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Review Article

Anemia in type 2 diabetes mellitus: revisiting iron deficiency and the therapeutic role of ferrous bisglycinate

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ABSTRACT

Anemia remains a major public health challenge in India and has important clinical implications for individuals with type 2 diabetes mellitus (T2DM). In this population, anemia is a significant comorbidity rather than an incidental finding, contributing to poorer glycemic control, increased risk of microvascular and macrovascular complications, reduced functional capacity, and overall diminished quality of life. Iron deficiency anemia (IDA) is the most prevalent in this patient population. These interconnected mechanisms contribute to both absolute and functional iron deficiency, yet anemia often remains underdiagnosed and undertreated in routine diabetes management. Conventional oral iron salts, though widely used, are frequently limited by gastrointestinal intolerance, interactions with dietary phytates, and poor long-term adherence, reducing their therapeutic effectiveness. Ferrous bisglycinate, a newer iron-amino acid chelate, has emerged as a promising alternative that addresses many of these limitations. Its chelated structure enhances bioavailability, minimizes gastrointestinal irritation, and allows more efficient absorption even in the presence of dietary inhibitors common in Indian diets. Clinical studies from India consistently demonstrate that ferrous bisglycinate can achieve significant improvements in Hb and ferritin levels at lower elemental iron doses compared with traditional iron salts, with better tolerability and higher adherence. This review consolidates current evidence on burden, mechanisms, and clinical relevance of anemia in T2DM and evaluates therapeutic advantages of ferrous bisglycinate. Together, these insights underscore the need for improved recognition of anemia in diabetes care and support the integration of newer, more tolerable iron formulations to enhance long-term clinical outcomes.

Keywords: Iron deficiency anemia, Type 2 diabetes mellitus, Ferrous bisglycinate, Oral iron therapy, Bioavailability

INTRODUCTION

Anemia is defined by the World Health Organization (WHO) as a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs. Diagnostic thresholds include hemoglobin levels <12 g/dl for non-pregnant women, <11 g/dl for pregnant women, and <13 g/dl for men.[1] Anemia affects more than 1.62 billion people worldwide, nearly one-third of the global population, with the highest burden observed in low- and middle-income countries.[2] India contributes one of the largest shares to this global burden and continues to struggle with persistently high prevalence despite multiple national health initiatives.

PREVALENCE OF ANEMIA IN INDIA

Recent national survey findings highlight that anemia remains a major public health challenge in India. NFHS-5

data demonstrate an overall increase in anemia prevalence across multiple demographic groups compared with NFHS-4 (2015-16).[3,4] Prevalence varies widely across states and union territories, ranging from 94% in West Bengal to 5% in Chandigarh.[3] Among children aged 6-59 months, anemia increased from 58.6% in NFHS-4 to 67.1% in NFHS-5, with the highest rates in Ladakh (92.5%), Gujarat (79.7%), DNH and Daman and Diu (75.8%), and Jammu and Kashmir (72.7%).[3,4]

Anemia among adolescent girls increased from 54.1% to 59.1%, with peaks in Ladakh (96.9%), Jammu and Kashmir (76.2%), West Bengal (70.8%), and Gujarat (69%).[3,4] Adolescent boys also showed an increase from 29.2% to 31.1%, with the highest prevalence reported in Ladakh (93.1%), followed by Jammu and Kashmir (53.5%), Bihar (34.8%), and West Bengal (38.7%).[3,4]

Pregnant women demonstrated a rise in anemia from 50.4% in NFHS-4 to 52.2% in NFHS-5, with particularly high prevalence in Ladakh (78.1%), Bihar (63.1%), West Bengal (62.3%), and Dadra and Nagar Haveli and Daman and Diu (60.7%).[3,4] Among all women aged 15-49 years, prevalence increased from 53.1% to 57%, with the highest levels reported in Ladakh (93.7%), West Bengal (71.4%), Assam (65.9%), and Bihar (63.5%).[3,4] Adult men (15-49 years) experienced a rise from 22.7% to 25%.[4] Although NFHS does not report data for the elderly, independent studies estimate that approximately 68% of individuals aged over 60 years in India are anemic.[5]

MULTIFACTORIAL ETIOLOGY OF ANEMIA

Anemia is a complex hematological disorder arising from a reduction in the number or functional capacity of red blood cells. Its etiology is multifactorial, encompassing nutritional deficiencies, chronic diseases, genetic disorders, infectious diseases, and environmental exposures.[6] Nutritional deficiencies, particularly IDA, remain the most common cause and may result from inadequate dietary intake, increased physiological requirements, chronic blood loss, or malabsorption. Folate and vitamin B12 deficiencies also contribute significantly, especially in individuals with gastrointestinal disorders.[6] Chronic diseases such as chronic kidney disease (CKD) lead to anemia of chronic disease (ACD), characterized by impaired erythropoiesis, altered iron homeostasis, and reduced erythropoietin (EPO) production.[6]

Genetic disorders, including thalassemia and sickle cell disease, further contribute to the national anemia burden through impaired hemoglobin synthesis.[6] Infectious diseases, such as malaria, HIV, and parasitic infestations, remain important contributors in many regions by inducing hemolysis, chronic inflammation, and impaired nutrient absorption. Additionally, environmental factors, particularly air pollution, have been associated with systemic inflammation and lower hemoglobin levels.[6]

PUBLIC HEALTH SIGNIFICANCE

Anemia is associated with significant clinical and societal consequences. It increases morbidity and mortality in women and children, contributes to adverse pregnancy outcomes, reduces occupational productivity, and impairs cognitive and behavioral development in children.[7] National programs such as Anemia Mukt Bharat (AMB) and the National Iron Plus Initiative (NIPI) aim to address these challenges through nutritional supplementation, screening, and community-level interventions.[8,9] However, several implementation barriers, including low supplementation adherence, gaps in the supply chain and point-of-care diagnostics, and the persistence of non-nutritional causes, continue to limit the effectiveness of these programs.[10]

ANEMIA IN THE CONTEXT OF CHRONIC METABOLIC DISEASE

While anemia affects diverse population groups in India, its impact becomes particularly concerning when it coexists with chronic metabolic disorders.[11] T2DM is one such condition, with rapidly increasing prevalence and an established link to multiple microvascular and macrovascular complications.[12] Growing evidence indicates that anemia is not merely a coincidental finding in individuals with T2DM. Instead, it represents a clinically meaningful comorbidity that can worsen glycemic control, increase the risk of complications, impair quality of life, and adversely influence long-term outcomes.[13] Understanding the epidemiological and mechanistic connections between anemia and diabetes is essential for improving patient-centered management strategies.

ANEMIA IN DIABETES: A NEW FIGHT AGAINST AN OLD ENEMY

Rising global burden of diabetes and its link to anemia

DM has emerged as a major global health burden, currently affecting hundreds of millions of individuals worldwide. According to the International Diabetes Federation (IDF) diabetes Atlas 2025, approximately 1 in 9 adults aged 20-79 years are living with diabetes, and more than 40% remain undiagnosed. The number of affected individuals is projected to escalate to 853 million by 2050.[14] While the condition is widely recognized for its vascular and metabolic complications, anemia is increasingly acknowledged as a prevalent and clinically significant comorbidity in people with diabetes.[12] Evidence shows that anemia in diabetes can worsen disease progression, reduce treatment effectiveness, and negatively impact overall quality of life.[12]

Chronic hyperglycemia and associated metabolic disturbances can alter micronutrient status in individuals with diabetes, contributing to deficiencies in vitamin B12, vitamin D, and iron.[15] These micronutrient deficits

may arise as a consequence of diabetes-related complications or, in some cases, act as contributing factors in disease progression. Emerging research also highlights a bidirectional relationship between iron metabolism and glucose regulation, reinforcing the interconnectedness of metabolic pathways in diabetes.[15]

Epidemiology of anemia in type 2 diabetes in India

India, one of the countries with the highest burden of diabetes globally, is also experiencing a significant overlap between T2DM and anemia, particularly IDA. A large multicentric retrospective analysis of 1,137 adults with T2DM revealed high rates of anemia and iron abnormalities. In this analysis, 10.8% had isolated iron deficiency (normal hemoglobin with low ferritin), 39.3% had IDA (low hemoglobin and low ferritin), and 39.6% had ACD (low hemoglobin with normal ferritin). Only 10.3% of participants had normal hemoglobin and ferritin values.[15] Women were disproportionately affected, constituting 65.3% of the IDA group and 57.7% of those with iron deficiency without anemia. Age and diabetes duration were also important determinants. Iron deficiency without anemia was more common in adults aged 30-50 years, while IDA predominated in those aged 50-60 years. ACD was most prevalent among individuals older than 60 years and was more likely in those with a diabetes duration exceeding 10 years.[15] These findings highlight the progressive impact of T2DM on iron metabolism and underline the need for early identification of anemia in diabetic populations.

Pathophysiology of anemia in diabetes

The development of anemia in diabetes is multifactorial, driven by several interrelated mechanisms including reduced EPO production, chronic inflammation, advanced glycation end products (AGEs), oxidative stress, autonomic neuropathy, and nutritional deficiencies (Figure 1).

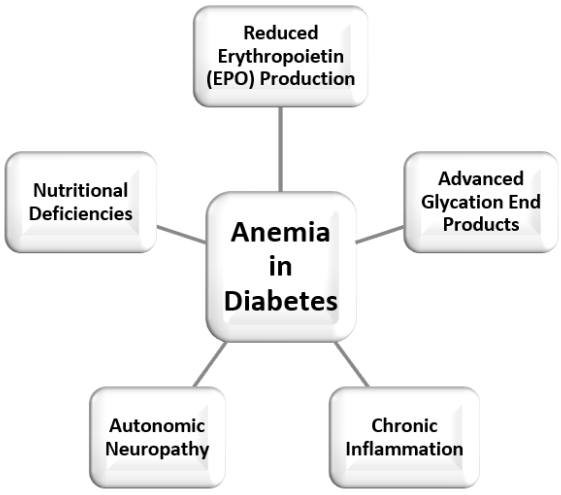

Figure 1: Pathophysiology of anemia in diabetes.

Reduced EPO production

Diabetes-related renal impairment reduces the kidneys' ability to produce EPO, a hormone essential for erythropoiesis. Even before overt nephropathy develops, microvascular damage and tubular dysfunction may impair EPO synthesis, resulting in levels that are inappropriately low relative to the degree of anemia.[16]

Chronic inflammation

Diabetes is characterized by chronic low-grade inflammation, marked by elevated cytokines such as IL-6 and TNF-α. These inflammatory mediators suppress bone marrow erythropoiesis and stimulate hepcidin production. Hepcidin decreases intestinal iron absorption and traps iron within macrophages, leading to functional iron deficiency.[16]

AGEs

Persistent hyperglycemia promotes the formation of AGEs, which can alter red blood cell (RBC) membrane structure, increase RBC rigidity, shorten RBC lifespan, and contribute to premature hemolysis.[16]

Oxidative stress

Enhanced oxidative stress in diabetes damages erythroid precursors and mature red blood cells, contributing to ineffective erythropoiesis and reduced RBC survival.[16]

Autonomic neuropathy

Diabetic autonomic neuropathy impairs renal perfusion and may blunt the hypoxia-driven reflex that normally stimulates EPO production.[16]

Nutritional deficiencies

Patients with diabetes, especially those with gastroparesis or long-term metformin use, are prone to vitamin B12 and folate deficiencies, which impair DNA synthesis and may result in megaloblastic anemia.[16]

Clinical impact of anemia in diabetic patients

Anemia in individuals with diabetes is associated with an increased prevalence of both microvascular and macrovascular complications. These include retinopathy, nephropathy, neuropathy, cardiovascular disease, and peripheral artery disease.[15] The presence of anemia may exacerbate tissue hypoxia, impair wound healing, and worsen overall metabolic control, thereby increasing the risk of long-term complications.

Clinical impact of IDA in diabetes

IDA has specific clinical implications in diabetes. Several studies indicate that HbA1c levels may be falsely

elevated in the presence of IDA, making accurate assessment of glycemic control difficult.[15] IDA is also associated with significantly higher fasting plasma glucose, postprandial glucose, and HbA1c levels compared with non-anemic individuals. Fasting plasma glucose level ≥143 mg/dl has been identified as a significant predictor of IDA, with a 2.3-fold higher risk even after adjusting for confounding factors such as age, sex and diabetes duration.[15] Patients with T2DM and IDA are also at increased risk of developing diabetic kidney disease.[17] This association may reflect combined effects of chronic inflammation, iron dysregulation, and impaired renal function commonly observed in longstanding diabetes.

FERROUS BISGLYCINATE: A NEWER GENERATION ORAL IRON FOR IDA TREATMENT

Challenges with conventional iron therapy

Despite high burden of anemia in diabetes, treatment remains challenging. Traditional oral iron preparations are widely prescribed but frequently associated with gastrointestinal adverse effects, including nausea, vomiting, abdominal discomfort, and constipation.[18] Moreover, their absorption is inhibited by common dietary constituents such as phytates, particularly relevant in Indian diets, leading to reduced bioavailability.[18] These limitations contribute to poor adherence and suboptimal clinical outcomes.

Emergence of ferrous bisglycinate as a promising option

Given the high prevalence and clinical consequences of IDA in individuals with diabetes, timely and effective management is essential.[18,19] Newer-generation iron formulations are gaining interest due to improved tolerability, enhanced absorption, and better patient compliance. Among these, ferrous bisglycinate, an iron-amino acid chelate, has emerged as a promising therapeutic option with superior bioavailability and gastrointestinal tolerability, offering potential advantages over conventional iron salts.[19]

Structure and mechanism of absorption

Ferrous bisglycinate is a highly stable iron-amino acid chelate in which a ferrous (Fe^{2+}) ion is bound to two glycine molecules.[18] This chelated structure allows the compound to be absorbed intact across the intestinal mucosa via amino acid transport pathways rather than the conventional iron transport mechanisms. Once inside enterocytes, iron is released and transported into the systemic circulation, where it is distributed to tissues for metabolic use. This targeted absorption pathway contributes to the improved gastrointestinal tolerability observed with ferrous bisglycinate compared with traditional iron salts.[20]

The chelated structure also reduces the interaction of ferrous bisglycinate with common dietary inhibitors such as phytates, which are prevalent in many Indian diets and significantly impair the absorption of conventional iron formulations.[19] As a result, ferrous bisglycinate maintains higher absorption efficiency even in the presence of these inhibitory food components.

Enhanced bioavailability and clinical evidence

Multiple studies have shown that ferrous bisglycinate possesses significantly higher bioavailability compared with conventional iron salts. Evidence indicates that its absorption is approximately twice that of standard iron formulations such as ferrous sulfate and ferrous fumarate.[18] This superior bioavailability translates into meaningful clinical advantages, including the ability to achieve therapeutic outcomes at lower elemental iron doses. These findings highlight the enhanced absorption efficiency of ferrous bisglycinate and support its use in patients requiring improved gastrointestinal tolerability and better adherence. Clinical data from India further strengthen the evidence base for ferrous bisglycinate as summarized in Table 1.

Table 1: A summary of key Indian clinical studies evaluating ferrous bisglycinate.

Clinical trial	Trial design	patient population	treatment duration	treatment groups	key findings
Singhal et al[20]	Prospective, randomized, comparative clinical study	N=250 antenatal women with IDA	60 days	Group 1: Ferrous sulfate (100 mg/day) Group 2: Ferrous fumarate (100 mg/day) Group 3: Ferrous ascorbate (100 mg/day) Group 4: Ferrous bisglycinate (30 mg/day) Group 5: Sodium feredetate (33 mg/day)	All the groups showed a significant increase in Hb level at Day 60 compared to baseline. 30 mg ferrous bisglycinate showed a comparable rise in Hb and ferritin compared to 100 mg ferrous ascorbate and significantly greater than 100 mg ferrous sulfate (p=0.014).

Continued.

Clinical trial	Trial design	patient population	treatment duration	treatment groups	key findings
Raiturker et al[18]	Retrospective analysis	N=374 pregnant women	Mean follow-up duration of 58 days	Combination of [Ferrous bisglycinate (60 mg) + zinc bisglycinate (15 mg) + folic acid (1 mg) + methylcobalamin (500 mcg)/day]	Mean increase in Hb level 2.41 gm/dl. Percentage of women with an Hb level of more than 11 gm/dl 62.4%. Compliance rate >98%.

In a randomized comparative study involving pregnant women with IDA, Singhal et al demonstrated that a low dose of ferrous bisglycinate (30 mg/day) resulted in hemoglobin improvements comparable to those achieved with much higher dose of ferrous ascorbate (100 mg/day) over a 60-day treatment period.[20] In a separate study of antenatal women, ferrous bisglycinate (30 mg/day) produced hemoglobin and ferritin responses similar to ferrous ascorbate (100 mg/day) and significantly superior to ferrous sulfate (100 mg/day; p=0.014).[20] Real-world evidence from retrospective analysis by Raiturker et al further demonstrated that a combination supplement containing ferrous bisglycinate (60 mg) resulted in a mean hemoglobin increase of 2.41 g/dl, with 62.4% of pregnant women achieving hemoglobin ≥11 g/dl and compliance rates exceeding 98%.[18] Overall, clinical findings across controlled trials and real-world settings consistently indicate that ferrous bisglycinate is highly effective, well-tolerated, and associated with excellent adherence. Its superior bioavailability, reduced gastrointestinal adverse effects, and demonstrated efficacy across diverse patient populations, including infants, children, pregnant women, and individuals with chronic disease, position it as a strong therapeutic option for the management of IDA.

Advantages over conventional iron salts in the Indian market

Ferrous sulfate has long been regarded as the reference standard for oral iron therapy in India due to its wide availability, cost-effectiveness, and established clinical use, with a relative bioavailability of 100%.[21]

Other commonly prescribed iron salts, including ferrous fumarate and ferrous gluconate, demonstrate similar absorption profiles, with relative bioavailability approaching that of ferrous sulfate.[22] Iron polymaltose complex (IPC) also exhibits comparable bioavailability.[23] Ferrous ascorbate, however, offers improved absorption, with studies reporting up to a 67% increase in bioavailability relative to ferrous sulfate.[24]

In recent years, newer-generation formulations have emerged with markedly enhanced pharmacokinetic profiles. Among these, ferrous bisglycinate has demonstrated more than threefold higher bioavailability compared with ferrous sulfate.[25]

This improvement is attributed to its amino acid chelation, which facilitates efficient intestinal uptake through peptide transport pathways while minimizing gastrointestinal irritation.

Microencapsulated liposomal iron similarly provides substantially enhanced absorption, approximately 2.7 times higher than ferrous sulfate, through a lipid-based encapsulation system that protects iron from gastrointestinal degradation and promotes mucosal delivery.[26] In contrast, ferric ammonium citrate shows lower absorption efficiency and is considered less effective in correcting iron deficiency.[27]

Table 2: Relative bioavailability of various iron salts available in the Indian market.

Iron salts formulations available in the Indian market	Relative bioavailability	GI Tolerability
Ferrous sulfate[21]	100% (Reference standard)	Poor (common side-effects)
Ferrous fumarate[22]	Approximately 100%	Poor
Ferrous gluconate[22]	Approximately 100%	Good
Ferrous bisglycinate[25]	>3 times higher than ferrous sulfate	Good (fewer GI effects)
Ferrous ascorbate[24]	Up to 67% higher than ferrous sulfate	Moderate
Ferric ammonium citrate[27]	Lower than ferrous sulfate	Good
Iron polymaltose complex[23]	Approximately 100%	Good (often fewer side effects)
Microencapsulated liposomal iron[26]	2.7 times higher than ferrous sulfate	Good

As summarized in Table 2, comparative data underscore the clear pharmacokinetic and tolerability advantages of newer formulations, particularly ferrous bisglycinate, over traditional iron salts used in the Indian market.

These characteristics make ferrous bisglycinate a promising option for improving clinical outcomes and adherence in patients requiring oral iron therapy.

CONCLUSION

Anemia remains a major public health concern in India and poses added challenges for individuals with T2DM. In this population, anemia is a clinically relevant comorbidity that worsens glycemic control, accelerates complications, and adversely affects overall outcomes. IDA is the most frequent form, driven by chronic inflammation, altered iron metabolism, and nutritional gaps commonly seen in diabetes.

Conventional oral iron salts, though widely used, are limited by poor gastrointestinal tolerance, dietary interactions, and low adherence, factors that often hinder effective and sustained correction of IDA. Ferrous bisglycinate, a newer iron-amino acid chelate, addresses many of these limitations through superior bioavailability, improved gastrointestinal tolerability, and reduced interaction with dietary inhibitors such as phytates. Evidence from Indian studies supports its ability to achieve comparable or better hematologic improvement at lower elemental iron doses.

Overall, ferrous bisglycinate offers a practical, well-tolerated option for managing IDA in individuals with T2DM, with the potential to improve treatment adherence and clinical outcomes. Integrating such newer-generation formulations into routine care may help strengthen anemia management and enhance long-term health in this high-risk population.

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