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REVIEW ARTICLE

A Review on Prevalence and Iatrogenic Etiologies of Anemia in Type 2 Diabetes Mellitus

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Abstract: Diabetes mellitus constitutes a rapidly expanding global health burden, significantly impacting morbidity and mortality through microvascular and macrovascular complications. Among these, anemia frequently manifests as an underdiagnosed comorbidity in patients with Type 2 Diabetes Mellitus (T2DM), often appearing earlier and with greater severity than in non-diabetic renal disease. This article elucidates the multifactorial pathogenesis of anemia in T2DM, moving beyond the traditional attribution to diabetic nephropathy alone. The pathophysiology involves a complex interplay of chronic systemic inflammation, inappropriate erythropoietin response, autonomic neuropathy, and nutritional deficiencies. Crucially, the management of hyperglycemia and associated hypertension introduces iatrogenic risks that exacerbate hematological indices. Pharmacological interventions, specifically biguanides (metformin), Thiazolidinediones (TZDs), and Renin-Angiotensin-Aldosterone System (RAAS) inhibitors, contribute to hemoglobin reduction through distinct mechanisms ranging from vitamin B12 malabsorption to erythropoiesis suppression and hemodilution. Identifying these drug-induced etiologies is paramount for clinical management. This review discusses about the current epidemiological data with insights into iatrogenic anemia, emphasizing the necessity for routine hematological screening to mitigate cardiovascular risks and improve quality of life in the diabetic population.

Keywords: Type 2 Diabetes Mellitus; Anemia; Diabetic Nephropathy; Iatrogenic Complications; Pharmacotherapy.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) has emerged as a pervasive lifestyle-related disease, driven by rapid urbanization, economic transitions, and sedentary behaviors. Physiologically, T2DM is characterized by insulin resistance and relative insulin deficiency, leading to chronic hyperglycemia. The global prevalence of this metabolic disorder is rising alarmingly; epidemiological projections estimate that by the year 2030, approximately 439 million individuals will be affected by T2DM [1]. This condition is not merely a disorder of glucose metabolism but a systemic disease associated with debilitating sequelae, including retinopathy, neuropathy, cardiovascular disease, and nephropathy, all of which significantly impair functional capacity and quality of life [2].

Among the myriad complications associated with T2DM, anemia remains a frequently overlooked yet clinically significant condition. The World Health Organization (WHO) defines anemia as a hemoglobin concentration lower than 130 g/L for men and 120 g/L for women [3]. In the context of diabetes, anemia is not an innocent bystander; it is an independent risk factor for the progression of microvascular complications and cardiovascular mortality. While anemia is classically associated with advanced renal failure, evidence suggests that hematological decline in diabetic patients occurs earlier and is more severe than in patients with renal impairment of non-diabetic origin [4].

The etiology of anemia in T2DM is multifactorial. It comprises of systemic inflammation, functional erythropoietin deficiency, damage to the renal interstitium, and alterations in iron metabolism [5]. Moreover, nutritional deficiencies specifically of folate and cobalamin (Vitamin B12) play a critical role. Of particular concern are the iatrogenic causes of anemia, where essential pharmacotherapies used to manage diabetes and its complications paradoxically contribute to hematological decline. Agents such as metformin, thiazolidinediones (TZDs), and inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS) have been implicated in the pathogenesis of anemia through diverse mechanisms [6]. This article discusses about the prevalence and pathophysiological underpinnings of anemia in T2DM, with a specific focus on drug-induced etiologies.

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2. Epidemiology and Prevalence

The epidemiological landscape of anemia in diabetes indicates a strong correlation between glycemic status and hematological parameters. Reports indicate that the number of individuals with diabetes reached 285 million in 2010, with projections suggesting a rise to 440 million by 2030 [7]. Within this expanding population, the prevalence of anemia is notably higher than in non-diabetic controls. Studies have documented that patients with T2DM are twice as likely to develop anemia compared to the general population [8].

2.1. Prevalence in Renal and Non-Renal Populations

While anemia is a well-established consequence of diabetic nephropathy, recent data highlights its prevalence even in patients with preserved renal function. Approximately one in five patients with diabetes and stage three chronic kidney disease (CKD) exhibits anemia [9]. However, distinct from CKD-driven anemia, a significant proportion of diabetic patients with normal serum creatinine levels also manifest low hemoglobin. Research involving unselected cohorts of adults with T2DM revealed an anemia prevalence of roughly 32% [10]. In populations strictly defined by normal renal function, the prevalence remains clinically significant at approximately 10% [11]. This suggests that factors extrinsic to renal filtration capacity, such as drug therapy and metabolic inflammation, drive hematopoiesis suppression in these patients.

2.2. Gender and Glycemic Control

Demographic analyses reveal a statistically significant relationship between gender and anemia susceptibility in the diabetic population. Anemia is fundamentally more prominent in diabetic females compared to their male counterparts [12]. Moreover, the severity of anemia correlates with the degree of glycemic control; patients with poor glycemic regulation exhibit a higher prevalence of anemia compared to those with optimal glucose targets. This relationship creates a vicious cycle where anemia compromises the patient's energy levels and ability to manage their condition, potentially accelerating the progression of vascular complications [13].

Table 1. Epidemiology of Anemia in Type 2 Diabetes Mellitus

Population Subgroup	Estimated Prevalence of Anemia	Observations
General T2DM Population	~20–30%	Twice as likely to develop anemia compared to non-diabetic individuals [8].
T2DM with Stage 3 CKD	~20%	Anemia onset occurs earlier than in non-diabetic renal disease [9].
Unselected T2DM Adults	32%	High prevalence even without specific risk stratification [10].
T2DM with Normal Renal Function	10%	Indicates significant non-renal contributors (e.g., inflammation, drugs) [11].
Gender Disparity	Higher in Females	Females with poor glycemic control are at significantly higher risk [12].

3. Pathophysiological Mechanisms

The development of anemia in T2DM is driven by a complex interaction of physiological and metabolic factors. Unlike the isolated iron deficiency seen in other populations, diabetic anemia is often a convergence of nutritional deficits, inflammation, and hormonal imbalances.

3.1. Erythropoietin Response and Autonomic Neuropathy

A central mechanism in diabetic anemia is the failure of the kidney to produce adequate erythropoietin (EPO) in response to falling hemoglobin levels. This phenomenon, termed "functional EPO deficiency," occurs earlier in diabetic nephropathy than in other forms of renal disease. Even in patients without advanced kidney disease or overt uremia, low serum erythropoietin levels have been consistently observed [14]. The exact mechanism for this blunted response involves damage to the renal peritubular fibroblasts, which are responsible for EPO synthesis. Additionally, diabetic autonomic neuropathy may contribute to this dysregulation by impairing the sympathetic signaling required to trigger EPO release during hypoxia [15].

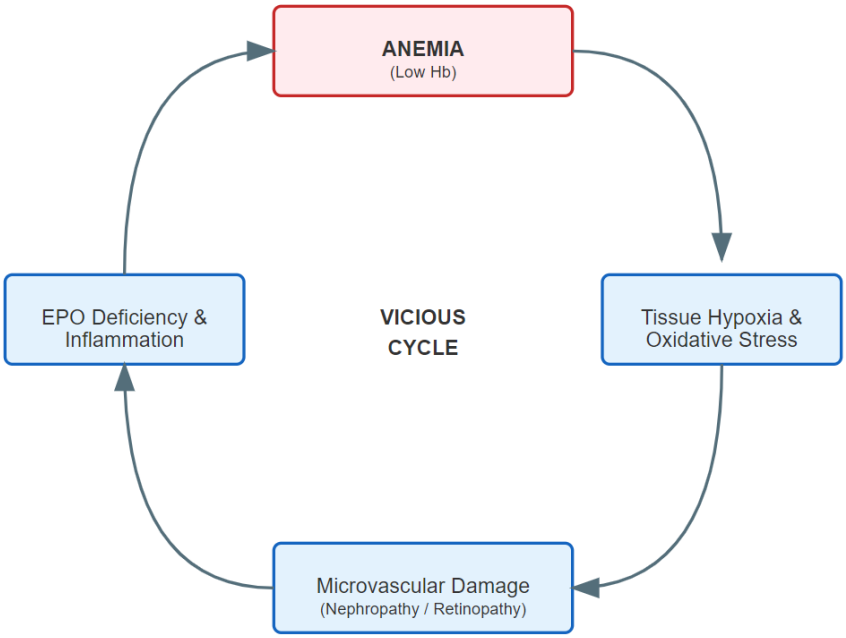

Figure 1. The Vicious Cycle of Anemia and Diabetes Complications

3.2. Chronic Inflammation and Iron Metabolism

T2DM is inherently a state of chronic, low-grade inflammation. Pro-inflammatory cytokines, particularly Interleukin-6 (IL-6), stimulate the hepatic production of hepcidin, a peptide hormone that regulates iron homeostasis. Elevated hepcidin levels inhibit ferroportin, preventing the release of stored iron from macrophages and hepatocytes and reducing intestinal iron absorption. This results in "anemia of chronic disease," where iron stores are adequate or elevated, but the iron is biologically unavailable for erythropoiesis [16]. Studies investigating insulin resistance have shown that it is associated with inadequate hepcidin suppression, leading to iron sequestration. Consequently, the suppressed liver hepcidin synthesis normally seen in response to anemia is overridden by inflammatory signals in T2DM, contributing to functional iron deficiency [17]

Table 2. Multifactorial Pathophysiology of Anemia in Diabetes

Mechanism	Pathophysiology	Clinical Consequence
Functional EPO Deficiency	Inability of the kidney to upregulate erythropoietin (EPO) in response to hypoxia/anemia.	Blunted erythropoiesis despite falling hemoglobin levels [14].
Autonomic Neuropathy	Damage to sympathetic nerves that signal the kidney to release EPO.	Loss of the erythropoietic feedback loop [15].
Chronic Inflammation	IL-6 mediated increase in Hepcidin levels.	"Anemia of Chronic Disease" – iron is sequestered in macrophages and unavailable for red blood cell production [16].
Nutritional Deficits	Malabsorption or dietary insufficiency of B12, Folate, and Iron.	Defective DNA synthesis (B12/Folate) or Heme synthesis (Iron).

4. Iatrogenic Etiologies of Anemia

While the intrinsic pathophysiology of diabetes contributes significantly to anemia, the pharmacological management of the disease and its comorbidities introduces a critical layer of complexity. Iatrogenic, or treatment-induced, anemia is a significant concern, particularly in patients with preserved renal function where physiological causes are less apparent. The concomitant use of oral antidiabetic agents and antihypertensive medications can inadvertently suppress erythropoiesis or alter hemoglobin kinetics.

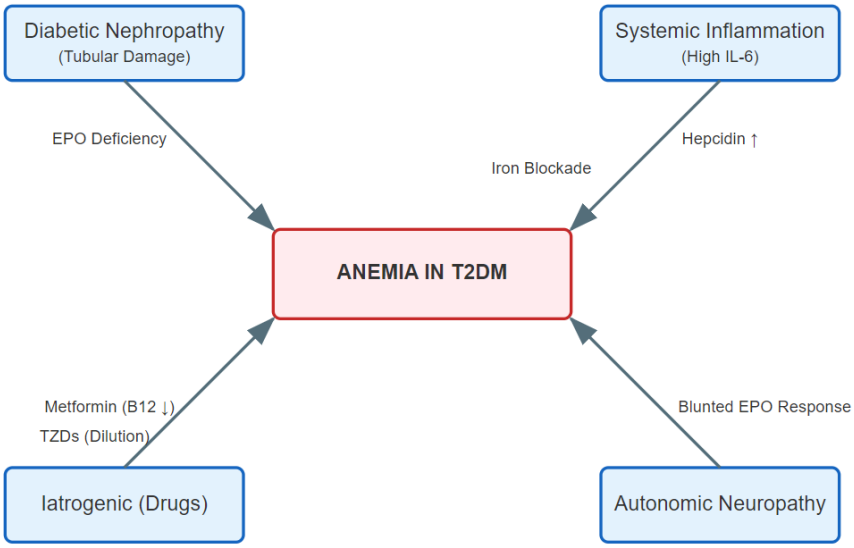

Figure 2. Multifactorial Pathogenesis of Anemia in T2DM

4.1. Metformin-Associated Vitamin B12 Deficiency

Metformin remains the foundational pharmacotherapy for the management of T2DM due to its efficacy in improving insulin sensitivity and its favorable safety profile. However, long-term metformin administration is strongly implicated in biochemical and clinical vitamin B12 (cobalamin) deficiency. The pathophysiology underlying this interaction is thought to involve the alteration of small bowel motility, which may promote bacterial overgrowth, and the interference with the calcium-dependent absorption of the vitamin B12-intrinsic factor complex in the terminal ileum [18].

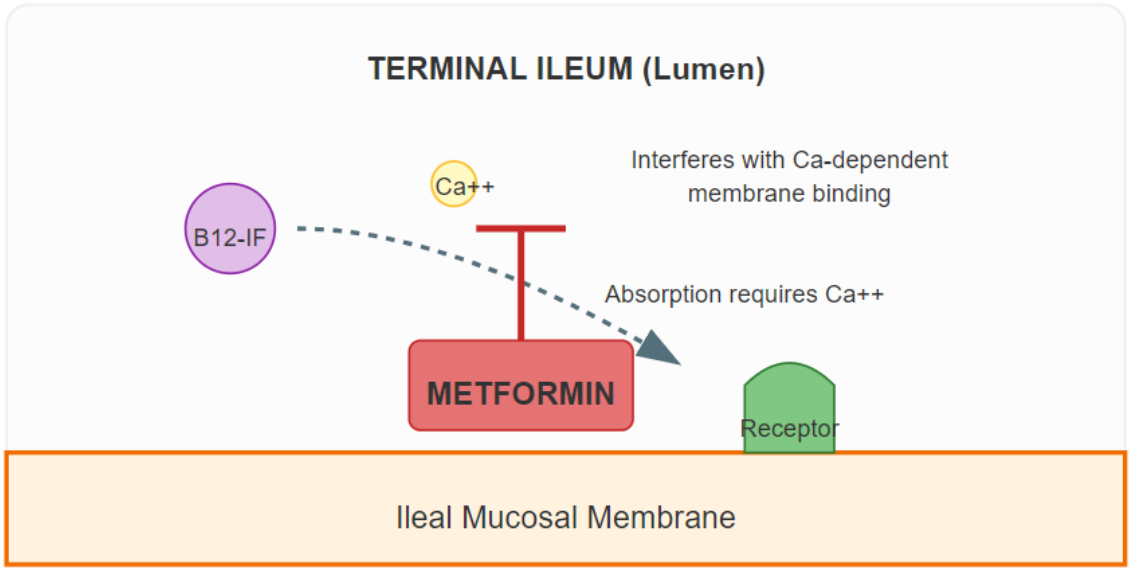

Figure 3. Mechanism of Metformin-Induced B12 Deficiency

Clinical data indicates that approximately 10% to 30% of patients on long-term metformin therapy experience vitamin B12 malabsorption, with 6% to 9% progressing to frank deficiency [19]. This deficiency manifests as megaloblastic anemia and may also exacerbate diabetic peripheral neuropathy, complicating the clinical assessment of neurovascular complications. Serum vitamin B12 levels demonstrate an inverse correlation with both the dosage and duration of metformin therapy. Additionally, autoimmune gastritis, which occurs with greater frequency in T2DM, may coexist, further impairing intrinsic factor production and precipitating iron deficiency anemia alongside B12 deficits [20].

4.2. Thiazolidinediones and Hemodilution

Thiazolidinediones (TZDs), such as pioglitazone, function as insulin sensitizers in muscle, liver, and adipose tissue. While effective for glycemic control, TZDs are frequently associated with a reduction in hemoglobin and hematocrit levels. The primary mechanism driving this reduction is hemodilution secondary to fluid retention, as TZDs stimulate sodium reabsorption in the renal collecting ducts, thereby expanding plasma volume [21].

However, the reduction in hemoglobin associated with TZDs is not exclusively dilutional. Emerging evidence suggests that these agents may exert a suppressive effect on bone marrow erythropoiesis or alter androgen metabolism. Glitazones have been observed to reduce androgen biosynthesis and increase the concentration of Sex Hormone Binding Globulin (SHBG), effectively attenuating androgen receptor activation. Since testosterone is a potent physiological stimulator of erythropoiesis, this anti-androgenic effect may contribute to the development of anemia, particularly in male patients with T2DM who already exhibit lower testosterone levels compared to non-diabetic controls [22].

Table 3. Iatrogenic (Drug-Induced) Causes of Anemia in T2DM

Drug Class	Specific Agents	Mechanism of Action	Management
Biguanides	Metformin	Malabsorption of Vitamin B12 via alteration of small bowel motility and calcium-dependent uptake [18].	Annual B12 screening; Calcium or B12 supplementation.
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone	(1) Hemodilution due to fluid retention. (2) Suppression of bone marrow erythropoiesis. (3) Reduced androgen levels [21, 22].	Monitor hematocrit; assess for fluid overload.
RAAS Inhibitors	ACE Inhibitors (e.g., Lisinopril), ARBs (e.g., Losartan)	Inhibition of Angiotensin II, which is a physiological stimulator of erythropoietin [23].	Monitor hemoglobin upon initiation; weigh renoprotective benefit vs. anemia risk.

4.3. Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) constitute the standard of care for diabetic patients with hypertension or albuminuria, owing to their established renoprotective properties. Paradoxically, the blockade of the Renin-Angiotensin-Aldosterone System (RAAS) can induce or worsen anemia. Angiotensin II acts as a stimulator of erythropoietin production; consequently, the pharmacological inhibition of this system removes a crucial signaling pathway for red blood cell production [23].

Studies demonstrate that both ACE inhibitors and ARBs cause a reversible decrease in hemoglobin concentrations. While this effect is often mild in patients with normal renal function, it can precipitate symptomatic anemia in those with underlying nephropathy. Moreover, erythrocytes in diabetic patients exhibit increased mechanical fragility and susceptibility to hemolysis. The additional erythropoietic stress caused by RAAS blockade, combined with microangiopathic changes in the vasculature, may favor hemolysis due to mechanical factors, further lowering hemoglobin levels [24].

5. Clinical Implications and Management

The presence of anemia in T2DM serves as a marker of disease severity and a predictor of adverse outcomes. Anemia is linked to an increased risk of cardiovascular disease, impaired cognitive function, and reduced physical capacity. It acts as a key indicator of kidney disease progression and amplifies cardiovascular risk factors [25]. Despite its high prevalence, anemia often remains unrecognized until it becomes symptomatic, by which time significant physiological impact may have occurred.

Early detection through routine screening is essential for mitigating complications. Current clinical evidence supports the regular monitoring of hemoglobin levels in all diabetic patients, particularly those with known renal impairment or those prescribed high-risk medications. When anemia is identified, a differential diagnosis must be pursued to distinguish between nutritional deficiencies (iron, B12, folate), renal causes, and iatrogenic factors. In patients on long-term metformin, annual screening for vitamin B12 status is advisable to prevent hematological and neurological sequelae. Similarly, for patients initiating RAAS inhibitors, a potential drop in hemoglobin should be anticipated and monitored [26].

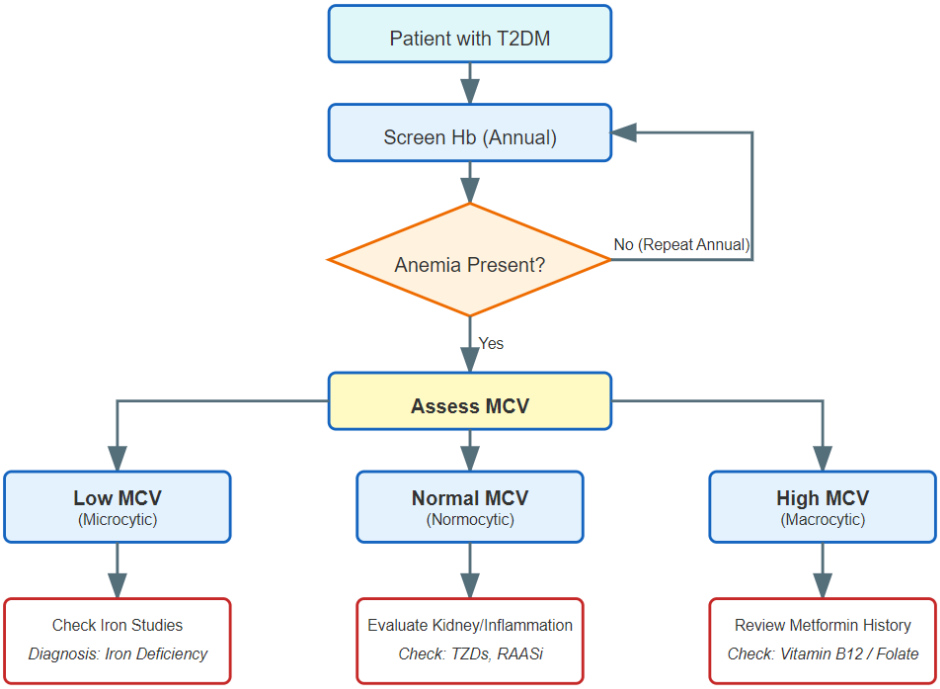

Figure 2. Screening and differential diagnosis of anemia in patients with Type 2 Diabetes.

Table 4. Clinical Screening and Differential Diagnosis Guidelines

Parameter	Anemia of Chronic Disease (Inflammation)	Iron Deficiency Anemia	Vitamin B12 Deficiency (Metformin-Induced)
MCV (Mean Corpuscular Volume)	Normal (Normocytic)	Low (Microcytic)	High (Macrocytic)
Ferritin	Normal or High	Low	Normal
Transferrin Saturation	Low	Low	Normal
Vitamin B12 Level	Normal	Normal	Low (<200 pg/mL)
Screening Frequency	Annual (part of complication screening)	If MCV is low	Annual for patients on Metformin >3-4 years

6. Conclusion

Diabetic foot ulcers are difficult to manage due to various factors like neuropathy, vascular insufficiency, and immune dysregulation. Conventional therapies, while essential, are increasingly constrained by antibiotic resistance and their inability to comprehensively address the multifactorial pathology of diabetic wounds. This review shows the potential of herbal and polyherbal strategies as superior adjunctive therapies. these interventions actively promote tissue regeneration, combat resistant pathogens, and ameliorate oxidative stress by utilizing the synergistic properties of diverse phytochemicals. Moreover, the convergence of traditional herbal medicine with modern nanotechnology marks a paradigm shift in DFU management. Advanced delivery systems such as transferosomes, SLNs, and bioactive scaffolds overcome the pharmacokinetic limitations of crude extracts, ensuring deep penetration and sustained therapeutic action.

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