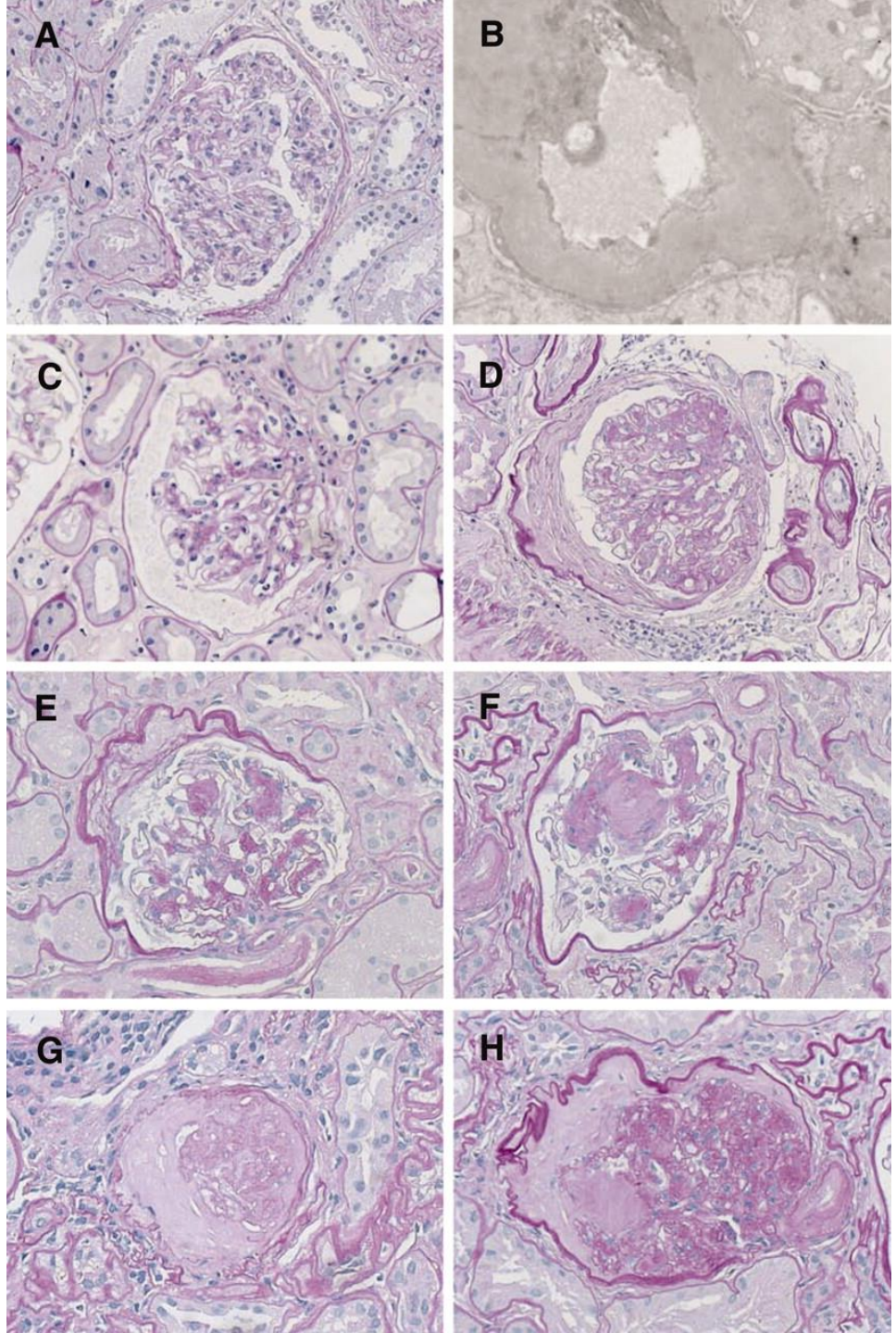


A and B Glomerulus showing only mild ischemic changes

C, D Class II glomeruli with mild and moderate mesangial expansion, respectively.

E and F Kimmelstiel–Wilson lesion.

G is an example of glomerulosclerosis that does not reveal its cause



Interpretation of results - eGFR

Stage	Description	GFR
1	Kidney damage, N or ↑GFR	≥90
2	Kidney damage, mild ↓GFR	60-89
3A	Moderate ↓GFR	45-59
3B	Moderate ↓GFR	30-44
4	Severe ↓GFR	15-29
5	Kidney failure	<15 (or dialysis)

Who to test for renal disease?

- Diabetes (Type 1 & 2)
- Episode of acute kidney injury (AKI)
- Hypertension
- Cardiovascular disease
- Multisystem diseases
- Structural renal tract disease
- Family history CKD
- Incidental haematuria or proteinuria

Mortality/Morbidity

- Hugely increased
  - 5 yr survival 63% and 24% (under and over 65)
  - 29 yr old has a life expectancy of 13 yrs

- 45% Cardiovascular

Type 1 Vs Type 2

- Nephropathy in type Type 1 diabetes
  - Nearly always due to hyperglycaemia
  - Strong genetic predisposition
- Nephropathy in T2DM
  - More common
  - May be due to hyperglycaemia
  - But often due to other causes particularly inflammation
  - Frequently multi-factorial

Primary prevention

- Treat associated risk factors such as hyperlipidemia, smoking, and hypertension (BP < 130/80 Hg), Obesity
- Early detection and optimal management of diabetes, especially in the setting of family history of diabetes
- Avoidance of potentially nephrotoxic substances such as NSAIDs

General Management

- Salt restriction
  - Reducing dietary salt intake,phosphorus and potassium restriction in advanced cases
- Weight loss
- Bariatric surgery
- Smoking Cessation

General management

- Smoking cessation
- Drug history – stop nephrotoxins
  - IV contrast, NSAIDs
  - assess metformin
- Cardio-renal patients – severe CCF
- Weight, consider bariatric intervention

Specific management

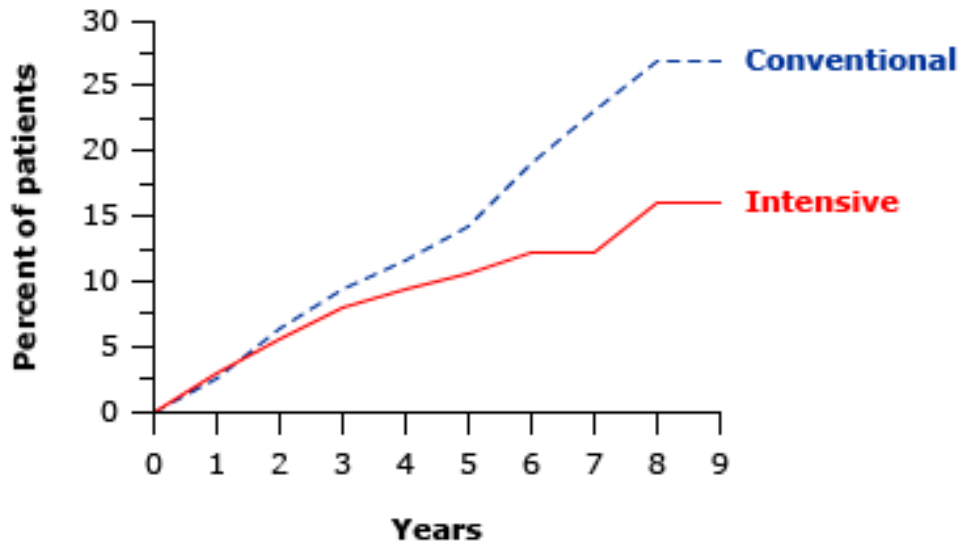
- Intensive combined therapy
- Target the many factors underlying disease
- Hyperglycaemia
- Hypertension
- Dyslipidaemia

Hyperglycaemia: Benefit of strict glycaemic control on kidney

Intensive therapy can :

- Reverse glomerular hypertrophy and hyperfiltration
- Delay development of elevated albumin excretion
- Stabilize or even reverse microalbuminuria
- Can slow progression of GFR decline

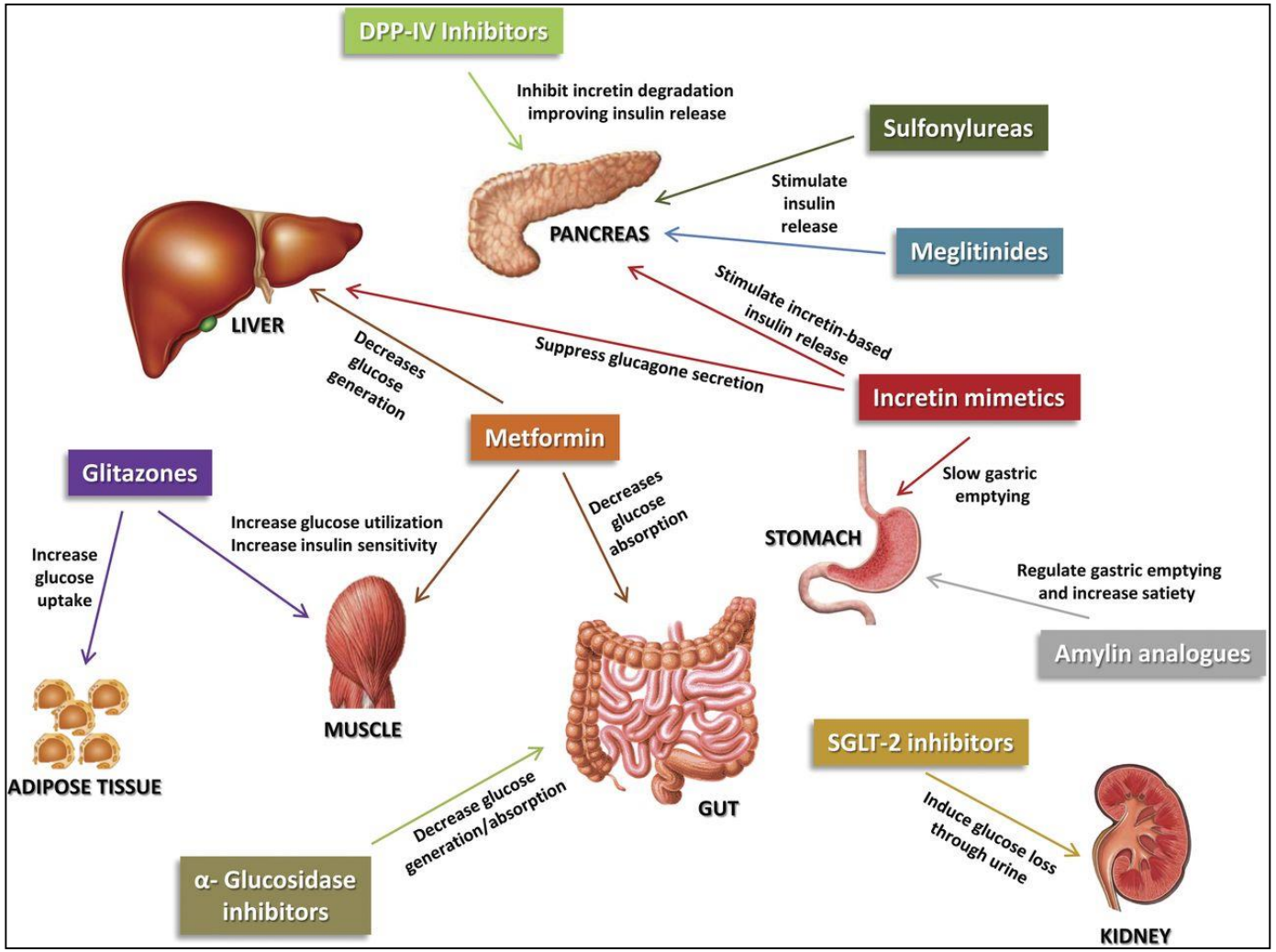
Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus



Cumulative incidence of moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years. There was an increasing benefit of intensive therapy over time ($p<0.04$).

Data from: The Diabetes Control and Complications Trial Research Group, N Engl J Med 1993; 329:977.

Main tissue and organ targets of glucose-lowering drugs.



Arnouts P et al. Nephrol. Dial. Transplant. 2013;ndt.gft462

NDT Nephrology Dialysis Transplantation

Drugs in diabetic nephropathy

1. **Metformin**
- not recommended with eGFR<30
2. **Sulphonylureas (Gliclazide)**
- Use with care in CKD – risk hypoglycaemia
3. **DPP4 inhibitors:** Sitagliptin (Januvia) Saxagliptin (Kombiglyze, Onglyza) Linagliptin (Trajenta)
4. **Sodium-glucose cotransporter 2 (SGLT2) inhibitors:** Forxiga, Jardiance
5. **GLP1 receptor agonists:** Exenatide (Byetta) Liraglutide (Victoza)

Insulin in diabetic nephropathy

- In advanced CKD - reduced degradation insulin and marked reduction in insulin requirement
- Reduce insulin dose with GFR<50 (~75%)
- Significantly reduce with GFR<10 (~50%)

Hemodialysis

- Procedure
  - A fistula or graft is created to access the bloodstream
  - Wastes, excess water, and salts are removed from blood using a dialyzer
  - Hemodialysis required approx. 3 times per week, each treatment lasting 3-5 hrs
  - Can be performed at a medical facility or at home with appropriate patient training

Hemodialysis (cont.)

- Hemodialysis Diet
  - Monitor protein intake
  - Limit potassium intake
  - Limit fluid intake
  - Avoid salt
  - Limit phosphorus intake
- Complications
  - Infection at access site
  - Clotting, poor blood flow
  - Hypotension

Peritoneal Dialysis

- Procedure
  - Dialysis solution is transported into the abdomen through a permanent catheter where it draws wastes and excess water from peritoneal blood vessels. The solution is then drained from the abdomen.
  - Three Types of Peritoneal Dialysis
    - Continuous Ambulatory Peritoneal Dialysis (CAPD)
    - Continuous Cycler-Assisted Peritoneal Dialysis (CCPD)
    - Combination CAPD and CCPD

Kidney Transplant

- Procedure
  - A cadaveric kidney or kidney from a related or non-related living donor is surgically placed into the lower abdomen.
  - Three factors must be taken into consideration to determine kidney/recipient match:
    - Blood type
    - Human leukocyte antigens (HLAs)
    - Cross-matching antigens

How Can You Prevent Diabetic Kidney Disease?

- Maintain blood pressure <130/80 mm/Hg
- Maintain preprandial plasma glucose5-7.2 mmol/l
- Maintain postprandial plasma glucose <10.0 mmol/l
- Maintain A1C <7.0% (tailored to patient)

Hypoglycaemia

In patients with diabetes and moderate to severe kidney dysfunction, the frequency of hypoglycemic episodes may be as much as five times that of patients without kidney disease.

- *Rabkin R, Ryan MP, Duckworth WC: The renal metabolism of insulin. Diabetologia 27:351 -357, 1984*

Key Messages

Be aware of renal function

Ensure patient is aware of Hypo management

Ensure that patient has ability to monitor blood glucose levels frequently

Case study 1 – MD 65 ♂

- Admitted for chest pain
- Initial assessment- NSTEMI
- BP = 160/98 mm Hg
- Creatinine = 121 µmol/L (eGFR 57ml/min)
- Proteinuria = 2+
- Other information: ?

Medication

- Metformin XR 2 gm
- Frusemide 40 mg OD
- Ramipril 10 mg OD
- Ibuprofen 200 mg PRN
- Aspirin 100 mg

Case study 1 – MD 65 ♂

On examination:

- Found to have an abdominal mass ? Liver
- Pedal oedema
- Systemic examination- NAD

Case study 1 – MD 55 ♂

- Ct with contrast for abdominal sweiing
- Coronary Angiogram tomorrow

What would you do next

- Withold Ramipril?
- Withold Ibuprofen ?
- Whithold Aspirin?
- Withold Metfromin?
- Withold all?
- Continue All?

Learning points

- Avoid nephrotoxics
- Contrast can be cause renal failure
- W/H Metformin and other nephrotoxics if precipitating factors present

Case study 2 – 67 yr old lady

- End stage renal failure from Diabetic Nephropathy
- Type 1 DM since age 7 yrs
- Poor control of Diabetes
- HbA1c between 7-11 % over the years

Case study 2 – 67 yr old lady

- Current meds:
- Lantus 30 u nocte
- NR 16 TDS
- Crestor 20 mg OD
- Hydrochlorthiazide 25 mg od

Case study 2 – 67 yr old lady

- Dialysis days-Tuesday, Thursday, Saturday

- BSL profile:
- Fasting- M10.2 , T5.4. , W18.0, T3.5, F14.5, S3.2
- Bed time – M4.5, T20..0, W5.0, T 15.0, F2.6, S 16.0

Case study 2 – 67 yr old lady

- Whats going on?
- How to correct it?

Case study 3 – MD 65 ♂

- Went to GP with blurred vision
- Family history: Mother had diabetes, hypertension and had been on dialysis, died 7 years earlier
- BP = 160/90 mm Hg
- Diagnosed with Diabetic retinopathy

Referred urgently to renal services

Case study 3 – MD 65 ♂

- Last HbA1c 10%
- Urea = 46.7 mmol/L, Creatinine = 1875 µmol/L, HCO_3 = 12 mmol/L, eGFR = 6 ml/min
- Haemoglobin = 6.9 g/dL
- Anaemia
- 9 centimetres kidneys bilaterally, echobright

Case study 3 – MD 65 ♂

- Education - Given “crash-course” on ESRF, diet, fluid restriction and dialysis

- Dialysis - Line inserted in right internal jugular vein. Converted to tunnelled line

Case study 3 – MD 65 ♂

- Poor compliance with dialysis schedule, diet and fluid
- Hyperkalaemic arrest after 4 months causing death

Learning points

- Poor compliance
- Lack of screening
  - With a strong family history was he screened (BP, urine dipstick, serum creatinine)?
- Acute presentation of a treatable chronic kidney disease problem
- Non-engagement with chronic disease process and died of a preventable cause

References

American Diabetes Association: Nephropathy in Diabetes (Position Statement). *Diabetes Care* 27 (Suppl.1): S79-S83, 2004

National Kidney and Urologic Diseases Information Clearinghouse. *Kidney Disease of Diabetes.* Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), DHHS; 2003.

United States Renal Data System. *USRDS 2003 Annual Data Report*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), DHHS; 2003.

DeFronzo RA: Diabetic nephropathy: etiologic and therapeutic considerations. *Diabetes Reviews* 3:510-547, 1995

National Kidney and Urologic Diseases Information Clearinghouse. *Kidney Failure: Choosing a Treatment That's Right For You.* Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH), DHHS; 2003.