CASE 4

Short case number: 3.14.4
Category: Renal and Urinary Systems
Discipline: Medicine_nephrology
Setting: Urban: General Practice
Topic: Diabetic Nephropathy / Chronic renal failure [SDL]

Case

68 year old Joseph Hernandez, has been a patient of the practice for many years, he was diagnosed with type 2 diabetes 15 years ago, his blood sugar control has been reasonably good, his most recent $HBA1_c$ 9%. He developed hypertension 2 years ago, but his blood pressure has become increasingly difficult to control.

His renal function has been deteriorating over the last 2 years with his most recent glomerular filtration rate [GFR] being measured at 40 ml/min/1.73m^2

Questions

1. What are the key features of the history and examination in the patient with diabetic nephropathy?
2. Describe the underlying pathophysiology of diabetic nephropathy.
3. Draw the relationship between serum creatinine and GFR.
4. How is GFR calculated?
5. In a table, detail the stages of chronic renal failure in relation to GFR measurement and the principles of management at each stage.
6. Describe the clinical features of chronic renal failure and the underlying pathophysiology.
7. Outline the biochemical features of chronic renal failure.
8. What measures can be implemented in the management of Joseph to slow his progression to end-stage renal failure?
9. What are the common causes of chronic renal failure and the percentage progression to end-stage renal failure?
10. Outline the principles of fluid and electrolyte management in the context of end-stage renal failure and dialysis.

Suggested reading:

- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014. Chapter 17.

ANSWERS

1. What are the key features of the history and examination in the patient with diabetic nephropathy?

History

- diabetes (screen patients with Type 1 annually from 5 years after diagnosis and with Type 2 annually from the time of diagnosis)
- passing of foamy urine
- otherwise unexplained proteinuria in a patient with diabetes
- diabetic retinopathy
- fatigue and dependent oedema secondary to hypoalbuminaemia (if nephrotic syndrome is present)
- other associated disorders such as peripheral vascular occlusive disease, hypertension, or coronary artery disease.

Physical

Generally diabetic nephropathy is considered after a routine urinalysis and screening for microalbuminuria in the setting of diabetes. Patients usually have physical findings associated with long-standing diabetes.

- hypertension
- evidence of diabetic retinopathy (fundoscopy or fluorescein angiography)
- peripheral vascular occlusive disease (decreased peripheral pulses, carotid bruits)
- evidence of diabetic neuropathy (decreased sensation, diminished tendon reflexes)
- evidence of fourth heart sound during cardiac auscultation
- nonhealing skin ulcers

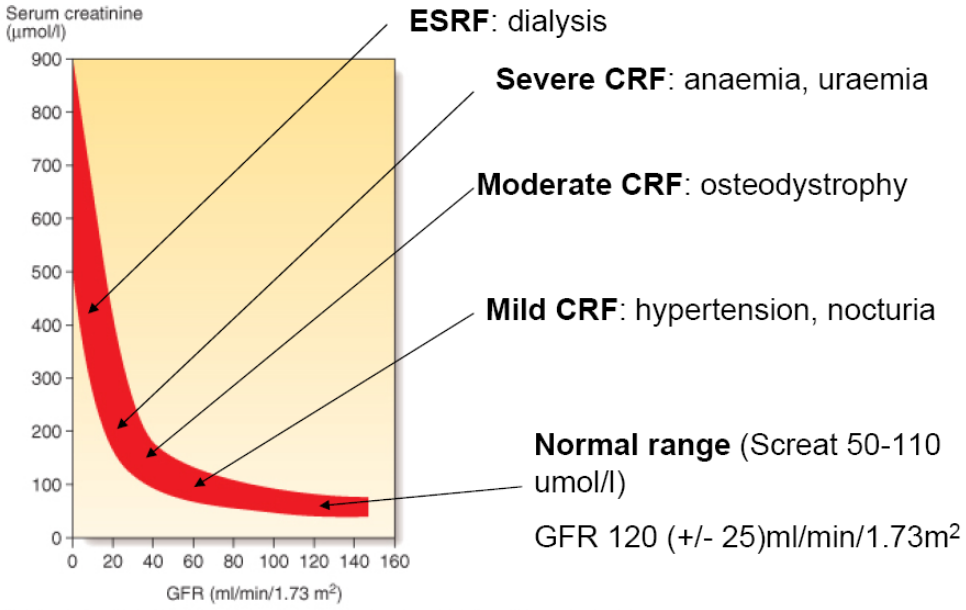
2. Describe the underlying pathophysiology of diabetic nephropathy.

The key change in diabetic glomerulopathy is augmentation of extracellular material. The earliest morphologic abnormality in diabetic nephropathy is the thickening of the glomerular basement membrane (GBM) and expansion of the mesangium due to accumulation of extracellular matrix. Large acellular accumulations may be observed in the solid spaces of the tuft. These are circular on section and are known as the Kimmelstiel-Wilson lesions/nodules.
The glomeruli and kidneys are typically normal or increased in size initially, thus distinguishing diabetic nephropathy from most other forms of chronic renal insufficiency.

The renal vasculature typically displays evidence of atherosclerosis, usually due to concomitant hyperlipidaemia and hypertensive arteriosclerosis.

Three major histologic changes occur in the glomeruli of persons with diabetic nephropathy. First, mesangial expansion is directly induced by hyperglycaemia, perhaps via increased matrix production or glycosylation of matrix proteins. Second, GBM thickening occurs. Third, glomerular sclerosis is caused by intraglomerular hypertension (induced by renal vasodilatation or from ischaemic injury induced by hyaline narrowing of the vessels supplying the glomeruli). These different histologic patterns to have similar prognostic significance. The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are hyperglycaemia (causing hyperfiltration and renal injury), advanced glycosylation products, and activation of cytokines.

3. Draw the relationship between serum creatinine and GFR.



Serum creatinine and the glomerular filtration rate (GFR). The inverse reciprocal relationship between GFR and serum creatinine is shown for a group of patients with renal disease. The band indicates the range of values obtained. Note that some individuals have a GFR as low as 30 – 40ml/min without serum creatinine rising out of the normal range. A normal GFR is 120 ± 25ml/min/1.73m^2.

4. How is GFR calculated?

GFR is the rate at which fluid passes into nephrons after filtration, it measures renal excretory function. The normal range depends on the size of an individual, and should be corrected for surface area - typically 1.73 m^2

GFR normal range = 120 ± 25ml/min/1.73m^2

Clearance of a solute from plasma into urine equals GFR, if the solute is freely filtered and neither secreted into nor absorbed from the renal tubules.

Equations can be used to estimate GFR from serum creatinine alone. The Cockcroft and Gault (C&G) equation is reasonably accurate at normal to moderately impaired renal function. However, it was designed to estimate creatinine clearance (CrCl), not GFR. CrCl is often used as a surrogate measure of GFR.

$$\text{CrCl (C\&G)} = \frac{(140 - \text{age}) \times \text{lean body weight (kg)} \times (1.22 \text{ males or } 1.04 \text{ females})}{\text{serum creatinine } (\mu\text{mol/l})}$$

Complex equations have been developed which are better at poorer levels of renal function, e.g. the Modification of Diet in Renal Disease (MDRD) study equation (online eGFR (MDRD) available at https://renal.org/information-resources/the-uk-eckd-guide/about-egfr/)

$$\text{CrCl} = 186 \times (\text{creatinine in } \mu\text{mol/l}/88.4)^{-1.154} \times (\text{Age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

These equations do not perform well in unusual circumstances, such as extremes of body (and muscle) mass.

5. In a table, detail the stages of chronic renal failure in relation to GFR measurement and the principles of management at each stage.

STAGES OF CHRONIC RENAL DISEASE [1]			
Stage	Description	GFR (ml/min/1.73m^2)	Action
1	Kidney damage[2] with normal or high GFR	≥ 90	Investigate, e.g. haematuria and proteinuria (see below)
2	Kidney damage with slightly low GFR	60 – 89 }	Renoprotection – blood pressure control, dietary modifications
3	Moderately low GFR	30 – 59	
4	Severe low GFR	15 – 29 }	Prepare for renal replacement therapy (if appropriate)
5	Kidney failure	< 15 or dialysis	
[1]US National Kidney Foundation Kidney Disease Quality Outcomes Initiative classification of stages of chronic kidney disease (Am J Kidney Disease 2002; 39(suppl 1): S1 – 266) [2]Kidney damage means pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies or GFR < 60 ml/min/1.73m^2 for 3 months. Symptoms unusual until ≥ stage 3.			

6. Describe the clinical features of chronic renal failure and the underlying pathophysiology.

Chronic renal failure (CRF) refers to an irreversible deterioration in renal function which classically develops over a period of years. Initially, it is manifest only as a biochemical abnormality. Eventually, loss of the excretory , metabolic and endocrine functions of the kidney leads to the development of the clinical symptoms and signs of renal failure, which are referres to as uraemia.

Disturbances in water, electrolyte and acid-base balance contribute to the clinical picture in patients with CRF, but the exact pathogenesis of the clinical syndrome of uraemia is unknown. Many substances present in abnormal concentration in the plasma have been suspected as being 'uraemic toxins', and uraemia is probably caused by the accumulation of various intermediary products of metabolism.

Clinical features – nocturia, due to the loss of concentrating ability and increased osmotic load per nephron, is often an early symptom. Patients may present with complaints which are not obviously renal in origin, such as tiredness or breathlessness. In end-stage renal failure (ESRF), patients

appear ill and anaemic. They do not necessarily retain fluid, and may show signs of sodium and water depletion. There may be unusually deep respiration related to metabolic acidosis (Kussmaul's respiration), anorexia and nausea. Later, hiccoughs, pruritus, vomiting, muscular twitching, fits, drowsiness and coma ensue.
Yellow complexion, pallor, JVP raised in fluid overload or pericardial tamponade, pericardial friction rub, pulsus paradoxus in pericardial tamponade, 'brown line' pigmentation of nails, excoriation, bruising, peripheral neuropathy (absent reflexes, reduced sensation, paraesthesia, 'restless legs'
One or other of the following may be evident :- dual lumen central venous catheter for dialysis access, arteriovenous fistulae for dialysis access, peritoneal dialysis catheter, scar to indicate transplanted kidney.

7. Outline the biochemical features of chronic renal failure.

Blood urea nitrogen and creatinine will be elevated
Hyperkalaemia or low bicarbonate levels may be present
Hyperphosphataemia due to reduced phosphate excretion, associated with hypocalcaemia (later this progresses to tertiary hyperparathyroidism with hypercalcaemia)
Metabolic acidosis due to the accumulation of sulfates, phosphates, uric acid etc.
Anaemia is common, often normochromic, normocytic, and usually correlates with the severity of renal failure

8. What measures can be implemented in the management of Joseph to slow his progression to end-stage renal failure?

Establish the current level of microalbuminuria with a random urine sample for urinary albumin:creatinine ratio if not performed in the last 6 months. (this may result in needing to perform a timed collection of urine).
Review Joseph's current medication and ascertain compliance prior to considering any change.
Intensive treatment of glycaemic control with the appropriate medications in an attempt to reduce HbA_{1c} towards target at 7% (treatment with metformin should be abandoned when creatinine is higher than 150µmol/l as the risk of lactic acidosis is increased).
Aggressive reduction of blood pressure ensuring that angiotensin II receptor antagonists (AIIRB) or angiotensin- converting enzyme (ACE) inhibitors are part of the regimen (need to monitor for hyperkalaemia).
Consider the possibility of critical renal artery stenosis given that Joseph's blood pressure has become increasing difficult to control. (renal function deteriorates on ACE inhibitors, renal ultrasound may reveal asymmetry of

renal size, CT angiography as the definitive test).
Aggressive cardiovascular risk factor reduction e.g. reducing lipids levels to target, aspirin etc.
Explain the need to treat any infection promptly, in 68 year old Joseph need to assess the possibility of prostatism with appropriate history and examination in view of the increased risk of a urinary tract infection with potential rapid deterioration in renal function.

9. What are the common causes of chronic renal failure and the percentage progression to end-stage renal failure?

COMMON CAUSES OF CHRONIC RENAL FAILURE		
Disease	Proportion of end-stage renal failure	Comments
Congenital and inherited	5%	e.g. Polycystic kidney disease, Alport's syndrome (hereditary progressive nephritis and deafness)
Renal artery stenosis	5%	
Hypertension	5 – 25%	It is uncertain whether such variation is due to true racial differences or to differences in diagnostic labelling
Glomerular diseases	10 – 20%	IgA nephropathy is the most common
Interstitial diseases	5 – 15%	
Systemic inflammatory Diseases	5%	e.g. SLE, vasculitis
Diabetes mellitus	20 – 40%	Large racial and national differences exist
Unknown	5 – 20%	

10. Outline the principles of fluid and electrolyte management in the context of end-stage renal failure and dialysis.

Commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uraemic symptoms, the presence of hyperkalaemia unresponsive to conservative measures, persistent extracellular volume expansion despite diuretic therapy, acidosis refractory to medical therapy, a bleeding diathesis, and a creatinine clearance or eGFR below 10mL/mi per 1.73m^2.

Haemodialysis relies on the principles of solute diffusion across a semi-permeable membrane. Movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate. There are three essential components to haemodialysis; the dialyzer (a plastic device with the facility to perfuse blood and dialysate compartments at very high flow rates), the composition and delivery of dialysate and the blood delivery system which is composed of the dialysis machine and the dialysis access.

Dialysate – the potassium concentration may be varied from 0 to 4 mmol//L depending on the predialysis plasma K^+ concentration

- the usual calcium concentration is 1.25mmol/L (higher calcium concentrations may be used in patients with hypocalcaemia associated with hypoparathyroidism)
- the usual sodium concentration is 140mmol/L

The haemodialysis procedure is targeted at removing both low- and high-molecular-weight solutes. The procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 300 – 500 mL/min, while dialysate flows in an opposite counter- current direction at 500 – 800mL/min. The *dose* of dialysis, which is currently defined as a derivation of the fractional urea clearance during a single dialysis treatment, is further governed by patient size, residual kidney function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions. It is usually carried out three times per week. Careful compliance with diet and fluid restrictions is required between treatments as recommended by a qualified dietitian experienced in the management of ESRD.

Peritoneal dialysis may be carried out as continuous ambulatory peritoneal dialysis (CAPD) in which two litres of a sterile, isotonic dialysis fluid are introduced through a permanent Silastic catheter into the peritoneal cavity and left in place for approximately 6 hours. During this time, metabolic waste products diffuse from peritoneal capillaries into the dialysate fluid down a concentration gradient. The fluid is then drained and fresh dialysis fluid introduced. The inflow fluid is rendered hyperosmolar by the addition of glucose; this results in net removal of fluid from the patient on each cycle (ultrafiltration). This cycle is repeated 3 – 5 times daily during which time the patient is mobile and able to undertake normal daily activities. Its long-term use may be limited by episodes of bacterial peritonitis and damage to the peritoneal membrane. Automated peritoneal dialysis (APD) is now widespread with a mechanical device performing the fluid exchanges during the night, leaving the person free, or with only a single exchange to perform, during the day. Diet and fluid is less restricted in CAPD compared to haemodialysis.