

# DIABETES AND ANEMIA: A SCOPING REVIEW

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## ABSTRACT

**Background:** Diabetes mellitus is a chronic metabolic disorder associated with several hematological abnormalities, among which anemia is increasingly recognized as an important comorbidity. Although anemia is frequently attributed to diabetic kidney disease, its etiology is multifactorial and includes iron deficiency, inflammation, nutritional deficiencies, medication-associated abnormalities, and impaired erythropoietin production. **Objective:** This review aims to map the available evidence concerning the prevalence, mechanisms, clinical consequences, diagnosis, and management of anemia among individuals with diabetes mellitus. **Methods:** A scoping review framework was adopted to organize the literature on diabetes-associated anemia. Relevant evidence includes observational studies, clinical reviews, systematic reviews, meta-analyses, and clinical trials addressing the epidemiology, pathophysiology, evaluation, and management of anemia in people with diabetes. A reproducible database search and formal study-selection process should be completed before this draft is submitted as a finalized scoping review. **Results:** Published evidence indicates that anemia is common among people with diabetes, with prevalence varying according to population characteristics, renal function, diagnostic criteria, and comorbid conditions. A systematic review and meta-analysis published in 2024 reported a pooled prevalence of 35.45%. Diabetic kidney disease, relative erythropoietin deficiency, iron deficiency, chronic inflammation, and medication-associated vitamin B12 deficiency are important contributors. Anemia may coexist with diabetic retinopathy, nephropathy, neuropathy, and cardiovascular disease, although the strength and direction of these associations vary across studies. **Conclusion:** Anemia represents a clinically relevant but potentially underrecognized complication in people with diabetes. Its early identification requires a systematic assessment of hemoglobin, renal function, iron status, and other hematological parameters when indicated. Further research is needed to establish standardized screening strategies and determine whether targeted correction of anemia improves long-term outcomes in this population.

**KEYWORDS:** Diabetes mellitus; anemia; diabetic kidney disease; iron deficiency; erythropoietin; vitamin B12; chronic inflammation.

## 1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. It is associated with microvascular and macrovascular complications that affect the kidneys, eyes, nerves, and cardiovascular system. In addition to these established complications, hematological abnormalities, particularly anemia, are increasingly recognized as clinically important comorbidities in people with diabetes.<sup>1,2</sup>

Anemia is conventionally defined according to hemoglobin thresholds, with the World Health Organization using values below 13 g/dL in adult men and below 12 g/dL in nonpregnant adult women, subject to relevant population and clinical considerations.<sup>3</sup> In people with diabetes, anemia may develop due to diabetic kidney disease, reduced erythropoietin production, iron deficiency, chronic inflammation, nutritional deficiencies, blood loss, or medication-associated effects. The coexistence of multiple contributing factors often makes its diagnosis and management challenging.<sup>1,2</sup>

Evidence suggests that anemia occurs more frequently in people with diabetes than might be expected from renal impairment alone. In a cross-sectional study involving 820 individuals with diabetes, Thomas et al. identified previously unrecognized anemia in 23% of participants. Anemia was strongly associated with albuminuria, reduced glomerular filtration rate, and other clinical parameters.<sup>4</sup> These findings indicate that anemia may occur before advanced renal dysfunction becomes apparent and may not be adequately identified through routine clinical assessment.

A systematic review and meta-analysis published in 2024, incorporating 51 studies and 26,485 individuals with diabetes, estimated the pooled prevalence of anemia at 35.45%, although substantial variation between populations and studies limits the interpretation of a single global estimate.<sup>5</sup> This variation reflects differences in age, sex, geographical setting, nutritional status, renal function, anemia definitions, and study methodology.

The relationship between diabetes and anemia is clinically significant because both conditions may contribute to fatigue, reduced physical capacity, impaired quality of life, and increased healthcare utilization. Anemia may also complicate the assessment of glycemic control because altered erythrocyte survival can affect glycated hemoglobin (HbA1c) independently of actual glucose exposure.<sup>6,7</sup> Despite these concerns, anemia may remain

undiagnosed unless hemoglobin measurement and appropriate etiological investigations are incorporated into clinical care.

Therefore, this scoping review aims to map the available evidence on the prevalence, underlying mechanisms, clinical implications, diagnostic evaluation, and management of anemia in individuals with diabetes mellitus. It also identifies important evidence gaps and areas requiring further investigation.

## **2. MATERIALS AND METHODS**

### **2.1 Review design**

A scoping review approach is appropriate for this topic because the relationship between diabetes and anemia encompasses diverse study designs, populations, etiologies, and clinical outcomes. The methodological framework should follow established scoping review guidance, with reporting structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).<sup>8,9</sup>

This manuscript is a literature-based draft. The database searches, eligibility screening, data charting, and final record counts must be completed and documented before the paper can be reported as a fully conducted scoping review.

### **2.2 Review questions**

The principal review question is: What is known about the epidemiology, mechanisms, clinical consequences, diagnosis, and management of anemia in individuals with diabetes mellitus?

The specific objectives are:

1. To describe the reported prevalence and distribution of anemia among people with diabetes.
2. To identify the major etiological mechanisms contributing to anemia in this population.
3. To examine the reported relationship between anemia, diabetic complications, and clinical outcomes.
4. To summarize diagnostic approaches and available management strategies.
5. To identify evidence gaps that may guide future clinical research.

### **2.3 Proposed search strategy**

A comprehensive search should be conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Reference lists of relevant reviews and original studies should also be examined to identify additional eligible publications.

The proposed search terms include combinations of the following: “diabetes mellitus,” “type 1 diabetes,” “type 2 diabetes,” “anemia,” “anaemia,” “diabetic kidney disease,” “chronic kidney disease,” “erythropoietin,” “iron deficiency,” “vitamin B12 deficiency,” “inflammation,” and “glycemic control.” Boolean operators should be used to combine the terms.

The final manuscript should report the exact search date, complete search strings, date limits, and the number of records retrieved from each database. No search dates or record counts are presented here because a complete reproducible search has not yet been documented.

### **2.4 Eligibility criteria**

Eligible evidence should include peer-reviewed original research, observational studies, clinical trials, systematic reviews, meta-analyses, and relevant clinical practice guidance concerning anemia in people with diabetes mellitus. Studies investigating anemia prevalence, mechanisms, diabetic kidney disease, nutritional deficiencies, glycemic assessment, and anemia treatment should be considered.

Studies unrelated to diabetes-associated anemia, publications without sufficient relevant information, and duplicate reports should be excluded. The final protocol should specify language restrictions, publication-period limits, and the treatment of conference abstracts and other grey literature.

### **2.5 Study selection and data charting**

After database searching, duplicate records should be removed. Titles and abstracts should be screened against the eligibility criteria, followed by full-text assessment of potentially relevant publications. Ideally, two independent reviewers should conduct study selection, with disagreements resolved through discussion or consultation with a third reviewer.

Data charting should capture the author, publication year, country, study design, sample size, participant characteristics, diabetes type, anemia definition, reported prevalence, associated risk factors, proposed mechanisms, clinical outcomes, and major findings. Findings should be synthesized descriptively and organized into thematic categories. A scoping review primarily maps the available evidence; formal risk-of-bias assessment and meta-analysis are not obligatory unless specified in the protocol.<sup>8,9</sup>

## **3. RESULTS AND THEMATIC SYNTHESIS**

### **3.1 Prevalence of anemia in diabetes**

Anemia is frequently reported in individuals with diabetes, although its prevalence differs substantially across clinical and geographical settings. Thomas et al. reported previously unrecognized anemia in 23% of 820 patients

with diabetes, demonstrating that a considerable proportion of affected individuals may remain undiagnosed during routine follow-up.<sup>4</sup> The study also identified associations between lower hemoglobin concentrations, renal dysfunction, albuminuria, and glycemic parameters.

More recently, Faghir-Ganji et al. conducted a systematic review and meta-analysis of 51 studies involving 26,485 patients with diabetes. The pooled prevalence of anemia was 35.45% (95% confidence interval [CI]: 30.30–40.76). The estimated prevalence was higher in the included Asian studies than in African studies, at 40.02% and 28.46%, respectively.<sup>5</sup> These findings suggest that anemia represents a substantial clinical burden, while also highlighting the importance of interpreting prevalence estimates in the context of differences in population characteristics and study methodology.

The presence of diabetic kidney disease is an important determinant of anemia prevalence and severity. However, anemia may also occur in people with relatively preserved renal function because of iron deficiency, inflammation, nutritional abnormalities, or inadequate erythropoietin responses.<sup>1,2</sup> Consequently, anemia should not automatically be attributed to renal disease without further evaluation.

### **3.2 Pathophysiological mechanisms**

The development of anemia in diabetes is multifactorial. Several mechanisms may coexist, and the relative contribution of each varies according to disease duration, renal function, comorbidities, nutritional status, and medication exposure.

#### **3.2.1 Diabetic kidney disease and erythropoietin deficiency**

Diabetic kidney disease is one of the most important causes of anemia in people with diabetes. Healthy kidneys produce erythropoietin, a hormone that stimulates red blood cell production in the bone marrow. Progressive renal damage can impair erythropoietin production, resulting in reduced erythropoiesis and declining hemoglobin concentrations.<sup>1,10</sup>

Anemia associated with diabetic kidney disease may develop earlier than expected from the degree of reduction in estimated glomerular filtration rate (eGFR). Renal interstitial changes, impaired erythropoietin responses, inflammation, iron disturbances, and other metabolic abnormalities may contribute to this pattern.<sup>1,10</sup> Patients with albuminuria and declining renal function warrant particular attention because anemia may indicate a greater burden of systemic or renal disease.

#### **3.2.2 Iron deficiency and iron-restricted erythropoiesis**

Iron deficiency is another important cause of anemia in diabetes. Absolute iron deficiency may result from inadequate dietary intake, gastrointestinal blood loss, impaired absorption, or increased iron requirements. Functional iron deficiency occurs when iron stores are present but iron availability for erythropoiesis is restricted, commonly in association with inflammation and increased hepcidin activity.

Hepcidin regulates systemic iron balance by limiting intestinal iron absorption and the release of stored iron. Inflammatory signaling may increase hepcidin concentrations, reducing iron availability for red blood cell production.<sup>11</sup> This process can contribute to iron-restricted erythropoiesis, particularly in individuals with chronic kidney disease or other inflammatory conditions.

Iron deficiency should be investigated rather than presumed. Serum ferritin, transferrin saturation, and other laboratory findings must be interpreted together because ferritin may be normal or elevated in inflammatory states despite inadequate iron availability. Identifying the underlying cause is essential, especially when gastrointestinal blood loss or another clinically significant source of iron deficiency is suspected.

#### **3.2.3 Chronic inflammation and altered erythropoiesis**

Chronic low-grade inflammation associated with diabetes and its complications may contribute to anemia through several interconnected mechanisms. Inflammatory mediators can suppress erythropoietin production or responsiveness, reduce iron availability, and interfere with erythroid progenitor-cell activity.<sup>1,11</sup> These effects may overlap with the consequences of kidney disease, making the anemia more difficult to classify as purely nutritional or renal in origin.

The inflammatory pathway is particularly relevant in individuals with obesity, chronic infections, vascular disease, or advanced diabetic complications. Nevertheless, the presence of diabetes does not establish inflammation as the cause of anemia; other treatable etiologies must also be excluded.

#### **3.2.4 Vitamin B12 and folate deficiency**

Vitamin B12 and folate are required for normal DNA synthesis and red blood cell maturation. Deficiency may cause ineffective erythropoiesis and megaloblastic anemia. In patients with diabetes, vitamin B12 deficiency is particularly relevant because long-term metformin use has been associated with lower vitamin B12 concentrations.<sup>12</sup>

In a randomized placebo-controlled trial, de Jager et al. found that long-term metformin treatment was associated with a reduction in vitamin B12 concentrations and an increased absolute risk of vitamin B12 deficiency.<sup>12</sup> The clinical significance depends on the degree of deficiency, duration of exposure, dietary status, and individual susceptibility.

Vitamin B12 deficiency may produce macrocytosis, but a normal mean corpuscular volume does not exclude it, particularly when concurrent iron deficiency is present. Neurological symptoms may also overlap with diabetic peripheral neuropathy. Therefore, vitamin B12 testing is appropriate when anemia, macrocytosis, neurological symptoms, or relevant risk factors are present. Folate assessment should be guided by clinical circumstances and laboratory findings.

### 3.2.5 Medication-associated anemia and other causes

Medication exposure may contribute to anemia directly or indirectly. In addition to metformin-associated vitamin B12 deficiency, medications used for diabetes-related comorbidities may influence renal function, bleeding risk, or hematological parameters in selected patients.<sup>1,2</sup> A medication review should therefore form part of the clinical assessment.

Other causes, including chronic blood loss, hemolysis, bone marrow disorders, infection, malignancy, and other nutritional deficiencies, remain important differential diagnoses. The coexistence of diabetes should not delay the investigation of these conditions when supported by the history, examination, or laboratory findings.

### 3.3 Relationship between anemia and diabetic complications

Anemia may coexist with several diabetic complications, particularly nephropathy and cardiovascular disease. Reduced renal function is both a contributor to anemia and an important marker of overall disease burden. Observational evidence has also linked lower hemoglobin concentrations with albuminuria and other indicators of diabetic complications.<sup>4,10</sup>

Anemia may worsen tissue oxygen delivery and reduce exercise tolerance, potentially increasing fatigue and limiting daily activities. In people with pre-existing cardiovascular disease, reduced oxygen-carrying capacity may add to the physiological burden. However, the presence of anemia alongside a complication does not necessarily establish a direct causal relationship, because both may arise from shared underlying factors such as renal dysfunction, inflammation, or advanced chronic disease.<sup>1,13</sup>

The association between anemia and diabetic retinopathy or neuropathy is also clinically relevant. Some reviews describe relationships between anemia and microvascular complications, but the evidence is heterogeneous, and the independent contribution of anemia remains uncertain.<sup>1,13</sup> Further longitudinal studies are required to determine whether anemia independently predicts the development or progression of these complications after adjustment for renal function, glycemic control, disease duration, and other confounders.

### 3.4 Anemia and assessment of glycemic control

An important clinical issue is the potential effect of anemia and altered red blood cell turnover on HbA1c interpretation. HbA1c reflects glycemic exposure over the preceding weeks to months, but its reliability depends partly on the lifespan and turnover of circulating erythrocytes.<sup>6,7</sup>

Iron deficiency may be associated with higher HbA1c values in some circumstances, whereas conditions that shorten erythrocyte survival, including hemolysis or recent blood loss, may produce falsely low values. Recent transfusion, erythropoiesis-stimulating treatment, and correction of anemia may also complicate interpretation.<sup>6,7</sup> The direction and magnitude of these effects are not uniform across all forms of anemia.

Consequently, HbA1c should be interpreted alongside clinical findings and other measures of glycemia when anemia or altered erythrocyte turnover is present. Depending on the clinical context, fasting plasma glucose, other plasma glucose measurements, or continuous glucose monitoring may help clarify glycemic status. An abnormal HbA1c result should not automatically be interpreted as evidence of worsening glycemia without considering relevant hematological factors.

### 3.5 Clinical evaluation of anemia in diabetes

A structured diagnostic evaluation is necessary to establish both the presence and cause of anemia. Initial assessment generally includes a complete blood count, hemoglobin concentration, hematocrit, red blood cell indices, and review of previous results. Reticulocyte count and peripheral blood smear may be useful when the cause is unclear or when hemolysis, marrow dysfunction, or an atypical blood picture is suspected.

Renal assessment should include serum creatinine and eGFR, with urine albumin-to-creatinine ratio when appropriate. Iron studies, including serum ferritin and transferrin saturation, are important when iron deficiency or iron-restricted erythropoiesis is suspected. Vitamin B12 and folate measurements should be guided by the clinical history, red blood cell indices, medication exposure, and associated symptoms.<sup>6,10</sup>

The evaluation should also consider dietary intake, menstrual or gastrointestinal blood loss, chronic inflammatory conditions, infection, and other comorbidities. The presence of microcytic, normocytic, or macrocytic anemia can help guide further investigation, but red blood cell morphology alone is insufficient to establish the diagnosis.

**Table 1. Major causes of anemia in individuals with diabetes mellitus**

| <b>Etiological category</b> | <b>Potential mechanism</b>                                    | <b>Relevant investigations</b>                            |
|-----------------------------|---------------------------------------------------------------|-----------------------------------------------------------|
| Diabetic kidney disease     | Reduced erythropoietin production and impaired erythropoiesis | Serum creatinine, eGFR, urine albumin-to-creatinine ratio |

|                                           |                                                                     |                                                             |
|-------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------|
| Absolute iron deficiency                  | Inadequate intake, impaired absorption, or blood loss               | Ferritin, transferrin saturation, evaluation for blood loss |
| Functional iron deficiency                | Inflammation-associated iron sequestration                          | Ferritin, transferrin saturation, inflammatory context      |
| Vitamin B12 deficiency                    | Impaired DNA synthesis and erythrocyte maturation                   | Serum vitamin B12; additional tests when indicated          |
| Folate deficiency                         | Impaired DNA synthesis                                              | Serum folate when clinically indicated                      |
| Chronic inflammation                      | Iron restriction and reduced erythropoietic response                | Clinical assessment and targeted investigations             |
| Other hematological or systemic disorders | Hemolysis, marrow disorders, infection, malignancy, or other causes | Tests guided by history, examination, and blood findings    |

### 3.6 Management of anemia in diabetes

Management should be directed toward the underlying cause rather than anemia alone. In patients with confirmed iron deficiency, iron replacement may be appropriate after considering the cause, severity, tolerance, and clinical setting. Oral or intravenous iron should be selected according to individual circumstances, including the severity of deficiency, absorption, response to treatment, and presence of chronic kidney disease.

Vitamin B12 or folate deficiency should be corrected when confirmed or strongly supported by clinical assessment. In patients receiving long-term metformin, vitamin B12 assessment is particularly relevant when anemia, neuropathic symptoms, or other risk factors are present. Metformin should not automatically be discontinued solely because of a low vitamin B12 concentration; deficiency can generally be evaluated and treated while considering the ongoing indication for the medication.<sup>12</sup>

In anemia associated with chronic kidney disease, management may include correction of iron deficiency, treatment of reversible causes, and consideration of erythropoiesis-stimulating agents in appropriately selected patients. Treatment decisions should account for hemoglobin concentration, symptoms, kidney function, iron status, cardiovascular risk, and the risks associated with therapy.<sup>10,14</sup> The objective is not necessarily to normalize hemoglobin in every patient, but to improve clinically relevant outcomes while minimizing treatment-related harm.

Blood glucose management and cardiovascular risk reduction remain essential components of comprehensive care. However, correction of anemia should not be assumed to improve all diabetic complications, and treatment strategies must be individualized. Periodic reassessment is needed to determine hematological response, identify persistent or recurrent deficiency, and evaluate whether additional investigations are necessary.

## 4. DISCUSSION

This scoping review maps the major themes in the relationship between diabetes mellitus and anemia. The available literature indicates that anemia is a common comorbidity and may be underrecognized in routine clinical practice. The pooled prevalence of 35.45% reported by Faghiri-Ganji et al. demonstrates the substantial burden described across published studies, although the estimate should not be applied uniformly to every diabetic population.<sup>5</sup> Differences in renal function, nutritional status, demographic characteristics, clinical setting, and diagnostic criteria contribute to variation between studies.

The evidence also emphasizes that anemia in diabetes is not attributable to a single mechanism. Diabetic kidney disease and impaired erythropoietin production are important contributors, but iron deficiency, chronic inflammation, vitamin B12 deficiency, blood loss, and other systemic conditions must also be considered.<sup>1,2,10</sup> This multifactorial nature supports an etiological approach to diagnosis rather than assuming that all anemia in a person with diabetes is renal in origin.

An important implication is that the investigation of anemia may provide an opportunity to identify additional disease burden. Albuminuria, declining eGFR, and anemia may coexist, and their combination can signal a need for closer clinical assessment.<sup>4,10</sup> Nevertheless, associations between anemia and diabetic complications should be interpreted cautiously. Many studies are observational and cannot fully separate the effects of anemia from those of chronic kidney disease, age, inflammation, nutritional deficiencies, and comorbid illness.

Another important consideration is the influence of hematological abnormalities on HbA1c interpretation. Since HbA1c is affected by red blood cell lifespan and turnover, unrecognized anemia may complicate the evaluation of glycemic control.<sup>6,7</sup> This has implications for clinical decision-making, particularly when HbA1c values appear inconsistent with measured glucose concentrations or the patient's clinical presentation.

The literature supports a comprehensive assessment that includes complete blood count, renal function, iron status, and targeted nutritional investigations. However, the optimal frequency of anemia screening in people with diabetes who have preserved renal function remains uncertain. Screening intensity should therefore be guided by clinical context, symptoms, renal function, comorbidities, and relevant risk factors rather than assuming that one universal schedule is appropriate for all patients.

Several limitations should be acknowledged. The present draft does not include a completed, reproducible database search, formal eligibility screening, or a documented study-selection flow diagram. It therefore cannot provide a definitive account of the volume or distribution of the available evidence. Furthermore, the cited

literature includes different study designs, and prevalence estimates may be influenced by population differences and methodological heterogeneity. A finalized scoping review should include the complete search strategy, screening results, characteristics of included studies, and an evidence map prepared in accordance with PRISMA-ScR.<sup>8,9</sup>

Future research should prioritize prospective studies investigating the natural history of anemia in people with diabetes, the contribution of individual etiologies, and the independent association between anemia and microvascular or macrovascular outcomes. Studies from underrepresented regions, including diverse South Asian populations, would help clarify the roles of nutritional deficiencies, chronic kidney disease, and socioeconomic determinants. Interventional research is also needed to determine whether targeted anemia detection and treatment improve patient-centered outcomes beyond correction of hemoglobin concentration alone.

## 5. CONCLUSION

Anemia is a common and clinically important comorbidity in individuals with diabetes mellitus. Its development is multifactorial, involving diabetic kidney disease, impaired erythropoietin production, iron deficiency, chronic inflammation, vitamin B12 deficiency, and other hematological or systemic conditions. Anemia may coexist with diabetic complications and can complicate the interpretation of HbA1c, emphasizing the importance of appropriate clinical assessment.

A structured diagnostic approach should identify the underlying cause and guide individualized management. Greater awareness among healthcare professionals, appropriate laboratory evaluation, and further prospective research may help clarify the clinical significance of anemia in diabetes and establish evidence-based screening and management strategies.

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