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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.

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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 is 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 could thus 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 glycation 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 proinflammatory 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, hyperosmolarity 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

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