Review

Anaemia, a common but often unrecognized risk in diabetic patients: A review

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Abstract

Anaemia in patients with diabetes, both type 1 and type 2, is a frequent clinical finding. The mechanisms of anaemia are multifactorial and often not very well understood. Iatrogenic causes, including oral antidiabetic drugs, ACE inhibitors and ARBs, and renal insufficiency are the major causes of anaemia in patients with type 2 diabetes. In patients with type 1, the cause is often an associated autoimmune disease, and screening for autoimmune gastritis, pernicious anaemia, Hashimoto’s thyroiditis, coeliac disease and Addison’s disease is recommended. Other rare causes – including G6PD deficiency, microangiopathic haemolytic anaemia and thiamine-responsive megaloblastic anaemia – should be suspected in young patients or when the classical causes are excluded. Early detection and recognition of the cause(s) of anaemia in patients with diabetes could help to prevent other clinical manifestations as well as the complications of diabetes.

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1. Introduction

World Health Organization statistics identify 171 million people with diabetes worldwide and suggest that this figure may increase to more than 350 million by 2025. Anaemia – defined as haemoglobin levels < 130 g/L in men and < 120 g/L in women [1,2] – is a common finding in patients with diabetes. The prevalence of anaemia in patients with type 2 diabetes (T2D) has been estimated to be up to 20% in an Australian population [3] and up to 45% in a Caribbean population [4]. Diabetic nephropathy is clearly a major cause of anaemia in patients with diabetes, but an increased risk for anaemia is also observed in patients with T2D with no renal impairment, as described in recent studies where the prevalence of anaemia was 32% in unselected patients with T2D [5] and 10% in patients with T2D and normal renal function [6]. Several studies have shown that anaemia is more frequent and more severe with any level of glomerular filtration rate (GFR) in patients with diabetes compared with other patients [7,8], highlighting the fact that other causes of anaemia are associated with diabetes.

Although frequent, anaemia is often overlooked in patients with diabetes, who might be especially vulnerable to the adverse effects of anaemia in the presence of cardiovascular disease and hypoxia-induced organ damage [9]. Anaemia also predicts progression of complications of diabetes [10]. Thus, although there is no evidence that curing anaemia improves clinical outcomes, early detection and recognition of the cause(s) of anaemia in patients with diabetes could help in its management [7,11].

This review presents several common and less common causes of anaemia in the context of different aetiologies of diabetes, including autoimmune anaemia associated with type 1 diabetes (T1D) and iatrogenic causes associated with T2D.
2. Diabetes and anaemia

2.1. Renal insufficiency

It is estimated that one in five patients with diabetes and stage 3 chronic kidney disease have anaemia [12,13]. Anaemia is associated with a more rapid decline in GFR [13]. The major causes of anaemia in patients with chronic kidney disease are iron and erythropoietin (EPO) deficiencies (Table 1). Decreased responsiveness to EPO, defined clinically as a requirement for higher doses of EPO to raise blood haemoglobin to target levels in the absence of iron deficiency, is more frequent in patients with diabetes [11,14].

2.2. Erythropoietin

Many hypotheses have been formulated to explain the earlier onset of anaemia in patients with diabetes and renal involvement (Table 1) [15,16]. EPO deficiency has been observed in patients with either T1D or T2D who have relatively normal estimated glomerular filtration rates (eGFRs) [15,16].

Anaemia with EPO deficiency has been associated with the presence of autonomic neuropathy [15,16]. Secretion of EPO is modulated by activity of the sympathetic nervous system. Thus, secretion of EPO may be expected to be impaired in patients with advanced diabetic neuropathy, or when the kidney is denervated either surgically or pharmacologically. However, it has been shown that a denervated kidney in the setting of transplantation can release EPO normally [17].

In most studies to date, the predominant risk factor for the development of anaemia in patients with diabetes is impaired renal function or albuminuria [10,18]. In particular, EPO decreases in inverse relation to increasing albuminuria and decreasing GFR [10,17,18]. However, proteinuria is not the causal factor for EPO-induced anaemia, as proteinuria of non-diabetic aetiology is not associated with renal-induced anaemia [16]. The latter finding strengthens the hypothesis that EPO dysfunction in diabetic patients is due to other pathophysiological mechanisms. Some potential factors include loss of EPO-secreting interstitial fibroblasts, associated with interstitial fibrosis [19], as well as disruption of the interstitial and vascular architecture, which interferes with oxygen sensing through hypoxia-inducible transcription factor (HIF)-1α [17].

Chronic exposure to hyperglycaemia could also lead to increased apoptosis of tubular cells, vasoconstriction and tubular ischaemia [20]. Moreover, hyperglycaemia is associated with increased degradation of HIF-1 [21], the most important regulator of EPO gene transcription, and which could directly impair EPO synthesis [22]. Personal (unpublished) observations of anaemia in the hyperglycaemic chick embryo model suggest that this mechanism of anaemia may be operative in vivo [23]. Other hypotheses include decreased biological activity of EPO due to its increased glycosylation in patients with diabetes [24] or EPO ‘resistance’ due to glycosylation of the EPO receptor (Table 1) [11,15,24].

Although erythropoiesis-stimulating agents have been used to treat renal anaemia for nearly two decades, debate persists over the optimal target haemoglobin levels and their effect on different clinical outcomes [25]. In the TREAT study, a target haemoglobin level >130 g/L in patients with T2D and advanced renal disease did not improve mortality or other cardiovascular complications, and stroke was statistically more frequent in the group receiving EPO treatment. However, there was a modest improvement in patient-reported fatigue in the treated group [25].

2.3. Chronic inflammation

Diabetes is considered a chronic inflammatory state characterized by increased circulating concentrations of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, tumour necrosis factor (TNF), transforming growth factor (TGF)-β and interferons (IFNs), several of which are involved in apoptosis of erythroid progenitor cells (Table 1) [26,27].

In patients with diabetes, the lifespan of red blood cells may be affected by various disturbances in the haematopoietic microenvironment such as chronic hyperglycaemia, hyperosmolality and advanced glycation end-products (AGEs) [28].

The formation of AGEs on the surface of diabetic erythrocytes enhances both their interaction and binding to endothelial cells, thereby increasing their removal from the circulation (Table 1) [29]. However, in one recent study, erythrocyte lifespan was not altered by diabetes [28].

2.4. Insulin resistance

There is evidence that insulin is required for the development of both early and mature erythroid progenitor cells [30,31]. Both insulin and insulin-like growth factor (IGF)-1 boost activity of HIF-1α. Insulin and IGF-1 can also influence erythropoiesis more directly (Table 1) [31]. EPO production in vitro by astrocytes in primary cultures is activated by insulin and IGFs [32]. EPO levels as well as haematocrit are somewhat elevated in foetuses whose mothers have poorly controlled diabetes [33,34]. This increase in EPO is at least partially attributable to hyperglycaemia-induced foetal hyperinsulinaemia, although it is thought that foetal hypoxia, associated with placental vascular defects, may also play a role.

Insulin resistance, but not insulin deficiency or hyperglycaemia per se, is associated with inadequate hepcidin levels. Reduced hepcidin concentrations may cause increased body iron stores in insulin-resistant states [35], suggesting that hepcidin may be directly regulated by insulin and that suppressed liver hepcidin synthesis may be an important reason for the iron overload seen in T2D patients [36].

2.5. Haemolysis

Several studies have observed a relationship between glucose-6-phosphate dehydrogenase (G6PD) deficiency and the diabetic state [37]. The first anecdotal report of such an association appeared in 1964 [38]. Experimental studies have since shown that high glucose concentrations activate protein kinase A, which leads to phosphorylation of G6PD and a decrease in
3. Causes

3.1. Autoimmune gastritis and pernicious anaemia

T1D is frequently associated with autoimmune causes of anaemia, mainly autoimmune gastritis and pernicious anaemia (Fig. 1). Prevalences of autoimmune gastritis and pernicious anaemia in patients with T1D are 5–10% and 2.6–4%, respectively, compared with 2% and 0.15–1% in the general population (Table 2) [45,46]. The prevalence of parietal cell antibodies (PCA) is even higher at about 21% in patients with T1D [46]. Autoimmune gastritis and PCA antibodies have been associated with female gender, autoimmune thyroiditis, long-term persistence of glutamate decarboxylase (GAD)-65 antibodies and the HLA-DQA1*0501-B1*0301 haplotype [47,48].

Autoimmune gastritis affects the parietal cell-containing gastric corpus and fundus with sparing of the antrum [49]. Antibodies targeted against gastric H⁺/K⁺-ATPase are detected in 60–85% of patients with autoimmune gastritis, while intrinsic factor antibodies are found in 30–50% of patients with autoimmune gastritis [46]. The target autoantigen in autoimmune gastritis is the 100-kD catalytic α subunit and the 60- to 90-kD...

Table 1
Causes of anaemia and their pathophysiological mechanisms in patients with diabetes.

<table>
<thead>
<tr>
<th>Causes of anaemia in diabetic patients</th>
<th>Mechanisms</th>
</tr>
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<tbody>
<tr>
<td>Reduced erythropoiesis</td>
<td>Decreased production, EPO resistance, EPO dysfunction</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Hyporesponsiveness to EPO action, iron and EPO deficiencies</td>
</tr>
<tr>
<td>Chronic inflammation, advanced glycation</td>
<td>Suppression and apoptosis of erythroid progenitor cells</td>
</tr>
<tr>
<td>end-products</td>
<td>Decreased lifespan of red blood cells</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Low levels of HIF-1α</td>
</tr>
<tr>
<td>Haemolysis</td>
<td>Decreased EPO</td>
</tr>
<tr>
<td>G6PD deficiency-related</td>
<td>Suppression of reticulocytes</td>
</tr>
<tr>
<td>Microangiopathy</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Iron and vitamin B12 deficiencies</td>
<td>Increased oxidative stress and apoptosis</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Decreased insulin production</td>
</tr>
<tr>
<td>Low levels of thyroid hormones</td>
<td>Blood cell deformation and decreased lifespan</td>
</tr>
<tr>
<td>Rare syndromes</td>
<td>Autoimmune cause in type 1 diabetes</td>
</tr>
<tr>
<td>Drug-induced anaemia</td>
<td>Glycation of transferrin receptors in type 2 diabetes</td>
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<tr>
<td>Oral antidiabetics</td>
<td>Decreased erythropoiesis</td>
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<tr>
<td>Metformin</td>
<td>Decreased EPO production</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Microangiopathic haemolytic anaemia</td>
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<tr>
<td>Sulphonylureas</td>
<td>Thiamine-responsive megaloblastic anaemia</td>
</tr>
<tr>
<td>ACE inhibitors and ARBs</td>
<td>Inhibition of angiotensin II-mediated erythropoiesis</td>
</tr>
</tbody>
</table>

EPO: erythropoietin; HIF-1α: hypoxia-inducible transcription factor-1α; G6PD: glucose-6-phosphate dehydrogenase; ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers.

Table 2
Prevalences of autoimmune diseases and their specific autoantibodies in patients with type 1 diabetes.

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeliac disease [63]</td>
<td>2–11%</td>
</tr>
<tr>
<td>Transglutaminase antibodies</td>
<td>8–12%</td>
</tr>
<tr>
<td>Addison’s disease [69]</td>
<td>0.5%</td>
</tr>
<tr>
<td>21-Hydroxylase antibodies</td>
<td>0.7–3.0%</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis [69]</td>
<td>10%</td>
</tr>
<tr>
<td>Thyroid peroxidase antibodies</td>
<td>15–30%</td>
</tr>
<tr>
<td>Autoimmune gastritis [46,69]</td>
<td>5–10%</td>
</tr>
<tr>
<td>Parietal cell antibodies</td>
<td>15–25%</td>
</tr>
</tbody>
</table>

its activity [39]. In red blood cells, glutathione and glutathione peroxidase are considered the main routes of elimination of hydrogen peroxide (H₂O₂). The NADPH needed for this reaction is provided by G6PD. Thus, in G6PD-deficient subjects, increased oxidative stress can result in red-cell haemolysis (Table 1) [40]. Epidemiological studies have demonstrated a positive association between G6PD deficiency and T2D in various non-Mediterranean populations, such as Chinese, Indian and African populations [41–43]. In a recent study, the prevalence of G6PD deficiency was higher in patients with ketosis-prone diabetes than in patients with T2D, and insulin deficiency was proportional to the decrease in G6PD activity [37]. Glucose intolerance and abnormal first-phase insulin secretion in response to intravenous glucose have been reported in G6PD-deficient subjects [38]. In experimental studies, high glucose levels decreased G6PD expression and activity in human islets. Inhibition of G6PD increased oxidative stress and apoptosis, and decreased insulin secretion in the MIN6 beta-cell line [44]. Conversely, overexpression of G6PD in the cell line improved insulin secretion in response to high glucose concentrations [44].
glycoprotein β subunit of gastric H+/K+ ATPase [49], CD4+ T-cells are detected in *Helicobacter pylori* infections and may play an initiating role in the pathogenesis of autoimmune gastritis and pernicious anaemia by inducing autoreactive T-cells through gastric H+/K+ ATPase–*H. pylori* molecular mimicry at the T-cell level [50]. Finally, parietal cell loss from gastric mucosa may result from CD4+ T-cell-initiated perforin-mediated cytotoxicity or Fas/Fas ligand (FasL) apoptosis [51].

Autoimmune gastritis is associated with iron deficiency anaemia more frequently than with classical pernicious anaemia and often precedes vitamin B12 deficiency for years. Iron deficiency is the direct consequence of the hypo- or achlorhydria induced by autoimmune gastritis that alters iron absorption [46]. Gastric autoimmunity is often symptomatic in parietal cell antibody-positive T1D (insulin-dependent) patients [52]. In other contexts, iron deficiency has been reported in patients with T2D independently of hypochlorhydria. In such cases, it has been hypothesized that chronic hyperglycaemia promotes modulation of transferrin receptors by glycation, which might impair the capacity of these receptors to bind iron and, thus, reduce iron availability [52].

Early detection of pernicious autoimmune anaemia is important for preventing the neurological complications associated with vitamin B12 deficiency and (pre)malignant gastric lesions associated with hypergastrinaemia in autoimmune gastritis. For patients with T1D, it seems prudent to test for autoimmune pernicious anaemia at the onset of diabetes and then annually for 3 years, then every 5 years thereafter, or at any time if there are clinical indications, as the test may later become positive [48], particularly in patients with persistent GAD-65 and thyroid peroxidase antibodies [48,53].

Patients with autoimmune gastritis/pernicious anaemia have a three- to six-fold increased gastric cancer risk, ranging from 0.9–9% [48,54]. Treating patients with autoimmune pernicious anaemia and/or autoimmune gastritis implies proper follow-up. At yearly intervals, gastrin, iron, vitamin B12 levels and a complete blood count should be performed. Iron (parenterally administered) and vitamin B12 supplements should be given to patients with iron deficiency and pernicious anaemia, respectively [48]. It remains controversial as to whether patients with autoimmune gastritis/pernicious anaemia should be placed under a surveillance programme with regular gastroscopy, including multiple gastric biopsy [48], although performing gastroscopy and biopsy at least once is suggested for patients with PCA, anaemia or high gastrin levels [48]. Patients with mild-to-moderate mucosal dysplasia should be followed endoscopically every 5 years [48]. Endoscopic surveillance at 5-year intervals has also been proposed for enterochromaffin cell-like (ECL) hyperplasia, especially in patients with high gastrin (> 300 ng/L) and chromogranin A (> 120 ng/mL) levels [55].

### 3.2. Coeliac disease

This disorder is reported in 1.8–14.6% of patients referred for evaluation of iron deficiency anaemia (IDA). The most frequent direct cause of anaemia is the combination of iron and vitamin B12 deficiency [56]. Coeliac disease (CD) is a chronic immune-mediated disorder triggered by alimentary gluten [57]. Patients with CD develop CD4+ T-cell responses against several distinct gluten peptides that are recognized in the context of CD-associated HLA-DQ molecules [58]. In addition, patients make antibodies specific for gluten proteins. Tissue transglutaminase (tTG) has been determined the major autoantigen in CD. Current tTG tests are based on IgA antibodies to recombinant human tTG, with sensitivity and specificity >90% and >95%, respectively [59]. Genetic susceptibility to CD is determined mainly by the HLA-DQ locus. The strongest association is observed with HLA-DQ2.5, with >90% of coeliac patients possessing one or two copies of this [60]. The association between CD and T1D is among the most intensely studied [61]. The prevalence of CD among patients with T1D has been estimated at...
approximately 4% (range: 2–11%; Table 2) [60,61], and the risk is higher with diabetes onset in childhood (age <4 years), but also with longer diabetes duration [62,63]. Conversely, CD has also been described in association with an increased risk of subsequent T1D before age 20 years [hazard ratio (HR): 2.4; 95% CI: 1.9–3.0] [64].

Testing for CD should be offered to children with T1D, given the high prevalence in such patients and the potential consequences of delayed diagnosis. Similarly, a second peak incidence is seen in T1D adults at around age 45 years, which emphasizes that screening for CD is also required for adult diabetes patients [65]. A gluten-free diet (GFD) can improve the overall clinical course and influence the evolution of associated diseases. In some cases such as iron-resistant anaemia, a GFD will contribute to its disappearance. In other disorders such as T1D, such a diet allows better control of the disease.

3.3. Anaemia and hypothyroidism

Thyroiditis is frequently seen in patients with T1D—the estimated rate is 10% in such patients (Table 2). The prevalence of anaemia in hypothyroidism is estimated to be between 20% and 60% [66]. Anaemia was found in approximately 43% of patients with overt hypothyroidism and in 39% with subclinical hypothyroidism [67]. Anaemia in hypothyroidism can be normochromic normocytic, microcytic hypochromic or macrocytic [67]. However, the most frequent type is normochromic normocytic because of hypoproliferative erythropoiesis. Indeed, the lack of thyroid hormones is responsible for bone marrow compression due to the reduced production of EPO arising from the lower need for O2 in the hypothyroid state [67]. Levothyroxine treatment increases circulating EPO concentrations [68].

3.4. Anaemia and Addison’s disease

Although rare (the rate is about 0.5%) in patients with diabetes, Addison’s disease is 10 times more frequent in patients with T1D than in the general population [69]. Addison’s disease often causes mild anaemia, and is a cause of anaemia that should be borne in mind in patients with T1D (Table 2).

4. Anaemia-causing diseases frequently associated with T2D

4.1. Anaemia and hypogonadism

T2D, obesity and insulin resistance are associated with low testosterone levels. Fifty per cent of patients with T2D have low free testosterone compared with 30% of control subjects (Table 1). The prevalence was higher in patients with diabetes after adjusting for BMI [70]. Testosterone contributes to the 10–20 g/L difference in haemoglobin concentration between adult men and women. Testosterone enhances the proliferation of erythroid burst-forming units by stimulating specific nuclear receptors [70]. It also plays an important role in the bioavailability of iron for erythropoiesis and is associated with increased levels of hepcidin, an iron regulatory peptide [71]. Accordingly, men with hypogonadism or those taking anti-androgenic drugs frequently have anaemia [72,73]. The prevalence of normocytic anaemia in men with hypogonadotropic hypogonadism and T2D was about 40%, and was directly correlated to free testosterone and inversely correlated to CRP concentration in middle-aged diabetic men [74]. Likewise, male patients with T2D and serum testosterone concentrations <10 nmol/L were more likely to have anaemia [adjusted OR: 1.7 (1.1–2.8)] [75]. In addition, oral antidiabetic drugs have been incriminated in cases of low testosterone levels. Glitazones reduce androgen biosynthesis, increase their binding to sex hormone binding globulin (SHBG) and attenuate androgen receptor activation, thereby reducing the physiological actions of testosterone and thus causing androgen deficiency (Table 1) [76].

5. Iatrogenic causes of anaemia in diabetic patients

5.1. Metformin and anaemia

5.1.1. Vitamin B12 deficiency

Metformin impairs absorption of vitamin B12 [54], and serum vitamin B12 levels are inversely correlated to dose and duration of metformin therapy [77]. The proposed mechanisms to explain metformin-induced vitamin B12 deficiency among patients with T2D include: alterations in small bowel motility, which stimulates bacterial overgrowth and vitamin B12 deficiency as a consequence; competitive inhibition or inactivation of vitamin B12 absorption; alterations in intrinsic factor (IF) levels; and interaction with the cubulin endocytic receptor (Fig. 1) [54]. Metformin has also been shown to inhibit calcium-dependent absorption of the vitamin B12–IF complex at the terminal ileum (Fig. 1) [78]. Studies suggest that 10–30% of patients on long-term metformin therapy experience vitamin B12 malabsorption, while 6–9% of patients develop vitamin B12 deficiency [54,79]. Vitamin B12 deficiency in patients on metformin therapy can take up to 10–15 years to develop [54].

Clinical practice guidelines do not recommend routine measurement of vitamin B12 serum levels in T2D patients [54,80]. However, it is clinically plausible to screen for B12 deficiency prior to initiation of metformin and later annually in elderly patients with a history of long-term (≥3–4 years) metformin use, high doses (≥2 g/day) of metformin and clinically worsening diabetes-related distal polyneuropathy [81]. The screening approach for vitamin B12 deficiency for diabetic patients and the general population is similar. Measurement of serum vitamin B12 concentrations should be the preliminary screening step for B12 deficiency in patients with T2D. Concentrations <200 pg/mL are usually diagnostic of vitamin B12 deficiency, while concentrations >400 pg/mL confirm the absence of vitamin B12 deficiency [82]. Measurement of serum methylmalonic acid (MMA) or homocysteine concentrations is a more sensitive and specific screening approach, especially in T2D patients with borderline serum vitamin B12 concentrations of 200–400 pg/mL and subtle haematological manifestations. Serum homocysteine and MMA concentrations of 5–15 μmol/L and <0.28 μmol/L, respectively, are considered within the normal range [81].
Megaloblastic anaemia in metformin-treated patients can be reversed by the administration of oral or parenteral (intramuscular or deep subcutaneous) vitamin B12. Parenteral routes may be preferred for patients with neurological deficits. Possible concomitant folate deficiency or insufficiency (not necessarily associated with metformin use) can be treated with folic acid (1–5 mg/day orally) for 1–4 months. It is important to avoid the administration of folic acid before cobalamin treatment, as folic acid can partially reverse some of the haematological abnormalities of vitamin B12 deficiency, but not the neuropsychiatric symptoms. It is currently not known whether calcium supplementation might prevent vitamin B12 deficiency [80], and calcium supplementation should not be prescribed for the prevention or treatment of metformin-induced vitamin B12 deficiency until this has been further elucidated [81].

5.1.2. Haemolysis

Metformin-induced haemolysis is apparently a very rare complication—only a few dubious cases have been reported so far in the literature. In two such cases, Coombs-negative haemolytic anaemia was attributed to decreased G6PD activity [83,84]. In one of them, the Coombs test was positive [85] and, in the other, red-cell G6PD activity was normal and the results of a direct Coombs test were equivocal [86].

5.2. Thiazolidinediones (TZDs) and anaemia

TZDs enhance insulin sensitivity in muscle, liver and adipose tissue via activation of the gamma isofrom of the peroxisome proliferator-activated receptor (PPAR–γ), a transcription factor that regulates the expression of specific genes, especially in adipose tissue [87].

Decreases in haematocrit (Hct) and haemoglobin (Hb) when using TZDs have been reported in many clinical studies (Table 1) [87–89]. The mild decrease in Hb/Hct that commonly arises after TZD treatment appears to be a class effect seen during the first 3–4 months of treatment, but is not progressive [88]. More specifically, small declines in Hb (about 10 g/L) and Hct (up to 3.3%) have been reported with rosiglitazone and pioglitazone [87]. Decreases in Hb levels to below the normal range have also been reported in 5% of patients treated with troglitazone [89]. Anaemia has been a severe adverse event with dual PPAR-α/PPAR–γ agonists and was dose-dependent [90].

Various mechanisms have been implicated in TZD-induced anaemia (Table 1). Erythrocytes may be cleared by apoptosis-like suicidal death of mature defective erythrocytes [91], and ciglitazone has been shown to trigger suicidal death or apoptosis among nucleated cells [92]. TZDs can expand body fluid volume (dilution) through stimulation and direct activation of epithelial sodium channels (eNaC) [93]. Experimental animal studies have shown that TZD administration was accompanied by fat accumulation in bone marrow, followed by impaired haemopoiesis and anaemia [94]. In vitro studies have found that, in erythroleukaemia K562 cells, the use of TZDs suppresses both proliferation and differentiation of erythroid precursors in cells, and downregulates the erythroid lineage transcription factor GATA-1 [95]. Furthermore, a recent study in humans has demonstrated that PPAR–γ can delay the maturation and proliferation of primary erythroid progenitor cells [96].

5.3. Sulphonylureas and anaemia

Rare haematological side-effects of sulphonylureas include haemolytic anaemia. Case series in the literature have reported acute haemolysis after the administration of glyburide [97]. Pure red blood cell aplasia was found in association with chlorpropamide therapy (Table 1) [98].

5.4. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)

Both ACE inhibitors and ARBs cause reversible decreases in Hb concentrations in patients with diabetes and chronic kidney disease [99]. Angiotensin II is an important regulator of erythropoiesis and has two key actions: first, it acts as a growth factor for erythroid progenitors and, in cooperation with EPO, increases red blood cell mass; and second, it acts as an EPO secretagogue (Table 1) [100]. Patients with renovascular hypertension and kidney transplant recipients with transplant renal artery stenosis have higher Hct levels than their counterparts with normal renal arteries [101]. Long-term administration of losartan in patients with diabetes and albuminuria is expected to lower Hb by 6 g/L [12]. Studies have shown that both these classes of agents can induce or worsen symptomatic anaemia in patients with nephropathy [102]. Double blockade with an ACE inhibitor and ARB combined is associated with greater decreases in Hb concentration [102].

6. Other conditions related to anaemia in diabetic patients

6.1. Microangiopathic haemolytic anaemia

Microangiopathic haemolytic anaemia is a rare complication of diabetes and the actual existence of the condition is uncertain [103]. It has, however, been reported that erythrocytes in patients with T2D have increased fragility and susceptibility to mechanical haemolysis [104]. This may favour haemolysis as erythrocytes circulate through the microangiopathic blood vessels, resulting in haemolysis due to mechanical factors (Table 1).

6.2. Rare syndromic causes

Anaemia may also be associated with a rare syndromic form of monogenic diabetes known as thiamine-responsive megaloblastic anaemia (TRMA) syndrome (Table 1) [105]. TRMA syndrome is an autosomal-recessive disorder characterized by diabetes, megaloblastic anaemia and sensorineural deafness due to mutations in SLCL192A, which encodes a thiamine transporter protein [106]. The onset of disease is usually during infancy or in early childhood, and most TRMA patients are from consanguineous families. In addition to these cardinal components, other findings such as thrombocytopenia, pancytopenia, optic atrophy, retinal degeneration, cardiomyopathy,
arrhythmias, congenital heart defects and stroke have been reported in association with TRMA syndrome [105,106]. Diabetes in this syndrome is due to a non-immune mechanism and is most likely secondary to impairment of islet cell function due to intracellular thiamine deficiency. The dose of thiamine necessary to treat or prevent the symptoms of TRMA syndrome and the timing of therapy are not yet clarified. The time of onset of histopathological changes caused by intracellular thiamine deprivation is also still not known. Theoretically, these alterations may even begin during intrauterine life. Nevertheless, it seems logical to assume that the earlier the treatment is started, the better the response will be in these patients [105].

7. Conclusion

Anaemia is one of the world’s most common preventable conditions, yet it is often overlooked, especially in people with diabetes (Fig. 2). Renal insufficiency and albuminuria are key elements in the understanding and investigation of anaemia. Patients with renal insufficiency should be controlled for low levels of EPO and anaemia associated with the use of drugs blocking the aldosterone–renin axis (ACE inhibitors and ARBs) as well as their chronic inflammatory status (CRP, IL, TNF), especially in the context of associated morbidities such as cardiac insufficiency. Oral antidiabetic drugs (especially metformin) should also be taken into account when screening for iron and vitamin B12 deficiencies. Anaemia in patients with T1D and normal renal function should lead to screening for other autoimmune-associated diseases, including autoimmune gastritis, coeliac disease and hypothyroidism or Addison’s disease. For patients with T2D and normal renal function, iatrogenic causes are more frequent and more commonly associated with oral antidiabetic drugs, ACE inhibitors and ARBs. In male patients, low testosterone levels may also contribute to the development of anaemia (Fig. 2).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2014.06.001.

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