Diabetes, Chronic Kidney Disease and Anaemia.
Information at Expert Level.
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Learning Outcomes

• To understand how diabetes can affect the kidneys and lead to the development of Chronic Kidney Disease (CKD).
• To understand how diabetes and CKD can cause anaemia to develop early in patients with these long term conditions.
• To understand the available treatment options for patients with diabetic CKD
• To understand which blood tests are used to diagnose anaemia and monitor the effect of the prescribed treatments.
• To understand the need to use caution when interpreting blood results required to monitor anaemia in diabetic CKD.
• To understand which factors can affect a good response to the treatment of the anaemia in these patients.
• To be aware of the national and international guidelines available for the management of anaemia in CKD.

Introduction

Diabetes, Chronic Kidney Disease (CKD) and anaemia could be described as an “unholy trinity”. The incidence of people developing either type 1 or type 2 diabetes has been increasing. A recent analysis has shown that the incidence of diabetes has increased fourfold since 1980 (NCD-RisC, 2016). There will be continued significant increases in the number of people developing diabetes over the next 15 years. In 2010, it was seen that approximately 285 million people worldwide were affected by diabetes. It is forecast that this figure may rise to 466 million affected people by 2030 (Jha V et al, 2013; Shaw, Sicree and Zimmet, 2010). During this period, it is expected that within Europe the mean annual increase in new cases of diabetes will range from 2,000 a year in Sweden and Hungary and up to 57,000 in Spain. Within the United Kingdom, this figure may be about 31,000 people diagnosed with diabetes (Whiting et al, 2011). The predicted rise in the number of people diagnosed with diabetes has been described a “tsunami” that is likely to cause major problems in the future (Spollett, 2013; Sherwin and Jastreboff, 2012). A tsunami is a series of waves over a period of time. If the rise in diabetes diagnoses is viewed as the first devastating wave, then the increase in the number of people developing CKD as a result of their diabetes may be seen as a part of this tsunami.

As renal function declines, the production of erythropoietin by the kidneys will fall. As a consequence of falling erythropoietin production, the patient will develop anaemia (Nangaku and Eckardt, 2006). This will be a subsequent, delayed wave in the “diabetic tsunami” and form the third member of the “unholy trinity”.

Diabetes

Diabetes is known as Kimmelstiel Wilson syndrome and was discovered in 1936 by Clifford Wilson and Paul Kimmelstiel. Diabetes is one of the main causes of CKD throughout the world with numbers varying in different countries. In the UK, the number of people diagnosed with CKD due to diabetes has increased since the start of this millennium. The 3rd Renal Registry Report (2000) showed this number to be around 10% of all new CKD diagnoses. In the 2015, 18th, Renal Registry Report shows this figure to be almost 27% of all new CKD patients (Ansell and Feest, 2000, Fogarty et al, 2015). Within Europe, diabetes has been recognised as the cause of CKD from approximately 15% of all cases in Serbia and the Netherlands up to circa 35% in Finland (Jha et al, 2013).

There is a significant health burden brought on by the complications of diabetes, which is a result of the continuing increase in the number of people developing diabetes. It is a complex disease with no currently known cure. The predicted rise of diabetic patients all over the world is becoming a public health pandemic with resultant implications for increasing health care costs (Spollett, 2013; Venkat Narayan et al, 2006). The epidemiology of world disease mortality and morbidity is changing from infectious diseases as the major cause of death to non-communicable disease (WHO, 2012, Atkins, 2005). The World Health Organisation has projected that diabetes will be the 7th leading cause of death in 2030 (Mathers and Loncar, 2005). In 2014, 9% of adults 18 years and older had diabetes. In 2012, diabetes was the direct cause of 1.5 million deaths with more than 80% of diabetes deaths occurring in low and middle-income (WHO 2014).
Physiology

Understanding the pathogenesis of diabetic nephropathy helps explain how a series of interlinked events occurs. Figure 1 describes the relationship between the trilogy of diabetes, CKD and anaemia as a consequence of high blood glucose (HBG). Most of the glucose and the other nutrients that the body requires are reabsorbed in the proximal tubules. Glucose is reabsorbed across the apical membrane of epithelial cells into the peritubular interstitium together with sodium by the Sodium and Glucose Cotransporter (SGLT2) (Ward et al, 2005; Ferrannini et al, 2013). As glucose is selectively reabsorbed in the proximal tubules, the appearance of glucose in the urine reflects high levels of plasma glucose or hyperglycaemia. As a consequence, this affects the plasma filtration process of the kidneys where morphological changes occur within the glomerulus. The derangement in the interaction between haemodynamic and metabolic causes explained in figure 2, leads to glomerular changes affecting the kidney function which leads to the progression of anaemia.

![Figure 1. Interlinking Anaemia, Kidney Disease and Diabetes (Cao et.al 2011, Macdougall 2001).](image)

**Physiology**

**Figure 1.** Interlinking Anaemia, Kidney Disease and Diabetes (Cao et al 2011, Macdougall 2001).

**Figure 2.** Metabolic changes caused by diabetes in the kidneys (Cao et al 2011 & Shena et al 2005)

**Figure 2.** The production of growth factor TGF-B1 by mesangial cells under influence of elevated glucose in the blood stimulates renal cells to produce humoral mediators, cytokines growth factor that is responsible for structural changes in the kidneys that cause decline in renal function which affects erythropoietin production.

**Figure 2.** Metabolic changes in the kidneys cause by diabetes (Cao et al 2011 & Shena et al 2005)
Oxidative stress or oxidant derived tissue injury is a key component in the development of diabetic nephropathy. It occurs when the production of oxidants or reactive oxygen species (ROS) exceeds local antioxidant capacity. In the presence of hyperglycaemia, the excessive intracellular generation of reactive oxygen species (ROS) has an important role with individual cells processing glucose across the plasma membrane into the cytosol, which aids in glucose homeostasis. Pathways in the kidney generate ROS, such as glycolysis, a defect in polyol pathway, uncoupling of nitric oxide synthase, xanthine oxidase, NAD(P)H oxidase and advanced glycation are all major contributors in the pathogenesis of diabetic nephropathy (Forbes, 2008).

The pathological classification of the histopathological changes of diabetic nephropathy is shown to be useful for clinicians to predict the value of renal outcomes. A study was conducted to find bio markers based on the biopsy results from patients, which resulted in showing that there is a link between the severity of the glomerular lesions, interstitial fibrosis and tubular atrophy (IFTA). Although the advantages of this are theoretically significant, the indices demonstrating the severity of vascular lesion may not predict kidney outcomes. (Cohen-Tervaert, 2010; Arya, 2010 and Yu, 2015)

Anaemia in Chronic Kidney Disease

If the increased incidence of diabetes is the first devastating wave of the Tsunami and CKD is a subsequent wave the later wave is the development of anaemia resulting from declining renal function. The relationship between anaemia and diabetes has been related to advancement of kidney disease which involves tubulointerstitial compartment damage and deficiency or resistance to erythropoietin. The genesis of anaemia is caused by a failure to increase the circulating erythropoietin level, in response to hypoxia, despite a reduction in haemoglobin, inflammation, reduced red cell survival, and autonomic neuropathy. Iron deficiency will occur in patients with diabetes as a consequence of a lack of absorption and gastroparesis.

The table shows the defined haemoglobins levels where anaemia may be diagnosed and further investigations should be instigated.

**Table 1**

<table>
<thead>
<tr>
<th>Gender &amp; Age</th>
<th>Hb level</th>
<th>Test required</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 18+ years</td>
<td>Less than 130.0g/L</td>
<td>WHO, 2011</td>
<td></td>
</tr>
<tr>
<td>Male 18 – 70 years</td>
<td>Less than 135g/L</td>
<td>European renal best practice (Locatelli et al 2013)</td>
<td></td>
</tr>
<tr>
<td>Male 70+ years</td>
<td>Less than 132.0g/L</td>
<td>European renal best practice (Locatelli et al 2013)</td>
<td></td>
</tr>
<tr>
<td>Female 18+ years</td>
<td>Less than 120.0g/L</td>
<td>WHO, 2011; European renal best practice (Locatelli et al 2013)</td>
<td></td>
</tr>
</tbody>
</table>

Predominant causes of anaemia will generally be bleeding, frequently from the gastrointestinal tract and iron deficiency. In people with CKD, there may also be other vitamin and mineral deficiencies such as Vitamin B12 and folate deficiencies. Prior to starting any treatment, it will be necessary to exclude and treat all other potential causes of anaemia. Before starting any treatment for anaemia of CKD, patients, irrespective of their level of kidney disease, age and gender should have the blood tests performed (NICE, 2015; KDIGO, 2012) as shown in Table 2.

**Table 2**

<table>
<thead>
<tr>
<th>Test required</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>Marker for anaemia of all causes</td>
</tr>
<tr>
<td>MCV and MCH</td>
<td>Low levels may indicate microcytosis, iron deficiency</td>
</tr>
<tr>
<td>Absolute Reticulocyte Count</td>
<td>Marker for reduced or increased erythropoiesis</td>
</tr>
<tr>
<td>Serum Ferritin level</td>
<td>Measure of Iron Stores</td>
</tr>
<tr>
<td>%TSAT</td>
<td>Measure of Iron Stores</td>
</tr>
<tr>
<td>C Reactive Protein</td>
<td>Elevated in the presence of infection or inflammation</td>
</tr>
<tr>
<td>Vitamin B12 level</td>
<td>Required in production of Red cells</td>
</tr>
<tr>
<td>Folate level</td>
<td>Required in production of Red cells</td>
</tr>
<tr>
<td>Calcium, Phosphate and PTH</td>
<td>Disordered bone metabolism may affect the bone marrow and lead to reduced erythropoiesis</td>
</tr>
<tr>
<td>Urea level</td>
<td>Raised urea levels will reduce Red Cell lifespan to 70 – 90 days (Bonomini and Sirolli; 2003; Meyer and Hostetter, 2007)</td>
</tr>
<tr>
<td>Thyroid Stimulating Hormone (TSH)</td>
<td>Low levels may affect bone marrow efficiency</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Increased levels may indicate excessive breakdown of RBCs</td>
</tr>
</tbody>
</table>

A further specific cause of anaemia in CKD may be excessive red blood cell destruction. As renal function declines, creatinine and urea levels will rise. Elevated urea levels will shorten the lifespan of the red blood cell to 70 to 90 days (Bonomini and Sirolli; 2003; Meyer and Hostetter, 2007). There could also be a deficiency in the production of red blood cells as a re-
sult of declining erythropoiesis and expression of endogenous erythropoietin (EPO) by the kidney.

Approximately 90% of endogenous EPO is produced in the renal peritubular fibroblast cells, which are found in the capillary endothelial lining contiguous to the tubules within the renal cortex. EPO is a glycoprotein hormone that signals the bone marrow to produce red blood cells. This hormone is comprised of 165 amino acids and sugars in a chain. EPO has a molecular weight of 30,400 Daltons (Jelkmann, 2010; Macdougall, 2011). Production of this hormone is stimulated by hypoxia as the number of red cells available to transport oxygen has fallen. EPO will act within the bone marrow on the red cell progenitors. It will bind to the colony forming units - erythroid (CFU-Es). This action will facilitate the maturation process and development of mature erythrocytes. Circulating EPO will prevent apoptosis or cell death of the red cell progenitors (Jelkmann, 2011).

As renal function declines, the ability of the peritubular fibroblasts to recognise reduced levels of oxygen transported will diminish. As a consequence of this problem, production of EPO and of red cells will decline and the CKD patient will become increasingly anaemic as the haemoglobin level falls. Although this may occur earlier especially where all other causes have been excluded, the evidence shows it will occur when the patient has reached CKD stage 3B with an eGFR of 45 ml/ min/1.73m² or less. In CKD patients with no other comorbidities this is generally seen and may require treatment when the eGFR has fallen to 30 ml/min/1.73m² (Hörl, 2007). However, this may not occur in all causes of CKD. It is recognised that where a patient has adult polycystic kidney disease, they will need minimal or no ESA therapy to support and maintain their haemoglobin level. It has been seen that the renal cysts and interstitial cells will produce increased levels of endogenous EPO. This rise in EPO in people with polycystic kidneys may be a consequence of ongoing reduced oxygen levels within the interstitial tissue while the hypoxia inducing factors 1 and 2 expressed in cells lacking polycystin – 1 continue to be typically controlled by oxygen (Mao, Xie and Ong, 2014)

Anaemia in Diabetic Kidney Disease (DKD)

In those with DKD, anaemia may be compounded for the following reasons. In diabetes the renal glucose threshold will be increased, reducing the amount of glucose excreted in urine. Glucose reabsorption from the proximal tubules is controlled by the Sodium – Glucose Cotransporter (SGLT2). The SGLT2 is found in the renal proximal tubules (Ferrannini et al, 2013). As more glucose is reabsorbed through the tubules, this will lead to atrophy of the tubules and the interstitial cells will become fibrosed. The tubules will lose form and cease to function effectively when the renal peritubular capillaries are damaged (Singh, Wintour and Farrington, 2008). As the EPO producing peritubular fibroblast cells are contiguous to the area of damage caused by chronic hyperglycaemia, these cells will also sustain damage.

The development of SGLT2 inhibitors has been shown to reduce the amount of glucose reabsorbed by the proximal tubules. As a direct consequence of SGLT2 inhibitors reducing glucose reabsorption, there may be secondary protection available to the kidney in patients with diabetes and kidney disease (Gilbert, 2014; De Nicola et al, 2014). Whilst there appears to be benefit in using SGLT-2 Inhibitors in early CKD, caution is advised in using this treatment in patients with eGFR of 60 - 45 ml/min/1.73m². The dose may continue but the dose will need to be reduced. This type of anti-diabetic medication should not be commenced as a treatment in patients with this level of renal function. Where the eGFR is consistently less than 45 ml/min/1.73m², this treatment should be discontinued as it is not deemed to be effective (Yarmout et al, 2014).

It is possible that an autonomic neuropathy will be present in diabetic patients and can damage nerves within the kidney which may lead to low EPO levels (Bilous, 2002; Mojiminiyi, 2006). Whereas anaemia will generally become symptomatic when the estimated glomerular filtration rate (eGFR) falls below 30ml/min (Macdougall, 2001; Babbitt and Lin, 2012), where a CKD patient is diabetic, it has been seen that they may present with symptoms of anaemia despite a relatively high eGFR: 45 ml/min/1.73m² to 60 ml/min/1.73m² (Mojiminiyi, 2006; Hörl, 2007; Thomas, 2009).

Whilst the anaemia may be related to the CKD, it may also be as a result of other potential causes such as an undiagnosed iron deficiency.

Iron Deficiency in Diabetic Kidney Disease (DKD)

It is recognised that iron and erythropoietin are required for the erythropoiesis of red blood cells (RBC). The lack of iron within the blood affects the cell life span which could also be contributed to by the following factors: blood loss, malabsorption, physiologic demands and use of erythropoietin therapy (ESA). Iron also helps in oxygen transport to the muscles providing myoglobin that helps in the treatment of condition such as restless legs. There are other benefits of having iron such as improved cognition, immune function and thermoregulation which controls the ability to react to cold related stress, and improvement in quality of life by increased physical performance (Wittwer, 2013).

The consequences of deteriorating kidney function resulting from diabetes will lead to the development of anaemia caused by iron deficiency for the following reasons.

Normal iron metabolism is disturbed through absolute iron deficiency, where there is no iron available for utilisation in erythropoiesis.

A functional iron deficiency often seen in those with DKD is caused by the presence of normal or raised iron stores that are not available for the erythropoiesis process due to blockage. The specific causes of these factors are: the presence of hepcidin, which affects the transportation of iron to be utilised by the bone marrow for erythropoiesis by blocking the ferroportin channel within the intestinal enterocyte (Anderson et al, 2009; Ganz and Nemeth, 2011)

Oxidative stress is also a factor related to disruption to the normal iron balance. Iron, which is known as non - transferrin...
bound iron (NTBI), has pro-oxidant characteristics and could be highly toxic to the cells. These are hydroxyl radicals that can damage a wide variety of cellular molecules and have detrimental consequences to the body (Macdougall & Geisser 2013). Normal iron losses are 1-2 mg daily in the non-kidney patient and this loss could increase rapidly with diabetic kidney disease (DKD).

Infections require a medium to grow which can be provided by high blood sugar levels and all living cells require iron. Diabetic patients may exhibit a flawed natural immune response that may lead to their vulnerability to infection (Ng, 2013). A recent study suggests that diabetic patients are three times as likely to develop infection. Where the diabetic patient has the co-morbidity of CKD the risks of developing infection are further increased (Smit et al, 2016). Where the patient has an infection, iron will not be available to form haemoglobin during the process of erythropoiesis (Wittwer and Bennett, 2011).

Iron deficiency may present early in the anaemia of CKD and necessitate supplementation as recommended by national and international guidelines (KDIGO, 2012, NICE, 2015). Iron stores will be utilised during erythropoiesis (Jelkmann, 2011) and be depleted.

**Measuring iron parameters**

National guidelines recommend investigating anaemia in CKD patients where the eGFR is less than 60 ml/min/1.73m², the haemoglobin (Hb) level has fallen to less than 110.0 g/Litre, serum ferritin level is less than 100 micrograms/Litre and the haemoglobin (Hb) level has fallen to less than 110.0 g/L. Where the patient has developed symptoms attributable to anaemia, (NICE 2015). Iron supplementation should be the first stage of managing anaemia. The recommended tests are outlined in the table below.

<table>
<thead>
<tr>
<th>Test</th>
<th>Iron depletion</th>
<th>Maintenance level</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Hypochromic Red Cells (%HRC)</td>
<td>&gt; 6%</td>
<td>&lt; 6%</td>
<td>NICE 2015 recommends this test is the first choice</td>
</tr>
<tr>
<td>Reticulocyte Hb content (CHr)</td>
<td>&gt;29 pg</td>
<td>&lt;29 pg</td>
<td>NICE 2015 recommends that CHr be used if %HRC is not available</td>
</tr>
<tr>
<td>Serum Ferritin</td>
<td>&gt; 100 mcg/L</td>
<td></td>
<td>Acute phase reactant. Ferritin level should be measured together with TSAT% if %HRC and CHr not available</td>
</tr>
</tbody>
</table>

| Transferrin Saturation%     | >20%           | <20%              | Acute phase reactant. TSAT% level should be measured together with Ferritin if %HRC and CHr not available |

| Metals like iron affect the glycation of proteins that result from increased glucose levels seen in diabetes. This can lead to the development of the reactive oxygen species present in oxidative stress. This is shown in the Haber – Weiss formula (Wittwer, 2013; Kehrer, 2000) Figure 5. |
Iron levels will increase within the lysosomes of the proximal tubules in the diabetic kidney. A variety of factors including a triumvirate of elevated blood glucose level, the end products of the advanced glycation process and raised lipid levels will increase the levels of iron available within the cells. This will in turn starts and drastically increases the oxidative stress and worsen the damage to the kidneys (Swaminathan et al, 2007).

Management of Anaemia

Erythropoiesis Stimulating Agents (ESAs)

National and International guidelines should be followed to treat the anaemia with iron supplementation and Erythropoietin Stimulating Agents (ESAs) (KDIGO, 2012; NICE, 2015). Until recently the only ESA treatment available was with the Recombinant Human Erythropoietin (rHuEPO) such as short acting Epoetin alfa and beta and longer acting ESAs: Darbepoetin alfa and Methoxy polyethylene glycol-epoetin beta. rHuEPO treatments have been available for over 25 years. Research and clinical trials into alternative ESAs are ongoing. Potential ESA treatments under investigation are Hypoxia Induced Factor (HIF) Stabilisers and EPO gene therapy (Macdougall, 2012; Jelkmann, 2013; Miyata et al 2013). The HIF stabilisers have the added advantage of being an oral therapy unlike the current injection only rHuEPO treatments (Jelkmann, 2013).

Following the release of the TREAT study in 2009, it was shown that there was a significant risk of CKD patients with diabetes suffering a stroke when the haemoglobin level was sustained at a normal level (Pfeffer et al, 2009). As a direct consequence of these findings the recommended aspirational haemoglobin levels when treated by ESA were reduced accordingly (KDIGO, 2012; NICE, 2011; NICE 2015).

ESA therapy has been shown to be effective in increasing the haemoglobin level in approximately 95% of all patients (Macdougall, 2001). Despite this fact, there are reasons why there is an inadequate response to this treatment. Johnson et al, 2007 explain these causes, which are outlined in table 4. NICE, 2015 and KDIGO, 2012 recommend how to overcome this lack of response to treatment.

Table 4: Hyporesponsiveness to ESA

<table>
<thead>
<tr>
<th>Cause</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Blood loss</td>
<td>Bleeding from the GI Tract, Urinary Tract, Epistaxes, angiodysplasia</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Absolute: Iron deplete Functional: no iron available for use</td>
</tr>
<tr>
<td>Infection / inflammation</td>
<td>Bacterial or viral infections</td>
</tr>
<tr>
<td>Concordance / compliance</td>
<td>Needlephobia, change in personal circumstance; Hospital / Nursing Home admission</td>
</tr>
<tr>
<td>Poor / inadequate dialysis</td>
<td>Problems with Peritoneal Dialysis or Haemodialysis</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Bone metabolism disturbance; raised PTH levels</td>
</tr>
<tr>
<td>Nutritional deficiencies</td>
<td>Vitamin B12; Folate, Vitamin C</td>
</tr>
<tr>
<td>Medication</td>
<td>Immunosuppressive medication Chemotherapy agents</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Solid tumours; haematological conditions: myeloma</td>
</tr>
<tr>
<td>Antibody – mediated Pure Red Cell Aplasia</td>
<td>Rare adverse event associated with subcutaneous administration of ESA therapeutic agents (Macdougall et al, 2015)</td>
</tr>
<tr>
<td>Primary bone marrow disorder</td>
<td>myelodysplasia</td>
</tr>
</tbody>
</table>

Haemoglobin A1c (HbA1c) and anaemia

HbA1c is a glycated form of haemoglobin that is commonly utilised as a measure of the control of blood sugar levels in diabetic patients over a 3 month period. This test is being used to diagnose diabetes. The actual value of the HbA1c level comprises 3 main strands (Hussain, 2015):

1. 1: The amount of haemoglobin found in reticulocytes when they leave the bone marrow
2. 2: The rate of Hb glycation as the red cells age. This is a specific function of the amount of glucose that the Hb is subjected to.
3. 3: The average age of the red cell.

Whilst studies in to the effects on Hb1Ac levels caused by anaemia appear to be limited, there are implied effects. Erythrocyte turnover appears to increase in anaemia, which leads to lower HbA1c levels. In patients with diabetic kidney disease whose anaemia is managed with ESA plus / minus intravenous iron therapy, HbA1c levels were lower following treatment irrespective of the actual glycaemic control (Ng et al, 2013) Where HbA1c levels do not agree with the actual clinical picture presented by the patient, prudence may need to be taken when interpreting these results (Hussain, 2015).

Figure 5.

\[
\begin{align*}
\text{Fe}^{3+} + \cdot O_2^- & \rightarrow \text{Fe}^{3+} + O_2 \\
\text{The second step is the Fenton reaction:} \\
\text{Fe}^{2+} + H_2O_2 & \rightarrow \text{Fe}^{3+} + OH^- + \cdot OH \\
\text{Net reaction:} \\
\cdot O_2^- + H_2O_2 & \rightarrow \cdot OH + OH^- + O_2
\end{align*}
\]
Conclusion

It has been shown that there has been and will continue to be a significant rise in the number of patients developing diabetes. This can be a devastating condition with the varied long term complications, which may affect different body systems and senses and be tsunami like in the overwhelming outcomes for diabetic patients. There is a demonstrated link between diabetes, kidney disease and anaemia, which may be associated with a higher morbidity and mortality in comparison to kidney patients without diabetes. It has been shown that ongoing hyperglycaemia can damage kidney cells leading to the development of CKD in up to 35% of patients with established diabetes. It will be an inevitable outcome of the injury to the renal tissue that anaemia will affect these patients. As glucose is reabsorbed through the proximal tubules, damage to the EPO producing cells may occur earlier than in CKD patients without diabetes as a co-morbidity.

Treatment of anaemia in diabetic patients with CKD is long established using ESA therapy and intravenous iron supplementation. Guidance for treating anaemia in patients with CKD and anaemia are available from National and International organisations. Monitoring blood results is essential to ensure haemoglobin levels are not normalised but remain within national and international recommended parameters. Iron stores need to be monitored as IDA is the most common cause of poor response to ESA therapy. HbA1c levels are utilised to assess glycaemic control in diabetic patients but should be interpreted with caution where diabetic patients with CKD are receiving ESA and iron therapy to manage anaemia.

If the diagnosis of diabetes and the complications of CKD and renal anaemia are devastating for the individual patient, the financial implications to the health economy are equally and potentially overwhelming.

Questions

1. How does the hyperglycaemia associated with the development of diabetes cause the long term complications which affect the kidneys?
2. Why do patients with CKD develop anaemia and why does this seem to occur earlier in patients with diabetes and CKD?
3. How is anaemia in these patients diagnosed and what specific blood tests are used to confirm a diagnosis?
4. How is anaemia treated in patients with diabetic kidney disease?
5. What is the rationale for administering iron supplementation in these patients?
6. What factors can precipitate a poor response to the treatment of anaemia in these patients?
7. When should caution be taken when interpreting the specific diabetic and anaemia related blood tests?
8. Is it advisable to normalise haemoglobin levels when managing anaemia in patients with these long term conditions?
9. What are the current national and international guidelines relating to the aspirational range for the specific anaemia management blood tests?
References:

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50. UK multicentre open-label randomised controlled trial of IV iron therapy in incident haemodialysis patients

51. 80. Protocol Short Title/Acronym: Proactive IV irOn Therapy in haemodiALysis patients (PIVOTAL) Trial

52. 81. Trial Identifiers: EudraCT Number– 2013-002267-25, ISRCTN – TBD, REC Number – 13/LO/1115


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