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# Anemia in diabetes mellitus: Pathogenetic aspects and the value of early erythropoietin therapy

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ABSTRACT

Anemia is a frequent, yet increasingly recognized, comorbidity in diabetes mellitus (DM), with prevalence often driven by multifactorial mechanisms. Hematinic deficiencies, common in this population, may arise from associated comorbidities or medications, such as metformin, as well as other drugs commonly employed for DM-related conditions. Among contributing factors, diabetic kidney disease (DKD) plays a pivotal role, with anemia developing more frequently and being more pronounced in earlier stages, than in CKD of other causes. This enhanced susceptibility stems primarily from the combined impact of impaired renal oxygen sensing and deficient erythropoietin (EPO) production linked to tubulointerstitial fibrosis. Additional mechanisms comprise glomerular dysfunction, shortened erythrocyte lifespan, uremia-induced bone marrow suppression, and increased bleeding risk. DM is also recognized as a chronic low-grade inflammatory condition, with its inflammatory burden driving iron maldistribution, suppression of erythropoiesis, and resistance to EPO. The diagnostic approach of anemia in DM mirrors that in the general population. Addressing modifiable causes such as hematinic deficiencies, and other chronic conditions, such as DKD and bone marrow disorders, is paramount. In total, the underlying pathophysiology of anemia in DM primarily reflects a state of absolute or relative EPO deficiency and/or diminished bone marrow responsiveness, effectively corresponding to 'anemia of chronic disease. Early initiation of EPO therapy, even in DM patients without overt DKD, may mitigate disease progression and improve outcomes. Future research should focus on diabetes-specific strategies integrating optimal EPO use, potentially implementing targeted management of renal and inflammatory contributors to anemia.

## 1. Introduction

Diabetes mellitus (DM) is currently one of the most significant global health challenges, affecting millions of individuals worldwide. The World Health Organization (WHO) estimates that over 460 million people currently live with diabetes, a number that is expected to rise substantially in the coming decades [1].

Anemia is a common comorbidity in individuals with DM, and its relevance has been increasingly recognized as a critical aspect of diabetic care. According to recent studies, anemia affects a significant proportion of individuals with diabetes, while also exerting a considerable impact on clinical outcomes and quality of life.

Erythropoiesis in the bone marrow depends on erythropoietin (EPO) signalling on erythrocyte progenitors. EPO is primarily produced by a specific subpopulation of fibroblasts located in the deep cortex and outer medulla of the kidney [2]. Its production is regulated by changes in the oxygen levels available to these cells. In anemic conditions hypoxia inhibits prolyl hydroxylase domain (PHD) enzymes, preventing the prolyl-hydroxylation and degradation of Hypoxia-inducible factor 1α (HIF1α) that typically occurs under normal oxygen levels [3]. This inhibition allows HIF1α to combine with HIF1β, forming a heterodimer. The heterodimerized HIF1 then functions as a transcription factor, driving the transcription of EPO.

The pathophysiology of anemia in diabetes is complex and incompletely elucidated. The most common underlying factor is decreased EPO secretion, either in absolute terms or relative to the degree of anemia, or reduced responsiveness in the bone marrow. From this perspective, anemia in DM can be essentially considered a form of

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**Table 1**
Factors underlying anemia in diabetes mellitus and their impact on erythropoietin secretion by the kidney or responsiveness in the bone marrow.

| Factors | EPO secretion | EPO responsiveness |
|---|---|---|
| Hematinic deficiencies | | |
| Iron | NA | ↓ |
| B12/folate | NA | ↓ |
| Others | NA | ↓ |
| Antidiabetic drugs | | |
| Metformin | NA | ↓ |
| Pioglitazone | ? | ↑ |
| SGLT2i | ↑ | NA |
| DPP4i | NA | ↑ |
| Insulin | NA | ↑ |
| Diabetic Kidney Disease | | |
| Azotaemia | NA | ↓ |
| Hyperfiltration | ↓ | NA |
| Albuminuria | ↓ | NA |
| Altered HIF-1α expression | ↓ | NA |
| Tubulointerstitial Fibrosis | ↓ | NA |
| BMAT dysfunction | NA | ↓? |
| Chronic low-grade inflammation | NA | ↓ |
| Myelodysplasia | NA | ↓ |
| Others | | |
| Erythrocyte fragility | NA | NA |
| ER glycation | NA | ↓? |
| ER autoantibodies | NA | ↓ |

BMAT: Bone Marrow Adipose Tissue; DPP4i; dipeptidyl-peptidase-4 inhibitors; EPO: erythropoietin; ER: Erythropoetin receptor; HIF-1α: hypoxia-induced factor $1^{\alpha}$; NA: not affected; SGLT2i: Sodium-glucose cotransporter 2 inhibitors.

functional EPO deficiency, a feature it shares with chronic kidney disease (CKD). However, while EPO analogs are the mainstay of treatment for anemia in CKD regardless of its cause, there are no specific recommendations regarding their use in diabetes without overt diabetic kidney disease (DKD), defined as an increased urinary albumin excretion (>30 mg/g creatinin) with or without diminished glomerular filtration rate (eGFR<60 ml/min).

This narrative review aims to explore the mechanisms, clinical implications, and potential therapeutic strategies for anemia in DM, with an emphasis on the potential benefits of early EPO treatment in certain cases, even in the absence of overt diabetic kidney disease (DKD).

## 2. Epidemiology of anemia in diabetes mellitus

A multitude of observational studies indicate that anemia, most commonly characterized by the WHO definition as a hemoglobin concentration <13 and < 12 g/dl for males and females, respectively, is highly prevalent among individuals with DM. A recent meta-analysis of observations mostly conducted in Asia or Africa, the overall pooled anemia prevalence in the diabetic population is as high as 35.45 %, with highest rates ascertained in studies of Asian origin [4]. The prevalence of anemia appears to increase with older age and longer DM duration [4–7], CKD [8], DM type (type 2 vs. type 1) [6,7], whereas data on the effect of gender are equivocal, without an overall gender-biased predominance [4,6,7]. Furthermore, its frequency may partly fluctuate depending on geographical region appearing higher in Asian studies than Africa, whereas data from Europe or America are too scarce for accurate estimations [4]. According to the same source [4] the prevalence of anemia in DM appears to increase over time.

## 3. Erythrocyte features in anemia of DM

Given the multifactorial nature of anemia in DM, its erythrocytic features are mandated by the primary underlying cause (see also below). For instance, iron or B12/folate deficiency are associated with diminished or increased mean corpuscular volume and mean hemoglobin concentrations, respectively. In contrast, anemia attributable to DKD or reduced EPO secretion or responsiveness exhibits features of that in chronic disease, namely being normocytic/normochromic or slight hypochromic. A higher red cell distribution width (RDW) in DM has been associated with a multitude of DM-related complications such as retinopathy, nephropathy and macrovascular disease [9]. In individuals without DM, RDW is also associated with a more adverse metabolic profile, whereas in contrast in DM, RDW shows an inverse relationship with HbA1c, likely reflecting progressively diminished peripheral erythrocyte survival [10].

## 4. Pathogenetic and pathophysiological aspects of anemia in DM

A variety of factors associated with, or mechanisms modulated by DM may contribute to the increased anaemic propensity in this population (Table 1, Fig. 1).

### 4.1. Hematinic deficiencies

#### 4.1.1. Iron

Individuals with DM1 (both children and adults) and DM2 have a

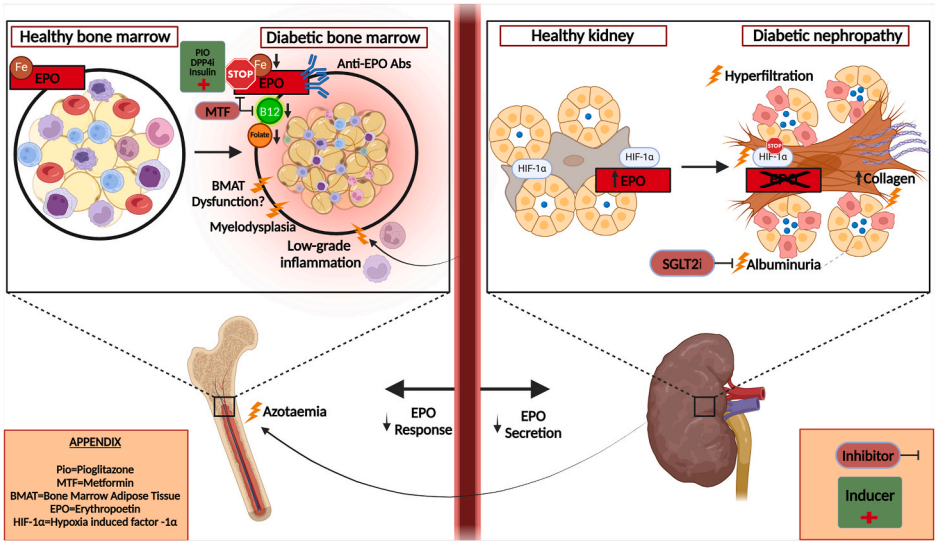


**Fig. 1.** Overview of the mechanisms implicated in the pathogenesis of anemia in diabetes mellitus by inducing a state of relative or absolute EPO deficiency and/or reduced bone marrow responsiveness.

higher prevalence of iron deficiency [11–13]. This may result from factors such as the use of antiplatelet or anticoagulant drugs, gastrointestinal polyps [14], colorectal cancer [15] or vascular dysplasias linked to chronic kidney disease or aortic stenosis [16]. Celiac disease, which co-occurs in 3–16 % of DM1 cases, can cause iron and other nutrient deficiencies due to malabsorption [17]. Notably, the reliability of standard iron tests may be affected by DM's inflammatory environment, requiring heightened clinical awareness to identify those who may benefit from iron supplementation, especially in those with chronic kidney disease or heart failure [18].

#### 4.1.2. Folate and vitamin B12

Folate and vitamin B12 are crucial for converting homocysteine to methionine, and their deficiency can lead to elevated homocysteine levels, a risk factor for both macrovascular and microvascular DM complications [19–23]. B12 deficiency may also cause sensory dysfunction resembling diabetic symmetric sensorimotor polyneuropathy (DSPN), or potentially contributing to its development [24]. Furthermore, several observations have linked chronic metformin treatment to B12 and folate depletion [25–28]. Therefore, maintaining adequate folate and B12 levels in DM patients goes beyond their role in erythropoiesis, as deficiencies may increase the risk of organ complications.

Folate deficiency has been associated with a more adverse metabolic profile in preclinical models [29] and human studies [30], while a low folate intake in young adults signifies an increased future risk for DM [31]. Conversely, folate supplementation may improve markers of glycemia and insulin resistance in patients with DM [32].

B12 deficiency is highly prevalent in T2D, typically in conjunction with chronic metformin therapy, with estimates ranging between 6.6 and 22.1 % and considerably higher among those with diabetic sensorimotor polyneuropathy [25,33–40]. The suggested mechanism implicates the disruption of the calcium-dependent intrinsic factor-B12 complex intestinal absorption [41]. Decreased B12 concentrations are also found in T1D [42]. In this population, autoimmune gastritis/pernicious anemia occurs roughly threefold more commonly than the general population [43]. Gut dysbiosis and bacterial overgrowth in DM [44–46] could also be implicated in B12 depletion via increased utilization by intestinal microbiota [45].

#### 4.1.3. Others

Copper is essential for erythropoiesis, and its deficiency can cause anemia and erythroid hypoplasia [47]. Poor glycemic control in T2D is linked to lower copper levels [48]. Copper deficiency, leading to myelopathy, can also result from bariatric surgery, often used to treat difficult-to-control T2D [49,50]. Similarly, low pyridoxal phosphate-B6 levels, important for erythropoiesis, are associated with DM [51] and certain chronic complications [52]. However, the role of copper or B6 deficiency in the wider T2D population remains uncertain.

### 4.2. Antidiabetic drugs

Within the armamentarium of antidiabetic drugs, certain medication classes have been implicated in increased anaemic propensity or conversely, improved hemoglobin levels.

An abundance of studies has linked metformin to increased anemia risk. Apart from folate/B12 deficiency, metformin has been associated with rare cases of haemolytic anemia where autoimmunity, G6PD-deficiency related, or unknown mechanisms have been implicated [53–55]. Evidence from large trials as well as real-world data indicate that a reduction of hemoglobin concentration occurs during the first months of metformin treatment and follows a non-progressive course, suggesting underlying factors other than folate/B12 deficiency [56]. Metformin can modulate normal haematopoiesis in ways with may be exploited in certain morbid conditions, such as a FOXO3-dependent HbF induction in sickle cell [57,58] or inhibition of nemo-like kinase (NLK) in Diamond-Blackfan anemia [59]. The latter can be postulated to contribute to anemia in otherwise haematologically healthy individuals [60].

Treatment with pioglitazone has been associated with small (<1 g/dl) decreases of hemoglobin concentration and increases the risk of anemia [56,61]. Thiazolidinediones promote sodium and water retention and hence increase plasma volume, suggesting a dilutional underlying component [62], however studies implementing body composition estimations have disputed this hypothesis [63,64]. The presence of other mechanisms has been supported by the persistence of anemia after pioglitazone withdrawal, despite the return of body weight to pre-treatment levels [65]. On the other hand, pioglitazone treatment increases the effectiveness of EPO with lower required doses in the long term in patients undergoing haemodialysis, an effect presumably mediated via its insulin-sensitizing effects [66].

No other antidiabetic classes have been associated with an increased risk of anemia. On the contrary, sodium-glucose co-transporter type 2 inhibitors (SGLT2i) appear to increase hemoglobin levels, presumably by inducing hemoconcentration and ameliorating renal hypoxia, resulting in more efficient EPO secretion [67]. A large cohort study conducted among participants in DAPA-CKD and CREDENCE trials has demonstrated that treatment with SGLT2i is associated with a lower incidence of new anemia among individuals with T2D and DKD, compared with those receiving GLP-1R agonists [68]. Dipeptidyl-peptidase-4 inhibitors (dpp4i) likely increase EPO responsiveness and decelerate hemoglobin decline in DKD [69,70]. Rare occasions of G6PD-related or immune-mediated hemolysis [71] and aplastic anemia [72] have been attributed to the use of, particularly earlier generation, sulfonylureas; apart from these, no evidence exist for an increased prospensity to anemia in those receiving insulin-secretors or insulin. In fact, insulin has been shown to potentiate the effects of EPO on erythroid progenitors *in vitro*, via both insulin- and IGF-1 receptor signalling [73].

### 4.3. Diabetic kidney disease

Anemia is common in chronic kidney disease across a wide spectrum of aetiologies, typically observed CKD of stages III or higher and becoming more prevalent with worsening renal function, reaching ~90 % in patients on dialysis [74]. Conversely, anemia at early stages or renal involvement in DM has been acknowledged as a risk factor for DKD progression [75]. Renal anemia harbours a multi-factorial pathophysiology. A central role is attributed to EPO deficiency, presumably due to the kidney being the major source of its production. Nevertheless, accumulating evidence indicates that defective EPO production in CKD emerges due to dysregulation of renal oxygen sensing rather than representing a decline in EPO production capacity, effectively rendering CKD a state of "functional HIF-1a deficiency" [76,77], as showcased by the efficacy of Hypoxia inducible factor prolyl hydroxylase inhibitors in the treatment of renal anemia in several clinical trials [78,79]. Even though the absolute EPO level may not be reduced in renal parenchymal disease, it is still inappropriately low for a given hemoglobin concentration, and this divergence becomes more pronounced as GFR further declines [80]. Other contributing factors include reduced erythrocyte lifespan in the uremic environment due to increased fragility and compromised deformability [81], platelet dysfunction leading to haemorrhagic propensity [82], as well as uremia-induced bone marrow suppression [83,84].

DKD is more associated with more frequent and more severe anemia, particularly at early CKD stages compared with CKD of other aetiologes [85,86], suggesting either a more aggravated renal anemia pathophysiology or the simultaneous effect of additional mechanisms. The latter notion is strengthened by the independent association of DM diagnosis with anemia, even after adjustment for GFR [87].

#### 4.3.1. Hyperfiltration and cardiac autonomic neuropathy

Glomerular hyperfiltration, a supra-physiological increase in GFR is considered the initial phase of DKD, before more apparent and partially irreversible functional or structural alterations take place; its prevalence greatly varies with reports ranging from 10 to 63 % for type 1 and 6–73 % for type 2 DM [88]. Even though its pathophysiology is complex an incompletely elucidated, a dysregulated blood flow within the renal tissue could result in oxygen abundance and promote proline hydroxylation of HIF-1a, leading to reduction of EPO secretion. A similar mechanism implicating perturbed renal hemodynamics could underly the observed association between diabetic cardiac autonomic neuropathy and anemia [89]. Thereby, regional blood volume regulation due to neurovascular dysfunction and sympathetic/parasympathetic disequilibrium [90] could lead to regional parenchymal hyperperfusion and decreased EPO secretion.

#### 4.3.2. Albuminuria

Increased albumin excretion in DKD, defined as a ratio of urinary albumin to creatinine concentration of >30 mg/g is associated with anemia independently of GFR 26430892, while a graded relationship between the severity of urinary albumin secretion and anemia has been demonstrated, for each GFR-determined CKD stage [91–95]. Anemia has been identified as an independent risk factor for albuminuria in DKD by other studies. Even though this may reflect reverse causality [96], anemia has also been shown to prospectively predict albuminuria progression among individuals with T2D. On the other hand, a recent analysis of 2011–2020 data from 8.868 participants with and without diabetes in the National Health and Nutrition Examination Survey (NHANES) revealed a U-shaped relationship between albuminuria and anemia, with both low and high hemoglobin values correlating increased urinary albumin excretion, although the association with anemia was stronger [97]. Although this may appear contradictory, this may reflect the known association between increased hemoglobin and an adverse metabolic profile among those without DM, partially driven by active smoking or obstructive sleep apnoea syndrome [98].

As mentioned above, the prevalence and degree of anemia in albuminuric DKD is not interpretable by a declining GFR. It has been suggested that albuminuria in DKD predisposes to iron deficiency anemia, owing to glomerular transferrin leakage in urine [99,100]. EPO has a molecular weight of 30 KDa which falls in the lower range of excreted proteins in DKD [101,102] while its urinary excretion has been shown to increase in cases of nephrotic range proteinuria [103,104]. The contribution of this mechanism however in earlier cases of albuminuric DKD has not been to date investigated. Likewise, whether albuminuria could merely represent a surrogate for DM-induced endothelial dysfunction and microvascular changes in renal interstitial tissue causing early EPO deficiency remains to be elucidated [105,106].

#### 4.3.3. Treatment with ACEi/ARBs

Angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) are the antihypertensive classes preferentially used in individuals with DM, especially in those with increased urinary albumin excretion, to reduce the rates of DKD progression and cardiovascular events [107]. Both medication classes have been shown to dose-dependently reduce hemoglobin levels [108,109] and increase anemia rates [110], which may dampen their cardioprotective effects [111]. The underlying mechanism likely concerns the inhibition of EPO expression in renal tissue by angiotensin II [112]; indeed, treatment with ACEi has been shown to rapidly decrease EPO levels [113]. Since angiotensin II exerts a proliferation-stimulating effect on erythrocyte progenitors [114], it appears likely that blockade of its signalling may disrupt normal erythropoiesis in bone marrow. The magnitude of expected hemoglobin reduction with ACEi/ARB treatment may be low in absolute terms [115], however it should be taken into account in the differential diagnosis of anemia in DM, given their universal use in this population.

#### 4.3.4. Altered HIF-1α expression in DM

Hypoxia-driven HIF-1α heterodimerization is crucial for the transcription of the EPO gene in the kidney. A negative effect of hyperglycemia on HIF-1α expression and stability has been demonstrated in human skin fibroblasts and renal tubular cells [116,117] whereas insulin exerts the opposite effect in various cell types [118,119]. It would hence be conceivable that insulinopenia and/or insulin resistance as well as hyperglycemia in the frame of DM could impair renal HIF-1α expression and EPO release. Even though there are observations suggesting a diametric, positive effect of hyperglycemia on HIF-1α [120], other DM-related metabolic abnormalities could also contribute to post-transcriptional disruptions of HIF-1α pathway. For instance, an increased non-esterified fatty acid concentration promotes prolyl-hydroxylation of HIF-1α via succinate reduction, rendering it susceptible to proteolysis [121]. Likewise, methylglyoxal, a byproduct of glycolysis increased in T2D, exerts detrimental effects on HIF-1α survival and heterodimerization [122].

#### 4.3.5. Tubulointerstitial immunofibrosis

Tubulointestinal fibrosis becomes a cardinal feature during the progression of renal disease. Thereby, EPO deficiency may emerge as a result of loss of functional interstitium due to scarring or alternatively, due to functional perturbations of EPO-producing fibroblasts, including but not limited to their myofibroblast activation. Indeed, among patients with early stages of renal involvement without GFR impairment, hemoglobin concentration has been shown to strongly correlate with the degree of interstitial fibrosis [75,123].

Interstitial fibrosis is marked by appearance of myofibroblasts producing collagen and other extracellular matrix components in the renal interstitium [124]. Myofibroblasts originate from the activation of resident fibroblasts [125] or mesenchymal transformation of proximal epithelial cells, pericytes, endothelial cells or macrophages undergoing mesenchymal differentiation [126–128]. This likely emerges during the course of renal damage in DM, under the influence of transforming growth factor β, hyperglycemia, RAAS components, advanced glycation end-products and increased urinary protein content, among others [129,130] and via diverse signalling pathways [129]. A key role in this transition has been attributed to connective tissue growth factor/cellular communication network 2 (CTGF/CCN2) [131,132]. Macrophage infiltrates may contribute to progression of renal disease, both via the secretion of pro-inflammatory cytokines (M1-like phenotype) or by partaking in the fibrotic cascade (M2-like phenotype) [127].

Interestingly, an increased albumin protein content originating from the glomerulus induces proximal tubular cell IL-8 expression, a potent neutrophil chemoattractant [133]. Accordingly, a role in the pathogenesis of DKD has been increasingly recognized lately for both IL-8 [134–136] and neutrophils, through the release of neutrophil extracellular traps (NETs) [137,138]. NET release has been shown to trigger the transition of endothelial to mesenchymal cells [139], hence promoting renal parenchymal fibrosis. Furthermore, experimental observations by our study group advocate for the presence of a crosstalk between neutrophils and tissue fibroblasts, mediated by NETosis in other disease models [140,141]. Thereby, exposure to NETs suffices to induce a pro-fibrotic, myofibroblast-like phenotype, characterized by up-regulation of cytoskeletal proteins alpha-smooth muscle actin (αSMA) and vimentin as well as connective tissue growth factor/cellular communication network-2.

It could be hypothesized, that in the case of DKD, neutrophils infiltrating the renal interstitium could through NETosis not only induce resident fibroblast differentiation towards myofibroblasts but potentially undermine their EPO-producing capacity. The above hypothesis is in accordance with previous observations demonstrating increased tubulointestinal expression of αSMA and vimentin in diabetic kidneys, also bearing a strong predictive value for progressive DKD [142].

### 4.4. Bone marrow adipose tissue dysfunction

Bone marrow adipose tissue (BMAT) constitute distinct functional units compared with other adipose tissue depots. In comparison, bone marrow adipocytes (BMAs) exhibit higher basal glucose uptake and are responsive to insulin, albeit to a lesser degree than white adipocytes [143], while they exhibit insulin resistance in T2D [144]. It has been speculated that the augmented basal glucose uptake by BMAs fuels *de novo* lipogenesis and produced fatty acids are utilized for energy productions for adjacent hematopoietic cells [143], while production and paracrine action of adipocines and cytokines supports their survival [145]. Based on available evidence, BMAT is considered to play a pivotal role both in healthy haemopoiesis (including erythropoiesis) and in haematological malignancies originating from both marrow [146].

Data from animal studies have demonstrated a significant BMAT expansion in mouse models of T1DM as well as T2DM, whereas in humans such alterations are of lesser magnitude and unclear significance [147]. Furthermore, bariatric surgery which is known to impose dramatic improvements on the glycemic status in patients with DM appears to improve BMAT insulin sensitivity [144], however its effects on BMAT volume are ambiguous and likely surgery-type dependent [148]. Overall, it could be hypothesized that alterations of BMAT physiology or volume in the context of systemic dysmetabolism and DM could affect erythropoiesis, presumably leading to anemia, there is however a lack of unequivocal evidence to support this notion.

On the other hand, EPO administration has been shown to decrease BMAs and BMAT volume in obese mice [149,150]. This suggests that the expansion of BMAT and the subsequent disruption of normal haematopoiesis could be a result of EPO deficiency. However, the causal relationship between these observations has yet to be established.

### 4.5. Chronic low-grade inflammation

Anemia in chronic inflammation emerges as a result of several pathogenetic aspects brought about by the inflammatory process. These include reduced iron availability for haematopoiesis due to hepcidin up-regulation and iron sequestration in the reticuloendothelial system, decreased peripheral erythrocyte survival due to macrophage activation and erythrophagocytosis. Furthermore, suppression of bone marrow erythropoiesis and resistance to EPO is induced by inflammatory cytokines such as tumor necrosis factor-alpha (TNFα), IL-1 or interferon gamma [151].

DM itself is marked by chronic low-grade inflammation, which is characterized by increased levels of acute-phase proteins and proinflammatory cytokines, such as TNF-α and IL-6, especially in individuals with existing DM-related complications [152–156]. These could not only directly affect erythropoiesis in bone marrow but also peripheral erythrocyte lifespan. However, a reduced peripheral survival has not been observed in even poorly controlled DM based on objective measures [157].

The elevated circulating acute-phase cytokines in DM could presumably up-regulate hepcidin, resulting in hypoferremia. Activin B also acts as a hepcidin inducer [158] and a positive correlation of activin B with HbA1c and insulin resistance markers has been noted in T2D [159], which could further restrict iron availability in the setting of hyperglycemia. Ferritin concentration is elevated in DKD compared to other CKD, suggesting either a role of chronic low-grade inflammation or the presence of dysmetabolic iron overload syndrome [86]. Despite available data showing increasing trends for hepcidin in T2D, low hepcidin levels have been demonstrated by most studies in states of insulin resistance and T2DM [160,161]. The exact mechanisms behind this discrepancy are unclear, however hepcidin suppression is a cardinal component of dysmetabolic iron overload in DM; hepcidin gene expression is induced by the signal transducer and activator of transcription-3 (STAT3) pathway [162] which is also stimulated by insulin [163]. It appears likely that chronic hyperinsulinemia in the setting of insulin resistance/T2DM may modulate STAT3 signalling and suppress hepcidin expression. On the other hand, similarly low hepcidin levels and increased intestinal iron absorption have been ascertained in insulin-deficient streptozotocin-induced DM mice [164].

In total, the chronic inflammatory niche is another plausible component of anemia in DM, its relative contribution is however challenging to estimate. The parallel development of metabolic iron overload should also be considered when interpreting routine laboratory estimates of iron status (e.g. iron, ferritin, transferrin saturation).

### 4.6. Myelodysplastic syndrome

An unexplained anemia of slowly progressive magnitude without apparent hematinic deficiencies may be caused by an underlying myelodysplastic syndrome (MDS). Myelodysplastic syndromes are bone marrow malignancies emerging through the clonal expansion of a hematopoetic precursor and resulting in ineffective erythropoiesis, anemia with dysplastic features and/or other cytopenias and an increased tisk of progression to acute leukemia [165]. EPO may be used for increasing hemoglobin and reducing transfusion dependency in patients with low-risk MDS, particularly in those with lower circulating EPO levels (200 IU/L) [166].

Obesity is a major risk factor for both MDS and T2D [167] and prevalence of T2D is higher in MDS patients than the general population, also associated with a more adverse cardiometabolic profile, lower performance status and quality of life [168]. Furthermore, MDS in T2D is associated with a greater likelihood of infection and more adverse prognosis, especially in those with low-risk features [169]. MDS likely underlies a small proportion of DM-associated anemia cases, however it should be suspected in the presence of concomitant leucopenia or thrombopenia, dysplastic erythrocyte features in peripheral blood smear or unexplained macrocytosis in the absence of B12/folate depletion.

### 4.7. Other putative mechanisms

Although devoid of concrete evidence to corroborate their importance, various other candidate mechanisms could hypothetically contribute to perturbed erythropoiesis and anemia in DM, and their putative role merits further investigation. Hyperglycemia and/or altered insulin signalling could impact erythrocyte energy status and intracellular metabolite content and result in increased fragility or susceptibility to oxidative damage [170,171]. Non enzymatic glycation of EPO receptor in the setting of hyperglycemia could affect the kinetics of EPO binding resulting in altered effects [172]. Furthermore, autoantibodies versus EPO receptor are occasionally encountered chiefly in patients with immune-mediated diseases, and their presence is associated with bone marrow erythroid hypoplasia and anemia [173]. Such autoantibodies were detectable in 7.3 % of T2D individuals participating in CREDENCE trial and their presence was associated with increased risk of the renal primary outcome, cardiovascular and overall mortality, but not with the risk of anemia. Likewise, autoantibody positivity did not hamper the beneficial effects of canagliflozin treatment on hemoglobin concentration [174].

## 5. Consequences of decreased hemoglobin concentration in DM

### 5.1. Spurious HbA1c

HbA1c values reflect the average glycemia of the preceding 2–3 months [175]. Anemia is a major source of HbA1c biological variability and may render its values unreliable. In general, conditions of high erythrocyte turnover tend to produce spuriously low HbA1c values, whereas suppressed bone marrow erythropoiesis has the opposite effect [176]. Currently, there exist no universal consensus as per the magnitude of HbA1c deviation from its “true” value that would be considered clinically significant, although from the standpoint of affecting patient

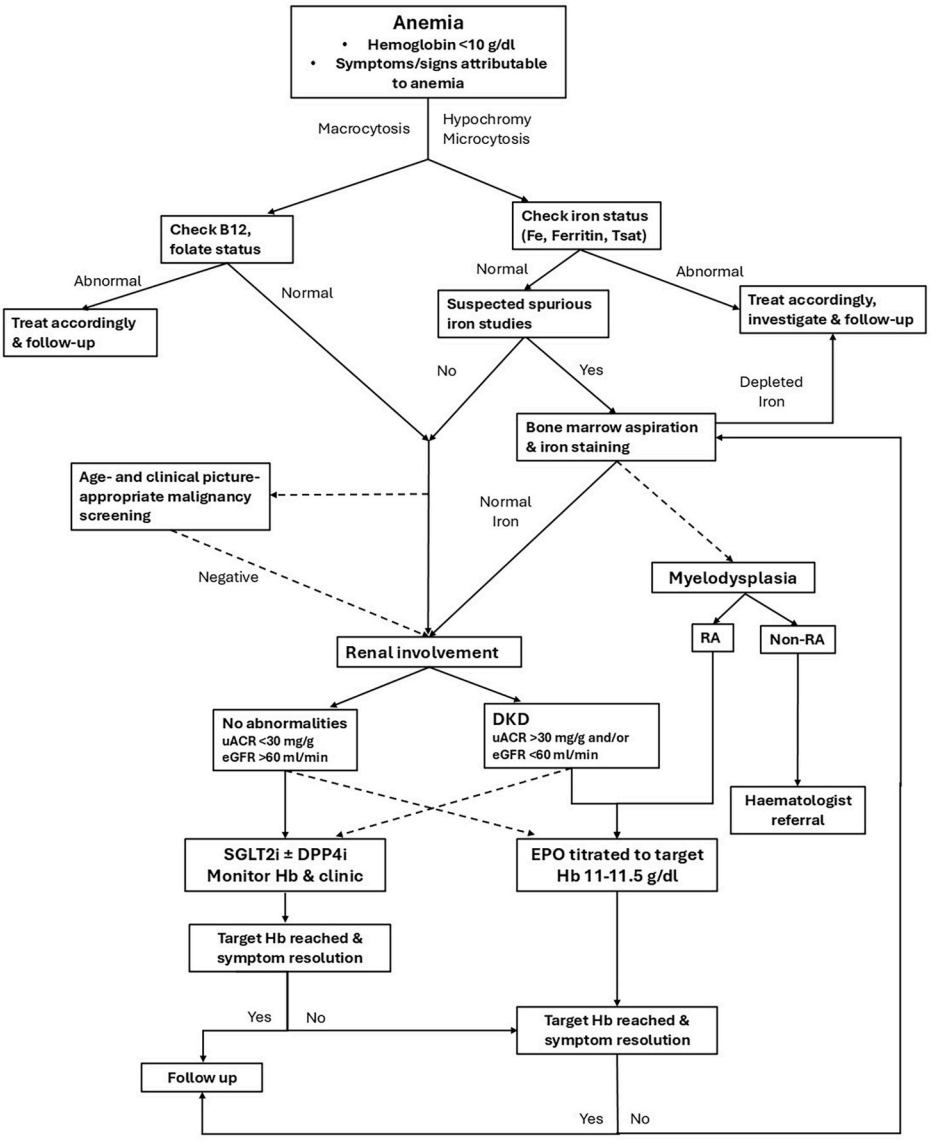


**Fig. 2.** Suggested diagnostic and therapeutic algorithm for anemia in diabetes mellitus.

care and modifying the risk of future complications, changes of ±0.5 % are considered significant by various sources [177].

### 5.2. *Effect on the risk of complications*

Quantifying the additive risk conferred by anemia on the risk of DM-related complications may be challenging, given that the presence of complications itself is associated with increased prevalence of low hemoglobin concentration [178]. Anemia is associated with present or incident microvascular disease, namely retinopathy [78,179–181] peripheral sensorimotor polyneuropathy [182], DKD [183–185] and diabetic foot ulceration [186–188]. The evidence regarding its relationship with macrovascular disease is equivocal for the general T2D population, (Relationship between Anemia and Chronic Complications in Chinese Patients with Type 2 Diabetes Mellitus, archives of Iranian medicine) although it likely exerts additive harming effects in those with DKD [189,190]. Furthermore, anemia adversely affects myocardial function [191] and is associated with an increased risk of heart failure hospitalization [192]. Anemia also associated with a considerably diminished quality of life in DM patients, although it is unclear whether this relationship is direct or mediated by the concomitant increased prevalence of chronic DM complications [193].

It is less clear whether treatment of anemia other than replenishing hematinic deficiencies is beneficial for DM complications. Evidence demonstrates potential benefits for erythropoetin use in diabetic retinopathy [194,195] and cardiac autonomic neuropathy [196]. Furthermore, EPO supplementation has shown to accelerate wound healing in both preclinical models [197,198] and DM patients [199], even at low doses not affecting hemoglobin levels [200]. An important hallmark was set by the Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin alpha) Therapy (TREAT). Therein, individuals with T2D, pre-dialysis DKD and hemoglobin <11 g/dl were randomized between darbepoetin alpha targeting a hemoglobin level of 13 g/dl versus placebo with rescue darbepoetin therapy if hemoglobin fell below <9 g/dl. After roughly 2.5 years, darbepoetin treatment resulted in fewer cumulative transfusions and a modest improvement in self-reported fatigue at the expense of an almost double risk for stroke (HR 1.92), with no benefits regarding primary outcomes (composites of death and cardiovascular disease, death and end-stage renal disease) [201]. The risk of stroke was independent of baseline hemoglobin concentration or darbopoetin dose [202].

## 6. The value of early EPO introduction

The high prevalence, multifactorial pathogenesis and impact of anemia on DM and its complications mandate a high degree of vigilance from the side of the clinician. Essentially, the diagnostic approach to anemia in DM does not substantially differ from that in the general patient population. Hematinic deficiencies should be screened as needed, depending on the features of anemia; currently, the Guidelines of the American Diabetes Association recommend B12 measurements in cases of anemia or peripheral neuropathy, whereas a consideration recommendation for presymptomatic screening among those on chronic metformin treatment [203,204]. The possibility of spurious iron store indices due to the chronic low-grade inflammation should be taken into account; in ambiguous cases, further diagnostic steps including bone marrow aspiration and iron staining may be implemented. This may be mandated already at an early stage of the investigation, particularly if other cytopenias coexist or erythrocyte abnormalities coexist, raising suspicion of an MDS.

In case no supplementations are deemed necessary or meaningful and further workup excludes other apparent causes, the further diagnostic approach and management of anemia in DM poses a clinical challenge. It is apparent that “diabetic anemia” essentially corresponds to a state of absolute or relative EPO deficiency and/or decreased responsiveness. From that perspective, it resembles anemia of CKD falling into the broader category of “anemia of chronic disease”.

Currently, no explicit recommendations exist for EPO use in DKD, other than those in effect for CKD of other etiologies [84]. In the absence of other causes, an anemic state is typically attributed to CKD when GFR drops below 60 ml/min. The hemoglobin threshold for prescribing an EPO analogue is individualized, although these agents are rarely used in values $>$ 10 g/dl. EPO administration is tailored to the lowest dose and frequency to maintain a hemoglobin value ~11 g/dl, and in any case below 11.5 g/dl. Considering that DKD is associated with more frequent and more severe anemia for a given stage of renal disease or even in cases with solely increased urinary albumin excretion, the extrapolation of these recommendations in the population of T2D patients with symptomatic anemia already at earlier stages of kidney involvement appears to be a reasonable approach.

Unfortunately, there is currently a lack of trials to justify the safety and efficacy (regarding outcomes, functionality and quality of life) of this approach. The disappointing results of the TREAT trial do not ought to hamper EPO use in DM patients in general, given the exaggerated hemoglobin target used in this study (13 g/dl). They rather highlight that EPO should be tailored to the lowest dose and frequency to maintain adequate functionality and Hb values 10–11.5 g/dl to reduce the likelihood of thrombotic events associated with its use above this hemoglobin range.

There is currently less sufficient evidence to support this practice among patients with no apparent renal involvement (normoalbuminuria, GFR). Considering the beneficial effects of SGLT2i (+0.5–0.7 g/dl) and potentially, DDP4i treatment on hemoglobin values, these classes should probably be preferentially used either as first line of therapy or during escalation of antihyperglycemic treatment in patients with anemia. Besides, among those with DKD, SGLT2i have an absolute indication as initial treatment to improve renal and cardiovascular outcomes [205]; consequently, in the algorithmic approach to the patient with T2D and DKD it is reasonable to assess the effects of this treatment on coexisting anemia, before resorting to treatment with EPO analogs. Conversely, caution should be exercised with the use of pioglitazone in patients with marginal hemoglobin values, given the known increased anemic propensity caused by the drug. A proposed diagnostic and therapeutic algorithm implementing the above considerations is presented in Fig. 2.

## 7. Concluding remarks

In conclusion, anemia in DM is prevalent and multifactorial, demanding resilience by clinicians to identify potential treatable underlying causes and guide further management. Being essentially a state of functional EPO deficiency, the timely introduction of EPO also in patients without overt DKD is reasonable, while considering the potential benefits and harms associated with its use. The potential utility of newer agents (e.g. HIF-prolyl hydroxylase inhibitors [206], il-6 inhibitor ziltivekimab [207]) in diabetic anemia remains to be scrutinized in future trials.

## CRediT authorship contribution statement

**Christina Antoniadou:** Writing – original draft, Writing – review & editing. **Efstratios Gavriilidis:** Visualization, Writing – original draft. **Konstantinos Ritis:** Conceptualization, Writing – review & editing. **Dimitrios Tsilingiris:** Conceptualization, Writing – review & editing, Project administration.

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