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The Immunometabolic Basis of Anaemia in Type 2 Diabetes Mellitus

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ABSTRACT

Anaemia is a frequent but often under-recognized complication of type 2 diabetes mellitus (T2DM). Traditionally, anaemia in diabetes has been attributed mainly to diabetic kidney disease and reduced erythropoietin production. However, growing evidence shows that anaemia in T2DM is also strongly influenced by immunometabolic dysfunction, where chronic metabolic stress, inflammation, oxidative injury, mitochondrial dysfunction, iron restriction, and impaired erythropoiesis interact. T2DM is characterized by insulin resistance, hyperglycaemia, lipotoxicity, adipose tissue inflammation, endothelial dysfunction, and immune-cell reprogramming. These changes activate innate and adaptive immune pathways, leading to increased production of inflammatory mediators such as interleukin-6, tumour necrosis factor-alpha, interleukin-1β, and C-reactive protein. Inflammation alters iron metabolism through the hepcidin–ferroportin axis, causing functional iron deficiency and reduced haemoglobin synthesis. At the same time, oxidative stress and mitochondrial dysfunction impair haematopoietic stem cells, erythroid progenitor maturation, red blood cell survival, and bone marrow microenvironment function. Diabetic kidney disease further contributes through tubulointerstitial injury, reduced erythropoietin synthesis, and hypoxia-signalling defects. This review examines the immunometabolic mechanisms linking T2DM to anaemia, highlighting inflammation, iron dysregulation, renal impairment, erythropoietic stress, mitochondrial damage, and therapeutic implications.

Keywords: Type 2 diabetes mellitus; anaemia; immunometabolism; hepcidin; erythropoiesis

INTRODUCTION

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and persistent hyperglycaemia [1-5]. It is also increasingly recognized as an inflammatory and immunometabolic disease. In T2DM, excess glucose, free fatty acids, advanced glycation end products, adipose tissue dysfunction, oxidative stress, and endothelial injury create a state of chronic low-grade inflammation [6-8]. This inflammatory environment contributes not only to insulin resistance and vascular complications but also to disturbances in blood cell production and iron metabolism. Anaemia is common among people with diabetes and is associated with fatigue, reduced exercise tolerance, impaired wound healing, cardiovascular strain, faster progression of kidney disease, and poorer quality of life [9-13]. A recent review describes anaemia in diabetes as a frequent comorbidity with multifactorial mechanisms, including haematinic deficiencies, diabetic kidney disease, erythropoietin impairment, inflammation, and hypoxia-related pathways. Historically, diabetic anaemia was explained mainly by reduced erythropoietin production in diabetic nephropathy. While renal disease remains a major contributor, this explanation is incomplete because anaemia may occur even before advanced kidney failure [14-18]. The broader concept of immunometabolism helps explain this early and complex relationship. Immunometabolism refers to the interaction between metabolic pathways and immune-cell function. In T2DM, immune cells respond to nutrient excess, hyperglycaemia, and lipotoxicity by changing their metabolic activity and inflammatory behaviour [19-25]. Current discussions describe T2DM as closely associated with chronic low-grade inflammation and immune-mediated metabolic dysfunction across adipose tissue, liver, skeletal muscle, and pancreatic islets [26-32]. This review explores how immunometabolic dysfunction in T2DM contributes to

anaemia through inflammation, iron restriction, oxidative stress, mitochondrial injury, kidney damage, erythropoietin deficiency, and impaired erythropoiesis.

Immunometabolism in Type 2 Diabetes Mellitus

The immune system and metabolic system are closely connected. In healthy states, immune cells use metabolic pathways such as glycolysis, oxidative phosphorylation, fatty acid oxidation, and amino acid metabolism to support appropriate immune responses [33-37]. In T2DM, persistent metabolic overload disrupts these pathways and causes immune cells to adopt pro-inflammatory phenotypes. Adipose tissue is a major site of immunometabolic disturbance in T2DM [38-43]. In obesity-associated insulin resistance, enlarged adipocytes become hypoxic, stressed, and dysfunctional. They release free fatty acids, chemokines, and pro-inflammatory adipokines that attract macrophages and other immune cells. These immune cells further increase inflammation by producing tumour necrosis factor-alpha, interleukin-6, interleukin-1β, and other mediators [44-46]. This inflammatory signalling interferes with insulin receptor pathways and worsens systemic insulin resistance. Immune dysfunction in T2DM affects both innate and adaptive immunity [47-52]. Reviews of diabetes-induced immune dysfunction show that T2DM is associated with impaired macrophage, neutrophil, and natural killer cell function, alongside chronic inflammation and increased susceptibility to infections. Single-cell studies also support the role of monocytes and T cells in driving systemic inflammation in T2DM[53-55]. This persistent immune activation creates a biological setting in which erythropoiesis is suppressed and iron becomes less available for haemoglobin synthesis.

Anaemia in T2DM: Beyond Renal Disease

Anaemia in T2DM is multifactorial. Common causes include diabetic kidney disease, reduced erythropoietin production, iron deficiency, vitamin B12 deficiency, folate deficiency, chronic inflammation, gastrointestinal blood loss, medication-related malabsorption, and shortened red blood cell survival [56-60]. Metformin therapy, for example, may contribute to vitamin B12 deficiency in some patients, while chronic kidney disease reduces erythropoietin production and alters iron handling. Diabetic kidney disease remains a central mechanism [61-65]. Chronic hyperglycaemia damages glomerular and tubulointerstitial structures. The renal peritubular fibroblast-like cells that normally produce erythropoietin may become dysfunctional as fibrosis, hypoxia, inflammation, and oxidative stress progress [66-67]. A classic review notes that chronic hyperglycaemia can create a hypoxic renal interstitial environment, impairing erythropoietin production and leading to anaemia. In diabetes, anaemia may appear earlier than expected for the degree of kidney impairment because inflammation, endothelial dysfunction, autonomic neuropathy, and oxidative injury also interfere with erythropoiesis [50-55]. However, many diabetic patients have anaemia that cannot be explained solely by reduced kidney function. Inflammatory iron restriction, mitochondrial damage, erythroid progenitor suppression, and red blood cell oxidative damage are increasingly important [56-60]. This is why the immunometabolic model is useful: it links metabolic stress to immune activation and then to defective red blood cell production.

Inflammation, Hepcidin, and Functional Iron Deficiency

One of the most important links between inflammation and anaemia is the hepcidin–ferroportin axis [17]. Hepcidin is a liver-derived peptide hormone that regulates systemic iron homeostasis. It binds to ferroportin, the main cellular iron exporter, causing ferroportin internalization and degradation. When hepcidin levels are high, iron is trapped inside macrophages and intestinal absorption of iron is reduced [18]. This lowers circulating iron availability for erythropoiesis, even when total body iron stores are adequate. Inflammation strongly increases hepcidin production, especially through interleukin-6 signalling. Haematology literature explains that interleukin-6 in acute and chronic inflammation increases hepcidin levels, producing iron-restricted erythropoiesis and anaemia of inflammation despite iron-replete macrophages [19]. Similarly, high hepcidin levels are known to cause iron-restricted or iron-deficient erythropoiesis in inflammatory conditions. In T2DM, chronic low-grade inflammation can therefore produce a pattern similar to anaemia of chronic disease [20]. The patient may have low serum iron and low transferrin saturation, but ferritin may be normal or elevated because ferritin is both an iron-storage protein and an inflammatory marker. This creates diagnostic complexity because iron deficiency and inflammation may coexist. In such cases, oral iron may be less effective if hepcidin remains high and prevents intestinal iron absorption [21]. The hepcidin–ferroportin pathway also explains why anaemia in T2DM may persist even when dietary iron intake is adequate. The problem is not only insufficient iron intake but impaired iron mobilization. Inflammatory cytokines reduce iron availability, suppress erythroid progenitor proliferation, and reduce the marrow response to erythropoietin [22]. This makes diabetic anaemia both a metabolic and inflammatory disorder.

Oxidative Stress, Mitochondrial Dysfunction, and Erythropoietic Stress

Oxidative stress is a major mechanism connecting T2DM to impaired erythropoiesis. Hyperglycaemia increases mitochondrial reactive oxygen species production, activates protein kinase C pathways, promotes advanced glycation end products, and reduces antioxidant defence [23]. Lipotoxicity and chronic inflammation further intensify oxidative injury. Mitochondria are particularly important in erythropoiesis. Although mature red blood

cells lack mitochondria, developing erythroid cells require mitochondria for haem synthesis, iron utilization, energy production, apoptosis regulation, and maturation [24]. During normal red blood cell development, mitochondria must later be removed through mitophagy. When mitochondrial function or clearance is defective, erythroid maturation may be impaired. Recent literature describes mitochondrial dysfunction as a central component of diabetes progression and complications [25]. Mitochondrial quality control systems, including mitochondrial biogenesis, dynamics, mitophagy, and redox regulation, help preserve metabolic homeostasis but become disrupted in diabetes. In the bone marrow, oxidative stress may damage haematopoietic stem and progenitor cells, reduce erythroid colony formation, and increase apoptosis [26]. Mitochondrial dysfunction may also interfere with haem synthesis because haem formation depends on mitochondrial iron incorporation into protoporphyrin IX. Red blood cells themselves are vulnerable to diabetic oxidative stress [27]. Hyperglycaemia promotes haemoglobin glycation and membrane protein damage, reducing red blood cell deformability and shortening erythrocyte lifespan. Oxidatively damaged erythrocytes are removed more rapidly by macrophages, increasing erythropoietic demand [28]. If the marrow cannot compensate because of inflammation, iron restriction, or erythropoietin deficiency, anaemia develops.

Cytokine-Mediated Suppression of Bone Marrow Function

Inflammatory cytokines directly impair erythropoiesis. Tumour necrosis factor-alpha, interleukin-1β, interferon-related signals, and interleukin-6 may suppress erythroid progenitor proliferation, reduce erythropoietin receptor signalling, and promote apoptosis of developing erythroid cells [29]. These effects are particularly relevant in T2DM because the disease is marked by persistent immune activation rather than short-term inflammation. The diabetic bone marrow microenvironment may also become dysfunctional [30]. Hyperglycaemia damages endothelial cells, alters stromal-cell support, promotes oxidative injury, and impairs microvascular perfusion. These changes can compromise haematopoietic stem cell niches [31]. In addition, insulin resistance may alter nutrient sensing in bone marrow cells, affecting their proliferation and differentiation. Therefore, anaemia in T2DM reflects not only reduced erythropoietin or iron availability but also impaired marrow responsiveness. Inflammation can also blunt the effect of erythropoietin [32]. Even when erythropoietin is present, cytokine-rich environments may reduce erythroid sensitivity to it. This partly explains why some patients with diabetes and chronic kidney disease show inadequate haemoglobin improvement unless inflammation, iron restriction, and renal factors are simultaneously addressed.

Diabetic Kidney Disease and the Erythropoietin Axis

The kidney is central to red blood cell production because it produces erythropoietin, the hormone that stimulates erythroid progenitor survival and maturation [33]. In diabetic kidney disease, glomerular injury, tubulointerstitial fibrosis, oxidative stress, capillary rarefaction, and chronic inflammation impair erythropoietin-producing cells [34]. This leads to an inappropriately low erythropoietin response for the degree of anaemia. The erythropoietin problem in diabetes is more complex than simple nephron loss. Hyperglycaemia and oxidative stress alter hypoxia-inducible factor signalling, which normally regulates erythropoietin gene expression under low oxygen conditions [35]. Tubulointerstitial damage may cause local hypoxia, but the diseased kidney may fail to mount an adequate erythropoietin response. Reviews on anaemia in diabetes emphasize diabetic kidney disease, erythropoietin deficiency, hypoxia-inducible factor pathways, and tubulointerstitial fibrosis as important mechanisms [36]. Anaemia can then worsen diabetic kidney disease by reducing oxygen delivery to renal tissue. This may intensify tubulointerstitial hypoxia, fibrosis, and inflammation, creating a vicious cycle between kidney damage and anaemia [37]. Anaemia also increases cardiac workload and contributes to cardiovascular morbidity, which is already elevated in T2DM.

CONCLUSION

Anaemia in type 2 diabetes mellitus is not merely a late complication of kidney failure. It is a complex immunometabolic disorder shaped by chronic hyperglycaemia, insulin resistance, adipose inflammation, immune-cell activation, oxidative stress, mitochondrial dysfunction, renal injury, iron restriction, and impaired erythropoiesis. Inflammatory cytokines increase hepcidin, reduce iron availability, suppress erythroid progenitors, and blunt erythropoietin responsiveness. Diabetic kidney disease further reduces erythropoietin production through tubulointerstitial damage and disrupted hypoxia signalling. At the same time, oxidative stress and mitochondrial injury impair marrow function, haem synthesis, and red blood cell survival. Understanding these mechanisms supports earlier diagnosis, better interpretation of iron markers, and more integrated management strategies. Effective care should address glucose control, inflammation, kidney protection, iron availability, nutritional status, and erythropoietic function. Viewing diabetic anaemia through an immunometabolic lens provides a broader and more biologically accurate framework for prevention, diagnosis, treatment, and future research.

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