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REVIEW ARTICLE

THE DIABETIC-ANEMIA NEXUS: IMPLICATIONS FOR CLINICAL PRACTICE

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Summary

Objectives: Due to a variety of factors, individuals with diabetes are more likely to develop anemia. Chronic kidney disease, a frequent consequence of diabetes, is one of the key contributing factors. Diabetic neuropathy is another reason that can result in gastrointestinal bleeding and iron malabsorption. Healthcare providers must be aware of the connection between diabetes and anemia in order to closely monitor and treat both disorders and lessen their detrimental effects on general health and quality of life. This review sought to explore the underlying factors that lead to anemia in diabetic individuals, as well as the most prevalent kinds of anemia and suggested management approaches.

Methods: PubMed, Cochrane Library and Google scholar were searched to find all relevant articles published in English until October 2023, using the specified search phrases, and we then brought up and analyzed all of the papers that matched the requirements.

Results and conclusion: Collectively, managing anemia in diabetes patients is a difficult issue that calls for a multimodal approach. Early detection and effective therapy of anemia in diabetic patients depend on routine monitoring of the blood levels of hemoglobin, glycemic control, blood pressure, foot health, renal and retinal functions, neuropathy, and other comorbidities.

Key words: Diabetes mellitus; Anemia; Erythropoietin

Introduction

Diabetes mellitus is a chronic metabolic condition that can cause high levels of blood sugar which, if left untreated, can eventually result in major health problems (1, 2). Anemia is one of these, and when it coexists with *diabetes mellitus*, can exacerbate symptoms and raise the risk of diabetes complications (3). Patients who have both *diabetes mellitus* and anemia may feel more exhausted, weak, and breathless than usual, which can reduce their physical performance and lower their level of well-being. Additionally, diabetic neuropathy, a common consequence of diabetes that involves nerve damage, particularly in the legs and feet, may get worse with anemia (4, 5). Anemia can also

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have an adverse influence on diabetes treatment, where in people with anemia, the HbA1c test findings may be deceptively low, that can result in a misdiagnosis or a false sensation of having good glucose control (6, 7).

The prevalence of anemia in people with diabetes varies according to the population investigated and the criteria employed to detect anemia (8). Anemia is more common in diabetics than in those who do not have the disease, according to studies. Anemia was found in more than 19% of the 1,962 patients with type 2 diabetes who were evaluated for it. Diabetic individuals with moderately impaired renal function had considerably higher anemia than individuals with mild renal insufficiency in the same research. Cardiovascular problems and retinopathy were additionally more common in those with *diabetes mellitus* and anemia (9). Higher prevalence rates of anemia in type 2 diabetic patients were noted in another studies, where anemia was found in about 34% of the total participants (10, 11). It is important to emphasize that these data are only estimates and should be interpreted in the context of the population investigated . Nevertheless, it is apparent that people with diabetes are at a higher risk of anemia, and it is critical for healthcare practitioners to screen for and monitor anemia in diabetics, since it can suggest the presence of microvascular problems and may necessitate immediate intervention to prevent additional complications. Accordingly, This review aimed at exploring the possible types of anemia in diabetic population with their underlying causes and risk factors, in addition to highlighting the implications for clinical practice of anemia to support the health care professionals with the essential guidelines for managing anemia and other related complications when present in patients with *diabetes mellitus*.

Methodology and search strategy

The search was conducted utilizing several databases, to find articles related to the relationship between diabetes and anemia in animal and human beings until October 2023. The major search databases used were PubMed, Cochrane Library, and Google Scholar. Using medical subject heading (MeSH) phrases and Boolean operators, a standard search was conducted in Cochrane and PubMed. While the "advanced search" option of Google Scholar was used. Diabetes complications, anemia, anti-diabetics, haematological abnormalities, and *diabetes mellitus* were among the key words that were searched.

Peer-reviewed English language studies describing at least one of the noted hematological abnormalities in diabetes individuals are required for inclusion criteria. Anti-diabetic drugs and their association with anemia, possible types of anemia in *diabetes mellitus*, and a consciousness of the clinical implications for our findings are the parameters to be evaluated in the current study in order to draw our conclusion. Gender, age, and publishing year were not subject to limitations, while editorial papers , abstracts, book chapters and thesis are all excluded.

***Diabetes mellitus* complications contributing to anemia**

Numerous risk factors might contribute to anemia in diabetes individuals. The two main risk factors are older age and long duration of the disease. Anemia in older diabetics is likely to have a variety of underlying reasons, such as reduced kidney function, bone marrow suppression, inflammation, and dietary inadequacies (12). Diabetic kidney disease (DKD), can also induce anemia in a number of ways such as defeciency of erythropoietin, iron insufficiency, a shorter lifespan of RBCs, excessive bleeding, oxidative stress, secondary hyper-parathyroidism, chronic inflammation, uremia, long-term suppression of erythropoiesis nutritional folate deficiency. According to reports, 1% of people with stage 3 chronic kidney disease (CKD), 9% of people with stage 4 CKD, and 33%-67% of those with stage 5 CKD have anemia (13–16). The most significant factor contributing to anemia in those with CKD is relative EPO deficiency. Diabetes also negatively affects hypoxia-inducible factors (HIFs), a key regulators of oxygen homeostasis via transcriptional activation of many oxygen-sensitive genes, including EPO in response to hypoxia. Also, in diabetes, multiple tissues are hypoxic and the adaptive responses to hypoxia are impaired due to insufficient activation of HIF signalling, which results from inhibition of HIF-1α stability and function due to hyperglycaemia and elevated fatty acid levels (17). It has been demonstrated that hyperglycemia prevents the HIF protein from stabilizing. HIFs play a role in the pathophysiology of diabetes as well as the emergence of both the microvascular and macrovascular consequences of the disease. HIF-1 α protein is increased when glucose management in diabetics is improved, and this has a variety of advantages, among which are at least partly mediated by HIF-1 α (18). The development of new drugs that pharmacologically regulate HIF may open up novel and interesting therapy options for anemia. Additionally, achieving and maintaining more physiological EPO levels

linked to HIF stabilization might help treating patients who are resistant to ESA therapy and result in better results at elevated hemoglobin targets (19).

In renal disease patients the RBC lifespans are reduced by 30 to 70%, which might give falsely low HbA1c readings. The mechanism underlying this phenomena is still not fully understood. RBC survival is normal when blood from uremic donors is given into healthy recipients, suggesting that the uremic milieu present in patients with chronic renal disease is the fundamental source of this event. On the other hand, improvements in chronic kidney replacement therapy would not enhance RBC survival (20). The red blood cells of patients with diabetes show changes in the membrane integrity, disorder in hemoglobin oxygen-binding and modification in mechanical characteristics. These changes contribute to reduced erythrocyte survival, and put diabetic patient at higher risk of cardiovascular complications and recurrent ischemic events in comparison to non-diabetic counterparts with normal renal function (21). On the other hand, uremia may impair renal function, increasing the likelihood of bleeding and iron loss in diabetes individuals with chronic renal impairment (22). Particularly hemodialysis patients are vulnerable to iron loss due to recurrent phlebotomies and blood clotting in the dialysis machine. Additionally, it has been demonstrated that people with chronic renal disease have poor potential for dietary iron absorption. A protein called transferrin transports iron from the RES and the digestive tract into the bone marrow where it is used by erythrocytes that are developing. Reduced transferrin levels in patients with DKD make it harder to mobilize iron and results in anemia (23).

Diabetic neuropathy, a consequence of diabetes that damages the nerves, can also predispose to anemia by affecting the nerves that govern the muscles in the intestine, and can result in impairment of the absorption of iron and other essential elements for the development of RBCs (24). Another potential defect that can be seen in patients with diabetic neuropathy is reduced or abolished EPO production. When the kidney is denervated in experimental models, EPO production is inhibited. Additionally, individuals who have primary autonomic nervous system problems experience reduced EPO production and a greater chance of developing anemia (25).

Hyperglycemia in patients with *diabetes mellitus* may induce oxidative stress leading to dramatic effects on the physiological functions and morphological structure of erythrocytes, leading to in insufficient microcirculation perfusion, oxidative stress and hypoxia, which if not treated properly may end-up with diabetic-induced oxidative stress anemia (26). In general, hyperglycemia, as an influential factor in cardiovascular injury, induces endoplasmic reticulum stress, mitochondrial dysfunction and causes accumulation of reactive oxygen species, all of which contribute to cellular damage with the onset of and progression of diabetic complications (27–29). Studying the association between oxidative stress and the prevalence of anemia in patients with diabetes revealed a significant relationship between the lack of glutathione, glutathione reductase, and glutathione peroxidase and the low hemoglobin concentration, and the red blood cells count and indices (30). Another potential factor for red blood cells damage and anemia, in addition to the high level of oxidative stress experienced by diabetic patients, is the erythrocytes' decreased antioxidant potential. Therefore, to prevent and treat this type of anemia in diabetics, it may be useful to increase the antioxidative capacity of erythrocytes to improve their structure and function (31).

It's also critical to remember that these risk factors may frequently interact to produce anemia, making it difficult to pinpoint a single cause. Additionally, it's essential to understand that not all diabetic individuals will experience anemia, and that each patient has a different risk level. As it will be indicated later in this review, some anti-diabetic drugs may raise the risk of anemia in people with diabetes, while others may produce anemia as a side effect. Additionally, when other disease, such as hypertension, co-exists with diabetes, the probability of developing anemia may rise. This is because an increased risk of microvascular and macrovascular problems, which can result in anemia, is linked to both hypertension and diabetes. Additionally, antihypertensive medications that interfere with the angiotensin system may increase the chance of anemia development (32, 33).

Possible forms of anemia in *diabetes mellitus*

There are several modes of anemia that can occur in individuals with *diabetes mellitus*, including: **Nutritional anemia**, this occurs when hematological nutrient concentrations required for RBC generation or maintenance are inadequate to satisfy those demands. Increased nutrients loss, nutrient deficiencies, impaired absorption, or altered metabolism of nutrients are all factors hat causet nutritional deficiency (34). Iron deficiency anemia is the most prevalent nutritional deficiency that causes anemia, although other nutritional deficiencies, such as deficiencies

of vitamins B12, B6, A, C, D, and E, folic acid, riboflavin, zinc, and copper, can also cause anemia (35). Nutritional anemia is not the most common type in diabetic patients; yet, iron deficiency was linked to shifts in glycated hemoglobin to elevated levels; however, this change happens largely between 5.5 and 5.5-6.0%. Although link between iron deficiency and HbA1c shifts between <6.5 and ≥6.5 percent was not detected, few participants in the study had both underlying deficiency in iron and HbA1c increases to ≥6.5, so generalizations about iron deficiency and the higher cut point are limited. Concerning folic acid levels in diabetic patients, previous studies have related reduction in folic acid levels to type 2 *diabetes mellitus* (36–38), while a glucose metabolism disorders, insulin resistance and inhibited the insulin signalling was related to chronic folic acid deficiency in another study (39). In a well-established scenario, certain studies have found a high frequency of vitamin B12 deficiency in patients with type 2 diabetes, which may be more prevalent in old persons, those with prolonged duration of *diabetes mellitus*, hypothyroidism, and those using metformin. However, more research is needed to discover the risk factors for B12 deficiency. The identification of these characteristics will help to improve monitoring and management of B12 deficiency in patients with type 2 diabetes (40, 41).

Hemolytic anemia, is produced by the breakdown of red blood cells and is induced by diabetes-related consequences like diabetic nephropathy or retinopathy, and the presence of *diabetes mellitus* is considered as a crucial survival risk factor for patients (42). In general, glycated haemoglobin shows the average glycemia during the previous three months. To lower the risk of chronic problems, the goal value of HbA1c in diabetes control is set below 6.5%. However, there are a variety of diseases that cause erythrocytes to live for a shorter period of time, giving a falsely low HbA1C reading. Hence, while HbA1C may be used as a screening test for clinical diagnosis of hemolysis in non-diabetic individuals with hemolytic anemia, it is regarded as a very poor indicator for overall glycemia and hemolysis in diabetic patients with hemolytic disorders (43). As a result, discrepancies between the levels of HbA1C and glucose in diabetic patients should notify health care professionals to the probability of complications associated with relatively short RBC survival, as in case of hemolytic anemia, and in these individuals, alternate methods of assessing blood glucose control, like fructosamine or regular laboratory or self-glucose monitoring, should be used (44). Microangiopathic hemolytic anemia, an uncommon consequence of diabetes, was reported in a mature-onset diabetic patient. The suggested mechanism of haemolysis is thought to be linked to defective cell membrane synthesis in a diabetic environment. Diabetics have an altered cholesterol-to-phospholipid ratio in the membrane's core, causing the red blood cell wall to become hard and non-deformable. As the abnormal cells circulate through the microangiopathic blood arteries, they get damaged. The addition of antiplatelet agents, which work by increasing the compliance of the cell membrane, could help in reduction of hemolysis (45). Additionally, hemolytic uremic syndrome (HUS), which is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury was shown to be associated with diabetic ketoacidosis (46).

Aplastic anemia: Aplastic anaemia is characterized by hypoplastic or aplastic bone marrow as well as a varied degree of insufficiency in at least two of the major blood cells: RBCs, WBCs, and/or platelets, when the body stops making enough new blood cells, the disease develops (47). Diabetes is not a direct cause of aplastic anemia, however diabetes-related comorbidities such as diabetic neuropathy may act as a trigger factor (48).

Anemia of chronic disease: refers to anemia that is normochromic, normocytic, and hypo-proliferative in the presence of acute or chronic inflammatory conditions as in case of chronic kidney disease and *diabetes mellitus*. Clinically, anaemia with inflammation have been reported to play a critical role in predisposing patients with *diabetes mellitus* to the progression of diabetic foot, with an inverse correlation identified between haemoglobin level and CRP, where progression of foot disease is linked to reduction in haemoglobin fall and rise in CRP level (49). Generally, chronic inflammation increases pro-inflammatory cytokines such as interleukin-6, which is essential for hepcidin production. Hepcidin limits the efficacy of iron recycling from red blood cells by inhibiting iron absorption in the GIT and the clearance of recycled iron from macrophages. Such functional iron deprivation impairs erythroid progenitor cell growth in the bone marrow, leading to iron-deficiency anemia (50).

Anti-diabetic medications and their association with anemia

There are reported cases of association between anemia and anti-diabetic drugs, where anemia can be a side effect of some anti-diabetic drugs, while others may make diabetics more susceptible to developing the condition

or may have no effect. The most prominent relation between anemia and anti-diabetic agents is reported to biguanides. The most well-known biguanide now on the market is metformin, which can interfere with vitamin B12 absorption and result in vitamin B12 deficiency and hemolytic anemia as side effects (51). A randomized controlled study was performed to investigate the relationship between metformin use and the risk of anemia in type 2 diabetes patients and the time-course for this. It was observed that metformin consistently results in an early drop in hemoglobin level and elevates incidence of moderate anemia (52). A marked decline in vitamin B12 levels and a significantly higher hazard of vitamin B12 deficiency have been revealed in diabetic patients, according to meta-analyses that reviewed all available trials on the relationships between metformin administration and vitamin B12 concentrations, anemia, and neuropathy in diabetics (53). It was proposed that metformin-induced anemia could be because its ability to blocking the absorption of B12 vitamin via a mechanism that is not fully clear, however could be due to the interference with the intrinsic factor-vitamin B12 complex binding that depend on calcium to the cubam receptors of the terminal ileum. The patient with diabetes may develop or worsen distal symmetrical and autonomic neuropathy as a result of the subsequent vitamin B12 deficiency (54). Physicians should therefore be concerned about the probable side effect of metformin with Every diabetic patient using metformin should undergo an annual vitamin B12 assessment, especially if metformin has been taken for more than 5 years, at which point hepatic stores of vitamin B12 would likely have been depleted. Treatment options comprise prophylactic vitamin B12 and calcium supplements, metformin discontinuationor, oral or IM vitamin B12 therapy to recover vitamin B12 storage, routine monitoring of vitamin B12 status, and vitamin B12 supplementation if metformin is still being used (55, 56).

Similarly, but to a lesser extent, the novel insulin-sensitizing drugs thiazolidinediones (troglitazone, pioglitazone, and rosiglitazone) can raise the risk of anemia probably by suppressing both differentiation and proliferation of erythroid progenitor cells or may due to plasma-fluid retention and weight gain caused by the formation of subcutaneous adipose tissue, even though clinical use of these medications may reportedly be limited due to the consequences of bone marrow stromal cell lineages and severe hepatotoxicity that occur mostly with troglitazone (57–59).

On the other hand, sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) and glucagon-like peptide-1 receptor agonists (GLP-1-RAs) are used in type 2 diabetes patients to manage hyperglycemia, with the added advantages of weight loss and lowered blood pressure (60). These glucose-lowering medications were demonstrated to have renoprotective benefits in patients with impaired glomerular filtration rate, according to a number of lines of evidence. These outcomes cannot be merely linked to the enhanced metabolic issues of *diabetes mellitus* but also to decreased oxidative stress and inflammation in many ways, which eventually may help against anemia (61). Liraglutide, exenatide, and semaglutide are examples of GLP-1-RA drugs that have been linked to a reduced risk of hypoglycemia, severe cardiovascular events, mortality, and anemia (62). Relatedly, sodium-glucose cotransporter-2 inhibitors (such as canagliflozin, empagliflozin and dapagliflozin) may also offer improved hematopoietic processes in patients with diabetes by their modulating effect on hematopoiesis and provoking of erythropoiesis (63). The elevated kidney release of erythropoietin (EPO) could be the cause of the higher erythropoiesis. By virtue of its effect as an intravascular pleiotropic cytokine, established to positively affect cardiomyocyte mitochondrial physiology, cell proliferation, angiogenesis,and anti-inflammation, as well as enhanced systemic tissue and myocardial oxygenation, the SGLT2-Is-mediated rise in EPO output, and consequent increase in haematocrit, could favour systemic organ protection (64). In a clinical trial, the impact of dapagliflozin on anemia was investigated, and it was shown that it could improve results regardless of baseline anaemia status and could contribute to anemia correction in comparison to placebo (65). Accordingly, SGLT2-Is and GLP-1-RAs may provide suitable agents to improve the red blood cell count, iron stores and hemoglobin beside their other organs protection effects in type 2 diabetes, although clinical monitoring is essential as a case of acute hemolytic anemia has been reported in a 30 years male after receiving semaglutide injection (66).

Dipeptidyl peptidase-4 inhibitors (DPP-4-Is; sitagliptin, saxagliptin, linagliptin, and alogliptin) have also been linked to a lower incidence of anemia in a similar manner. This novel class of anti-diabetic drugs has been shown to enhance glycemic control, maintain beta-cells function, and have favorable cardiovascular safety profiles in type 2 diabetes (67). Generally, Dipeptidyl peptidase-4 reduces the activity of EPO by cleavage and negatively controls colony-stimulating factor potential and stress hematopoiesis. Such activities may theoretically suggest that DPP-4-Is could enhance EPO hyporesponsiveness which would then regulate hematopoietic stem cells and progenitor cells leading to augmentation in EPO production to cause the creation of erythroid colonies. The inhibitors of DDP-4

also have anti-inflammatory, anti-oxidant beside their anti-hematopoietic disorder activities (68). In a clinical investigation that explored the impact of DPP-4-Is on anemia in patients with hemodialysis, linagliptin use was shown to result in either a decrease in the dose of erythropoiesis-stimulating-agent (E-S-A) with an improve in renal anemia. According to this trial, this drug can reduce E-S-A dose without affecting iron metabolism, and DPP-4-Is can raise erythropoietin concentration by blocking DPP4's effect (69). Although there are some potential challenges that must be addressed by clinicians, DDP-4-Is therapy shows a lot of promise as an unique approach to encourage hematological recovery following chemotherapy or stem cell transplantation. Moreover, it will be fascinating to continue researching how gliptins affect hematopoiesis in people with diabetic-renal disease and anemia because of the possible impact on EPO and RBC recovery (70). Collectively, to fully understand the complex interaction between anti-diabetic medicines and anemia, more studies are recommended in order to properly comprehend the processes underlying these relationships. Also clinician should be aware that the risk of anemia varies among patients and not all patients taking the anti-diabetics develop anemia. They are also advised to determine whether a medication is the cause for anemia or the underlying disease, and change the course of diabetes treatment accordingly.

Clinical implications for anemia in diabetic patients

Anemia is highly prevalent in diabetic patients can negatively impact their quality of life by causing fatigue, weakness, and difficulty with daily activities. Therefore, healthcare practitioners are advised to be aware of this high frequency and recognize anemia as a potential consequence while caring for diabetic patients in order to improve the life's quality of patients. This can be performed by regular hemoglobin monitoring and a thorough examination of diabetic individuals with anemia to avoid complications and enhance outcomes (71). However, diabetic anemia can be difficult to diagnose since it can be caused by a number of reasons, including chronic renal disease, neuropathy, hyperglycemia-induced oxidative stress, diabetic retinopathy and other factors such as the antidiabetic medications (72). Additionally, anemia can alter blood sugar levels in a variety of ways, including false elevated blood sugar values. This is specially noted to be induced by iron deficiency, and can lead to serious hypoglycemic events if health care professionals treat the false high blood sugar too aggressively (73, 74). A systematic review of different studies indicated that iron deficiency anemia was associated with higher HbA1c levels in individuals with or without diabetes. It's possible that more glucose molecules adhere to fewer red blood cells is the cause of such condition. HbA1c values in the study participants dropped after iron replacement (75). Conversely, factors that shorten the survival of RBCs may alter HbA1c levels in the blood. For example, haemolytic anaemia can result in a falsely low HbA1c, hence a diabetic patient with haemolytic anaemia may be incorrectly identified as a well-controlled diabetic (76). In addition to monitoring blood hemoglobin and sugar levels, monitoring of other comorbidities, iron stores, blood pressure, kidney function, retinal function, neuropathy and foot health is also essential to prevent further complications (77). Patient education and preventive measures are recommended to prevent anemia in diabetic patients via helping them to understand the risk factors, symptoms and management options, in addition to keeping a balanced diet, avoiding smoking, and regular physical activity (78). Multiple agents are required to manage anemia and other comorbidities in diabetic individuals. Diabetes medications, such as metformin, can induce anemia by decreasing vitamin B12 absorption, while SGLT2-Is, GLP-1-RAs and DPP-4-Is were shown to be associated with low incidence of anemia. As a result, healthcare practitioners should carefully check diabetes patients' prescriptions to detect and address any medication-induced sources of anemia. Iron, vitamin B12, and folate supplements may be recommended. Erythropoiesis-stimulating drugs may be used to treat anemia caused by chronic renal disease (79, 80). However, iron supplementation is not always suggested for all patients including pregnant women, where both iron deficiency and hyperglycemia are highly prevalent. Although iron supplements are prescribed during pregnancy to address iron shortage, it has been reported that in women who are already iron-replete, this might lead to iron excess and a higher likelihood of certain pregnancy problems. Therefore, it is generally recommended that pregnant women receive advice on whether or not to add iron to their diets based on their existing iron status as well as their other documented risk concerns for gestational diabetes (81). *In vitro* and in animal models, high iron dosages can cause lipid peroxidation. For a short or long period of time, therapeutic levels of iron supplementation will cause DNA damage. Increased heme-iron consumption or iron status, as evaluated by several biomarkers, particularly serum ferritin, may raise the chance of gestational diabetes, that may be induced by iron oxidative stress-mediated lipid oxidation and/or damage of DNA. Yet, research on the effect of low-dose iron therapy on DNA damage, lipid peroxidation, and gestational diabetes is limited. Prospective studies of low-dose iron replacement (60 mg daily or less) for pregnant women are needed to explore the link between oxidative stress

due to iron and gestational diabetes, particularly in iron-replete women (82). In elderly patients, any degree of anemia is regarded as a substantial independent risk factor to morbidity and death. A retrospective analysis of 981 individuals aged 60 years and more was performed. In the population sample, 25% had diabetes, and 5.4% had both diabetes and anemia. A total of 4.89% of the study population had peripheral artery disease (PAD). Diabetes patients with anemia had greater comorbidities, PAD, hospitalization, and medical procedures than non-anemic diabetics. The cumulative survival of individuals with both diabetes and anemia was lower at 36 months compared to non-anemic diabetics, where anemia was regarded a major risk factor for mortality in diabetic patients (83). Among the several kinds of anemia in the elderly, anemia linked with chronic inflammation appears to play a unique role, since it is the most difficult to manage. The cause of this nonspecific inflammatory reactions in the elderly has yet to be determined. It appears more likely that oxidative stress associated with aging is the true source of the inflammation in the elderly, and that this oxidative stress is also a primary cause of anemia (84). In elderly patients, erythropoietic medications have the promise to be helpful. C oncerns about their negative effects, however, have prompted the quest for alternatives. Given the etiopathogenetic mechanisms underlying anemia of inflammation in the ageing persons, an incorporated nutritional-dietetic approach using nutraceuticals could be capable of manipulating oxidative stress and associated inflammation to help to preventing the onset of this anemia and its detrimental consequences on patients' life performance and satisfaction (85). EPO can be used to treat anemia in diabetic individuals as a therapy option. Nevertheless, various obstacles must be addressed before EPO may be considered a successful therapy for diabetes. EPO has been shown to raise blood viscosity and hence increase the risk of stroke in people with diabetes and renal impairment (86). In hypertensive individuals, EPO may be contraindicated because of its possible attitude in increasing the mean arterial pressure (87). High EPO levels have been related to proliferative diabetic retinopathy, which may be caused by excessive microvascular angiogenesis (88). Moreover, as a growth factor and proliferating agent, EPO may results in tumorigenesis as well as encourage the spread of existing tumors, particularly in the treatment of cancer and anemia patients (89–91).

In conclusion, anemia is a prevalent complication of *diabetes mellitus* and can negatively affect a patient's overall well-being, or even life threatening in some cases. Healthcare professionals need to be aware of the causes, manifestations, and consequences of anemia in individuals with diabetes. Therefore, early anemia detection, diagnosis, and management is crucial to avoid the complications and enhance outcomes in diabetes patients.

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Conflict of interest

There are no potential conflicts of interest to declare.

Adherence to Ethical Standards

This part is not applicable in our study. Where the manuscript is a review article, that did not deal with human or animal samples. It just gathered investigational information from the previously published articles.

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