POSITION STATEMENT

Indian College of Physicians Position Statement on Anemia in Metabolic Syndrome

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Executive Summary

Preamble

- Anemia is common in metabolic syndrome and its component disorders
- Management of anemia improves outcomes in metabolic syndrome and its component disorders

Clinical Presentation

- Anemia worsens glycemia and its complications
- Anemia/iron deficiency worsens heart failure; may be associated with stroke and peripheral vascular disease; and worsens the outcome of diabetic foot
- Renal impairment causes anemia, and anemia contributes to worsening of renal impairment

Associated Conditions

- Anemia and iron deficiency are common in obesity and nonalcoholic fatty liver disease (NAFLD). Iron overload is equally detrimental, and has shown to be associated with higher risk of NAFLD.
- Iron overload may be associated with polycystic ovary syndrome
- Anemia and iron overload are risk factors for development of gestational diabetes mellitus

Therapeutic Significance

- Anemia may interfere with diagnostic and monitoring tests of glycemia
- Overcorrection of anemia (Hb > 13 g/dl) in renal impairment is associated with adverse cardiovascular outcomes
- Certain drugs used for management of metabolic conditions may cause anemia* or increase hematocrit†

Screening and Diagnosis

- All persons with metabolic syndrome or its component conditions must be screened for anemia.
- Screening must include clinical assessment, complete blood count and peripheral blood film.
- A pragmatic clinical, biochemical and hematological workup should precede management of anemia.

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Iron Management

- Various oral iron preparations with different properties are available. Ferrous ascorbate and fumarate are preferred options.
- Newer generation intravenous iron preparations‡ are safe and effective. Intravenous iron should be used in severe anemia, anemia requiring rapid response, and if oral iron is found to, or expected to, be ineffective, poorly tolerated, or not adhered to.
- Iron therapy should be monitored at regular intervals to avoid overload.

Adjuvant Management

- Non-pharmacological measures (diet) must be instituted to improve hemoglobin
- All treatable causes of anemia, including vitamin B12 and folic acid deficiency, must be addressed.
- Iron deficiency should be corrected prior to use of erythropoiesis –stimulating agents (erythropoietin, darbopoietin), in management of anemia of chronic kidney disease.

*pioglitazone, metformin and renin-angiotensin blockers; †DPP4 inhibitors, SGLT2 inhibitors; ‡iron carboxymaltose, iron sucrose

Summary

This Indian College of Physicians (ICP) position statement on anemia and metabolic syndrome provides clinical insights and recommendations on screening, evaluation and management of anemia with metabolic syndrome and its component disorders.

Introduction

The metabolic syndrome is a conglomeration of several interrelated risk factors of cardiovascular disease and type 2 diabetes mellitus (T2DM) that includes glucose intolerance or insulin resistance, increased blood pressure, obesity and dyslipidemia. According to the International Diabetes Federation (IDF), an individual with metabolic syndrome must have central obesity plus any two of four additional factors such as raised triglyceride (TG) level (≥150 mg/dL), reduced high density lipoprotein (HDL)-cholesterol (<40 mg/dL in men and <50 mg/dL in women), raised blood pressure (systolic BP ≥130 or diastolic BP ≤85 mm Hg) or raised fasting plasma glucose (≥100 mg/dL or previously diagnosed T2DM).[1] The worldwide prevalence of metabolic syndrome ranges between 10% and 84% and varies based on the ethnicity, age and gender; IDF estimates that one-fourth of the world's population suffers from metabolic syndrome.[2] In India, it is considered as one of the major public health problem and the prevalence in urban region of India ranges between 25% and 45%[3,4] and in rural India, a prevalence of 26.6% (95% CI: 24.6–28.8%) has been reported.[5]

Anemia constitutes another major global health problem, which is often linked with chronic metabolic conditions. The World Health Organization (WHO) defines anemia as a condition in which the number of red blood cells (RBC) or their oxygen-carrying capacity is insufficient to meet physiologic needs and it is thought to vary by age, gender, altitude, smoking, and pregnancy status. Globally, anemia affects 1.62 billion people (95% CI: 1.50–1.74 billion), which is approximately one-fourth of the population.[6] According to the recent National Family Health Survey (NFHS-4 for 2015-16), more than half the women and one fourth of the men across states in India are anemic.[7]

Anemia is often reported in patients with metabolic syndrome; however, the coexistence of these modifiable risk factors are often disregarded. Metabolic syndrome is associated with 5-fold risk of developing diabetes mellitus and 3-fold risk of developing cardiovascular disease such as stroke or heart attack and 2-fold risk of cardiovascular disease-related mortality.[8] However, associated anemia can further amplify the risk of morbidity and mortality, and can adversely affect the overall quality of life.[9-11] Thus, devising treatment strategies for anemia in patients with metabolic syndrome is imperative to improve the overall clinical outcome. The purpose of this position statement is to provide clinical insights and evidence-based recommendations for managing anemia in metabolic syndrome and its component disorders.

Physiology of Iron Metabolism and Homeostasis

The maintenance of iron homeostasis involves regulation of iron absorption, utilization, transportation, storage and reutilization (Figure 1).[12] The nonheme iron, available in many food sources, is mainly absorbed from the duodenum after reduction to ferrous (Fe2+) by ferrireductase in the enterocytes; it is then transported through cell membrane by divalent metal transporter 1 (DMT1). The cytosolic iron is exported into circulation by the iron exporter ferroportin (Fpn), following oxidation of Fe2+ to ferric (Fe3+) by the ferroxidase hephaestin. The Fe3+ in the plasma binds to transferrin (Tf) for transportation and it is acquired by cells via transferrin receptor (TfR1). Iron from dietary sources is predominantly utilized by erythropoietic bone marrow cells for erythropoiesis; while the excess or the unused iron in the circulation

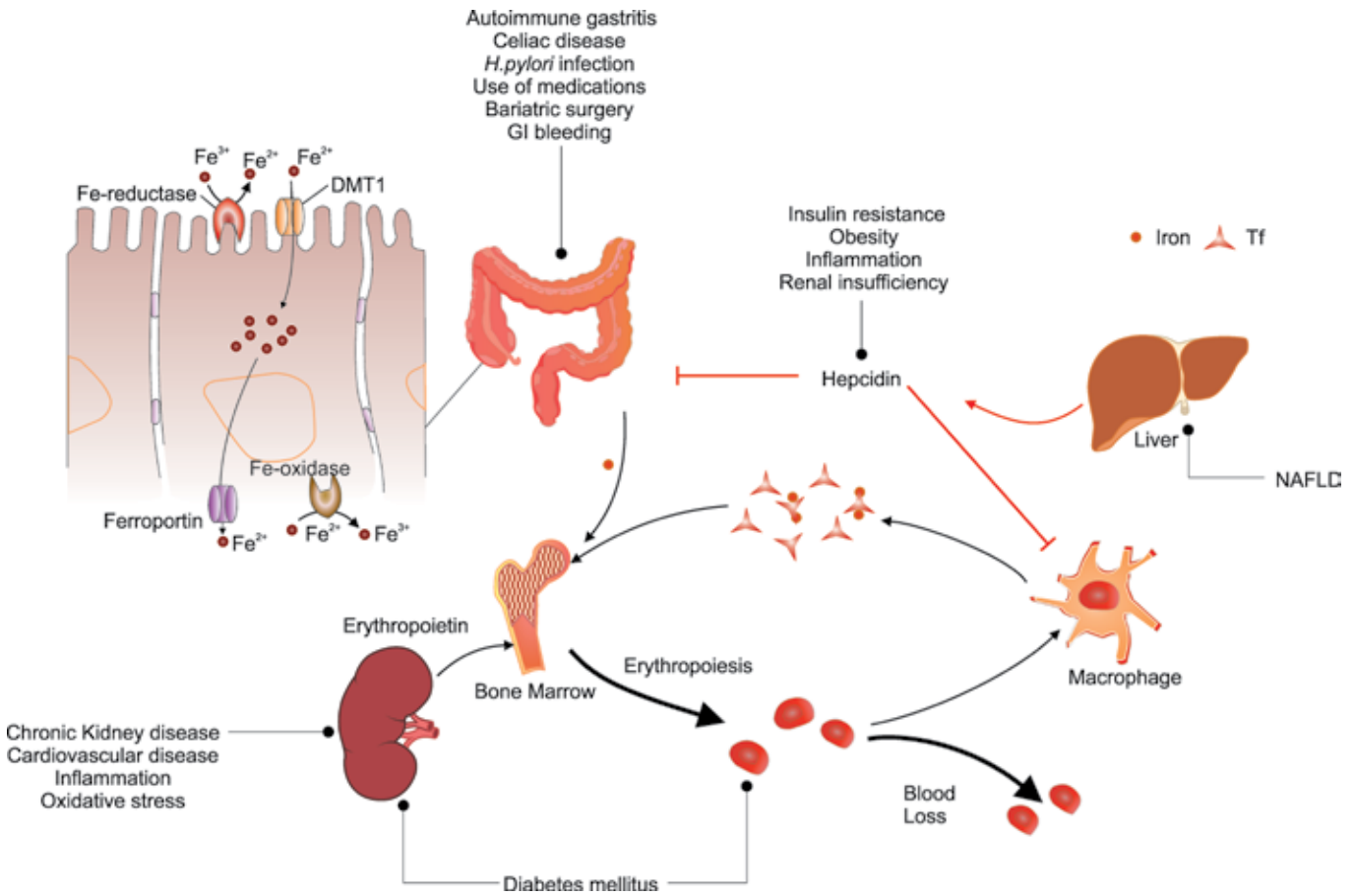

Fig. 1: Influence of metabolic syndrome and its component disorders on iron homeostasis

is stored in the liver hepatocytes or macrophages, mainly in the form of ferritin. Another source of iron for erythropoiesis is from reutilization from macrophages, particularly splenic macrophages. Iron is also found to be accumulated in tissues such as heart and pancreas in iron overload disorders.

A systemic iron homeostasis is maintained by hepcidin, a circulating peptide hormone predominantly produced by liver, in a negative-feedback mechanism. The hepcidin levels are regulated in response to iron overload, inflammation, hypoxia, iron deficiency and erythropoietic activity. Typically, hepcidin binds to iron exporter Fpn and decreases the serum iron levels by inhibiting the iron absorption in duodenal enterocytes and the release from macrophages and hepatocytes.[12]

Anemia and Diabetes Mellitus

Anemia is a commonly observed condition in patients with diabetes and it contributes to the progression of diabetes-related complications.[13] The prevalence of anemia ranges from 13% to 45% in patients with diabetes, depending upon the ethnicity and diagnostic criteria used[14-16] and it is especially high when associated with renal impairment.[17] In addition, the risk of anemia increases with severity of renal impairment in patients with diabetes and they are more likely to develop macrovascular complications.[17] It is also observed that diabetes patients who have poor glycemic control are at higher risk of anemia (odds ratio: 3.71; 95% CI: 1.09; 12.56) than those patients with good glycemic control, and the likelihood to develop anemia is even greater in patients having renal insufficiency (odds ratio: 5.78; 95% CI: 1.34; 24.92).[18] The pathophysiology linking anemia and diabetes mellitus (both type 1 and type 2) is multifaceted (Figure 2).

Type 1 diabetes mellitus

Anemia in type 1 diabetes mellitus (T1DM) is mainly associated with autoimmune disorders such as autoimmune gastritis and pernicious anemia. The prevalence of these autoimmune disorders is 3 to 5-fold higher in T1DM patients than in general population.[19] Iron deficiency anemia (IDA) is a frequent finding in patients with autoimmune gastritis, with a prevalence ranging from 20%-40%, and it often develops before pernicious anemia or at times both may coexist. Pernicious anemia due to vitamin B12 deficiency may occur in 15%-25% of patients and it is considered as an end-stage of autoimmune gastritis.[19] Patients with T1DM having autoimmune gastritis harbor antibodies to gastric parietal cells. Progressive loss of H+/K+ATPase containing parietal cells results in decreased gastric acid secretion (hypochlorhydria or achlorhydria), which may reduce the availability of iron for absorption, leading to IDA. The

destruction of intrinsic factor-secreting parietal cells may lead to failure in the production of intrinsic factor and prevent the formation of the vitamin B12-intrinsic factor complex, causing malabsorption of vitamin B12 in pernicious anemia. On the other hand, *Helicobacter pylori* infections may play a role in the pathogenesis of autoimmune gastritis and pernicious anemia by inducing autoantibodies to parietal cells.[19]

Patients with T1DM have been associated with malabsorptive disorder like celiac disease, which is a chronic immune-mediated disorder characterized by mucosal inflammation and villous atrophy due to dietary gluten intake.[20,21] Iron deficiency and vitamin B12 deficiency are commonly reported in this condition due to impaired absorption or blood loss due to gastrointestinal bleeding. Thyroiditis is also frequently observed in T1DM patients and almost 20% to 60% of patients with hypothyroidism are reported to have anemia. Inadequate thyroid levels may result in reduced production of erythropoietin and subsequently leads to bone marrow repression.[22]

Type 2 diabetes mellitus

Both erythropoietin deficiency and hyporesponsiveness may contribute to early anemia in patients with diabetes mellitus, particularly those having kidney disease or even mild decline in renal function.[11,23] Sympathetic denervation of kidney due to autonomic neuropathy and chronic hyperglycemia are important factors that potentiate hypoxia in the renal interstitium, leading to impaired erythropoietin production by peritubular fibroblasts.[24] Hyperglycemia worsens the function of hypoxia-inducible factor 1 (HIF-1), a key regulator of erythropoietin production during hypoxia, which is also involved in vasculogenesis and cellular metabolism. Reduced action of HIF-1 may cause interstitial fibrosis and generate hypoxia, which ultimately decrease the ability of peritubular fibroblast to produce erythropoietin. Several other factors that promote erythropoietin stress due to hypoxia are diabetic nephropathy, neuropathy, chronic inflammation, increased advanced glycated end products, use of antidiabetic medications like metformin, and testosterone deficiency.[24] Additional contributing factors include decreased life span of RBC, abnormal RBC and occult blood loss.

Inadequate erythropoietin response is linked to erythropoietin deficiency, reduced functional erythropoietin, increased glycosylation, and erythropoietin resistance due to glycation of erythropoietin receptors. These factors may in turn cause hypoxia and lead to overstimulation and production of erythropoietin, which may ultimately result in apoptosis of peritubular cells. Increased levels of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF-α), transforming growth factor (TGF-β) and interferons (IFNs) also causes apoptosis of erythroid progenitor cells. Moreover, advanced glycation end products and chronic hyperglycemia may reduce deformability and lifespan of erythrocytes and causes reduction in hemoglobin (Hb) levels.[24]

Additionally, the dipeptylpeptidase-4 (DPP-4) enzyme has been found to be involved in the hematopoiesis, by regulating hematopoietic stem cells, hematopoietic progenitor cells and supportive cells of bone marrow through modification of certain cytokines, chemokines, and growth-modulating factors.[25] In presence of a pathophysiological state or modified physiological homeostasis, alteration in the functional activity of colony stimulating factors, erythropoietin and IL-3 by the DPP-4 may affect the hematopoiesis.[25,26]

IDA is another major cause of anemia in CKD and may occur in patients with diabetes mellitus due to restricted dietary intake, impaired iron absorption and increased loss of blood due to gastrointestinal bleeding. Impaired iron absorption is probably due to the increased level of hepcidin in response to inflammation. In patients with diabetic kidney disease, hemodialysis procedure, uremia-related gastrointestinal ulcers are the common causes of anemia secondary to blood loss. Hemolytic anemia due to glucose-6-phosphate dehydrogenase (G6PD) deficiency is also been associated with T2DM patients, especially in African, Chinese and Indian populations. In a diabetic state, reduced activity of G6PD results from phosphorylation of G6PD through activation of protein kinase A.[27]

Thiamine responsive megaloblatic anemia (TRMA) otherwise known as Roger's syndrome, is an autosomal recessive disorder, usually associated with early onset diabetes mellitus, anemia and deafness. It occurs due to mutations in the gene SLC19A2 encoding thiamine transporter protein. The resulting ineffective response of thiamine in several tissues, including pancreatic β cells, causes diabetes mellitus. The onset of anemia is usually between infancy and adolescence.[28] TRMA is rare outside of consanguineous pairings and few cases have been reported in countries such as Brazil, Japan, Italy, Iran, Oman and Pakistan and in ethnic populations such as Israeli Arab, Lebanese, African Americans, and Kashmiri families in Great Britain.

Anemia and Diabetes-Related Microvascular Complications

Diabetic Nephropathy

The risk of developing anemia in patients with diabetes mellitus having associated kidney disease is 2 to 10-fold greater than in those patients having kidney disease of other causes.[11] In addition, the onset of anemia is earlier and tend to be more severe in patients with diabetic kidney disease than in those having similar degree of kidney disease without diabetes.[29] Anemia caused due to diabetic kidney disease can further accelerate the progression of kidney disease in a vicious manner.[23] There are no evidences of direct action of anemia in diabetic nephropathy, however,

hypoxia and oxidative stress arising from anemia together with reduced erythropoietin production are the mechanisms involved in the microvascular damage in kidney, resulting in end-stage renal disease. Additionally, increase in renal sympathetic nerve activity due to anemia may result in increased glomerular pressure and proteinuria, which further intensifies the worsening.[23] In patients with diabetes having early stages of kidney disease, an increase in iron excretion is observed. Urinary loss of transferrin and erythropoietin usually occurs in nephrotic syndrome and results in iron and erythropoietin deficiency. There is also increased transferrin catabolism and decreased erythropoietin production and response, which contributes to anemia.[11]

Diabetic Retinopathy

Patients with low levels of Hb (<12 g/dL) are twice as likely to develop diabetic retinopathy; however, the propensity increases with the severity of anemia, particularly when the levels of Hb drop below 6 g/dL. Low Hb is also associated with a 5-fold risk of proliferative retinopathy.[30,31] The common ocular manifestations related to anemia are conjunctival pallor, retinal hemorrhages, venous and arteriolar tortuosity, cotton wool spots, and papilledema.[32] Retinal hypoxia due to reduced capillary blood flow and capillary occlusion, is considered as a crucial component involved in the pathogenesis of retinopathy. It promotes the production of vascular endothelial growth factor and stimulates vascular permeability, neovascularization, retinal edema and exudate formation.[23] Erythropoietic stress due to diabetic kidney disease is also known to be associated with the progression of diabetic retinopathy.[33]

Diabetic neuropathy

Anemia is common in patients with neuropathy, particularly in those having autonomic failure. Diabetic autonomic neuropathy can cause anemia and decrease in erythropoietin levels even when the kidney functions have not deteriorated. Anemia in early diabetic nephropathy is caused mainly due to ineffective response of erythropoietin to low Hb levels because of impaired sensing mechanism associated with diabetic autonomic neuropathy. Furthermore, in these patients, loss of appropriate erythropoietin production is caused due to efferent sympathetic denervation of the kidney.[34]

Diabetic foot ulcers

Anemia has been reported in about 49% to 60% of patients with diabetic foot ulcers.[35,36] Patients with anemia are at increased risk of diabetic foot ulcer-related lower extremity amputations, subsequent high level amputations and prolonged hospitalization following surgery.[35,37,38] It is known to worsen the ischemic state and delay the wound healing due to reduced oxygen availability, which results from low Hb levels, reduced capillary blood flow, increased blood viscosity and reduced peripheral perfusion.[23] Impaired HIF-1 function and chronic inflammation also contributes to the delayed wound healing in diabetic foot ulcers.[39]

Anemia and its Influence on Glycated Hemoglobin

The glycated hemoglobin (HbA1c) is a widely accepted indicator of long-term glycemic levels and it is used for monitoring the glycemic changes in response to diet and medication in addition to diagnosing diabetes mellitus.[40] However, the use of this tool is limited in certain clinical conditions that may influence the factors involved in HbA1c measurement. Any condition that increases the erythrocyte survival or decreases the RBC turnover results in erroneously elevated HbA1c – eg. IDA, vitamin B12 deficiency and asplenia.[41,42] An elevated HbA1c is also observed in clinical scenarios such as uremia, severe hypertriglyceridemia (>1750 mg/dL), hyperbilirubinemia (>20 mg/dL) and chronic alcohol consumption due to other mechanisms. The conditions that are associated with decreased erythrocyte survival or increased RBC turnover results in lower HbA1c levels – eg. anemia due to acute or chronic blood loss, hemolytic anemia, chronic anemia associated with end-stage renal disease, and use of vitamin E, ribavirin, and interferon-alpha.[41,43] During pregnancy, up to the second trimester, HbA1c levels are falsely lowered and hence it is less reliable for diagnosing or monitoring gestational diabetes.[44,45] The HbA1c measurement is also unreliable in patients with Hb variants (hemoglobinopathies).[46,47] There are several variants identified worldwide, however, the most common are HbS and HbC. The most prevalent variant in South-east Asian countries is HbE.[48] The levels of HbA1c may be falsely high or low depending upon the assay method used.[46]

In these clinical conditions, alternative tools like fructosamine, glycated albumin, 1,5-anhydroglucitrol (1,5-AG) can be utilized to measure glycemic status.[49] The continuous glucose monitoring can be used as an adjunct in measuring the glycemic levels. Fructosamine and glycated albumin may indicate the average glycemic level over 2 to 3 weeks. However, in patients with low levels of serum protein or albumin (nephrotic syndrome or severe liver disease), fructosamine assay may not be recommended. Plasma 1,5-AG may reflect the average glycemic levels over 48 hours to 2 weeks and can be used to detect post-prandial hyperglycemia and glycemic variability. However, the results should be interpreted with caution in patients with kidney disease and gestational diabetes.[45] Thus, in renal failure patients, HbA1c assessed using thiobarbituric acid method is useful as it is more likely to reflect accurate levels.[50] In gestation diabetes, 75 g or 100 g oral glucose tolerance test (OGTT) can be considered for screening or diagnosis.[51]

Anemia and Cardiovascular Disease

Anemia is commonly observed in patients with cardiovascular

disease such as myocardial infarction, stroke and heart failure.[52-54] Nearly 10%-20% patients with coronary artery disease (CAD)[55] and one-third of those with congestive heart failure (CHF) have anemia.[56,57] The presence of anemia can worsen cardiac complications and is often correlated with poor outcomes, including increased hospitalization rate and mortality, decreased physical function, and poor quality of life.[58]

Congestive Heart Failure

The prevalence of anemia increases with severity of heart failure (based on New York Heart Association [NYHA] functional classification) and with the presence of chronic kidney disease.[59,60] Factors that lead to the development of anemia in heart failure encompass comorbid chronic kidney disease, diminished erythropoietin production, hemodilution, aspirin-induced gastrointestinal blood loss, cytokine-mediated inflammation, gut malabsorption, iron deficiency, reduced glomerular filtration rate and plasma flow, decreased bone marrow perfusion and use of angiotensin receptor blockers and (ACE) inhibitors.[59]

Conversely, anemia can also aggravate the progression of heart failure. Tissue hypoxia with release of nitrous oxide causes arterial vasodilation and decreased peripheral vascular resistance. This in turn causes activation of sympathetic system, causing increased heart rate and stroke volume, and reduced renal blood flow and glomerular filtration rate. These changes trigger the renin–angiotensin system (RAAS) along with antidiuretic hormone, causing fluid retention, increased plasma volume and ultimately culminate in left ventricular hypertrophy and dilation, and worsening of heart failure.[61] Cardiovascular remodeling is also linked to altered activity of sympathetic nervous system and RAAS, along with the erythropoietin deficiency.[59]

Stroke

Various types of anemia have been associated with increased risk for ischemic stroke, and increased mortality. In a recent meta-analysis, a prevalence rate of nearly 22% of anemia among stroke patients was reported.[62] A significantly higher risk of stroke was observed in patients with chronic kidney disease, particularly in the presence of anemia,[63] which may be attributable to the decline in erythropoietin production in conjunction with creatinine clearance.[64,65]

Anemia may induce hyperkinetic state and influence endothelial adhesion molecule genes, which may cause thrombus formation. Turbulence and rise in blood flow may lead to migration of thrombus and cause artery-to-artery embolism. The IDA can result in secondary reactive thrombocytosis. In addition, impaired erythrocyte deformability, through changes in oxygen capacity or blood flow abnormalities, may reduce tissue oxygen delivery. In hypoxic state, endothelial dysfunction via inflammatory pathway can cause ischemic brain tissue damage. Inflammatory markers such as IL-6, TNF-α and C-reactive protein are also elevated in anemic patients and could possibly impact the prognosis after stroke. In addition to these mechanism, anemia associated with acute bleeding can increase the risk of thrombus formation due to increased platelet adhesiveness and decreased fibrinolytic activity.[66,67]

Anticoagulants and antiplatelet drugs used for management of stroke may also cause occult gastrointestinal bleeding leading to IDA. Thus, timely intervention and quick treatment decisions for stroke patients with anemia are considered crucial to reduce the risk of life-threatening adverse outcomes.[62]

Anemia and Peripheral Vascular Disease

In patients with peripheral artery disease (PAD), anemia is associated with an increased risk of acute myocardial infarction and it is considered as an independent risk factor for mortality or limb amputation in hospitalized patients. In a multicentre registry, anemia was found to be present in almost 50% of patients hospitalized for PAD. These patients also had comorbidities such as diabetes, CAD, CHF and chronic kidney disease.[68] Chronic anemia may exacerbate lower limb ischemia due decreased supply or increased demand for oxygen, particularly in patients with underlying CHF or CAD. In addition, vitamin B12 deficiency and increased levels of proinflammatory cytokines may have a role in limb ischemia.[68,69]

Role of Medications in Anemia

Use of certain anti-hyperglycemic agents (AHAs) like metformin and thiazolidinediones, and antihypertensive medications like angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors are associated with the risk of developing anemia. Long-term use of metformin is known to cause megaloblastic anemia due to alterations in small bowel motility, which can stimulate bacterial overgrowth, competitive inhibition or inactivation of B12 absorption, alterations in intrinsic factor levels, interaction with the cubilin endocytic receptor and inhibition of calcium-dependent absorption of the vitamin B12-IF complex at the terminal ileum.[70] Typically, the clinical symptoms become evident after 5-10 years of treatment, depending upon the metformin dose, but the impairment of vitamin B12 absorption may begin within four months after treatment initiation.[71] Thiazolidinedione use may result in anemia due to fluid retention, and fat accumulation in the bone marrow.[72] In few case studies, use of sulphonylureas have been associated with haemolytic anemia.[73,74] Use of ARBs and ACE inhibitors may precipitate anemia by direct blockade of the pro-erythropoietic effects of angiotensin II on red cell precursors, degradation of physiological inhibitors of hematopoiesis and suppression of insulin-like growth factor (IGF)-I.[75-77]

Interestingly, use of certain AHAs like DPP-4 inhibitors and sodium glucose co-transporter type 2 (SGLT2) inhibitors have

been identified to show beneficial effects in anemia.[78-80] It has been speculated that DPP4 inhibitors may enhance the erythropoietin levels through anti-inflammatory action, improvement in bone marrow function, and inhibition of impaired activity of DPP4 on erythropoietin.[79] Certain DPP-4 inhibitors have been associated with reduction in the dose requirement of erythropoietin stimulating agents (ESA) in T2DM patients undergoing hemodialysis.[80,81] The SGLT2 inhibitors, through their renoprotective effects, have been found to enhance the erythropoietin production by improving the tubulointerstitial hypoxia and oxidative stress. It improves the reticulocyte count, followed by increase in Hb and hematocrit levels.[78]

Anemia and Obesity

Iron deficiency and IDA are the common observations in both men and women at various stages of obesity.[82] Several studies have reported low serum iron levels and serum transferrin saturation percentages (TSAT) in patients with high BMI compared with patients having low BMI.[83] Besides poor nutrition and increased iron requirement, high prevalence of iron deficiency in obese patients is mainly attributed to reduced dietary iron absorption from duodenum due to increased hepcidin level. Increased hepatic hepcidin production is primarily induced by inflammatory cytokines due to chronic low-grade inflammation in obese condition.[83] In addition, visceral and subcutaneous adipose tissues in obesity may also secrete hepcidin and contribute to the circulating levels. Pro-inflammatory cytokines such as IL-6 and TNF-α secreted from adipose tissues are also known to interfere with erythropoietin production and impair the response of erythroid precursors, thus causing anemia in obese patients.[84]

Bariatric surgeries are indicated in morbidly obese patients, but often results in diminished absorption of nutrients from intestine, reduced gastric acid secretion or intestinal bleeding.[85] The commonly performed procedures such as Roux-en Y gastric bypass (RYGB) surgery, adjustable gastric banding, and sleeve gastrostomy are found to be associated with incidence of iron deficiency or IDA.[82]

Anemia and Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a common disorder among patients with metabolic disorders such as obesity and T2DM and it is known to affect iron homeostasis in a multifarious manner. It has been observed that approximately one third of adult NAFLD patients were iron deficient (defined by TSAT <20%) due to increased hepcidin levels in the presence of obesity-related chronic inflammation.[86] Another one-third of NAFLD patients having metabolic syndrome components is associated with iron overload condition, called dysmetabolic iron overload syndrome (DIOS), which is characterised by normal TSAT level but high ferritin levels.[87,88] The mechanism of iron overload in NAFLD is not clearly established, however, it has been hypothesized that iron deposition might result from impaired iron export from hepatocytes and mesenchymal Kupffer cells due to downregulation of Fpn 1, which is cause by low-grade systemic inflammation. In response to intrahepatic iron accumulation, hepcidin production is increased, resulting in decreased duodenal expression of Fpn 1. However, decreased liver expression of Fpn 1 continues to retain hepatic iron.[89] In addition, low copper bioavailability contributes to iron accumulation in NAFLD. Elevated levels of hepcidin in urine, serum and liver were observed in patients with NALFD having DIOS than in normal individuals, patients with NAFLD without iron overload or patients with hemochromatosis.[90,91] Although there is an increased levels of hepcidin, it may be ineffective for iron regulation.[92] Interestingly, in NAFLD associated with obesity, both iron deficiency and DIOS are associated with increased hepcidin concentration, which is associated with decreased iron absorption from duodenum and impaired iron transport from the reticuloendothelial system to bone marrow. In DIOS, increased hepcidin concentration is due to increased hepatic iron stores, however in iron deficiency, increased hepcidin is linked with low grade inflammation (increased levels of IL-6). Limited evidences suggest that excess iron may further aggravate the progression of NAFLD towards non-alcoholic steatohepatitis and hepatic fibrosis.[87]

Anemia and Lipids

The evidences for the association between anemia and dyslipidemia are rather scanty. Increased levels of cholesterol and triglyceride are occasionally observed among patients with anemia having associated metabolic disorders;[93] however, the direct association of dyslipidemia in iron metabolism is not clearly understood. Few studies have postulated the correlation of increased hepcidin levels (due to underlying obesity, other inflammatory condition or compensatory mechanism in overload) with low HDL.[94] In addition, a strong positive correlation was observed between lipid parameters (total cholesterol [TC, low density lipoproteins cholesterol [LDL-C] and TG) and serum ferritin.[95] The iron-storage protein, serum ferritin is recognized as an acute phase marker of inflammation such as chronic kidney disease and as a determinant of metabolic syndrome, NAFLD, and hyperinsulinemia. Therefore, the association of ferritin and dyslipidemia could represent a cardiometabolic risk factor.[95]

On the other hand, hypocholesterolemia has been observed in various chronic anemia like thalassemia major, thalassemia intermediate, sickle cell disease, G6PD deficiency, spherocytosis, aplastic anemia and myelodysplastic syndrome.[96] The pathophysiology of hypocholesterolemia resulting from anemia includes plasma dilution, increased cholesterol

requirement associated with erythroid hyperplasia, proinflammatory cytokine release, increased cholesterol utilization by the reticuloendotheliial system, or liver injury secondary to iron overload.[96]

Anemia and Gestational Diabetes Mellitus

The worldwide prevalence of gestational diabetes mellitus (GDM) is found to be up to 28% among pregnant women[97] and in India it ranges between 3.8% and 17.8% [98] The common risk factors of GDM include familial history of diabetes, obesity, pregnancy-related weight gain, older maternal age, comorbidity of essential hypertension or polycystic ovary syndrome (PCOS). The presence of GDM increases the risk of fetal loss, preeclampsia, later development of T2DM, cardiovascular diseases and imminent adverse metabolic effects on the child.[99-101]

Various studies have explored the association between altered Hb levels and risk of GDM and it has been found that pregnant women with low levels of Hb is less likely to develop GDM. A retrospective case-control study reported the reduced probability of GDM in pregnant women with IDA. In the same study, the prevalence of GDM was negatively correlated with severity and duration of anemia.[102] Further studies have shown high maternal Hb was associated with the increased risk of GDM. Hb level >13 g/dL in early pregnancy is considered to be an independent risk factor of GDM.[102] The relationship between various serum biomarkers of iron (serum iron, ferritin and hepcidin) and GDM was also evaluated.[103,104] Increased serum ferritin and hepcidin was found to be associated with GDM, however, findings of studies suggesting the association between serum iron and risk of GDM are inconsistent.[105,106] It is further postulated that excess iron intake could be associated with increased risk of GDM. For every 1 mg of dietary heme iron intake, there is a 51% increase in the risk of GDM.[107] Another study showed that non-anemic women who have high total iron intake are twice likely to develop GDM than those who have low iron intake.[108]

Increased oxidative stress due to excess iron and resulting generation of reactive free radicals are proposed to be involved in development of diabetes mellitus during pregnancy. Iron deposition and oxidative stress in pancreatic β cells may result in impaired insulin synthesis and secretion. Excess iron may also induce insulin resistance and cause reduced glucose uptake by adipocytes and muscles, and increased hepatic glucose production.[109]

Anemia and Polycystic Ovarian Syndrome

PCOS is commonly observed in premenopausal women and it is characterized by excess androgen levels and ovarian dysfunction.[110] The metabolic risk factors like obesity and insulin resistance are often associated with PCOS and contributes to the risk of T2DM.[111] In addition, a mild iron overload, characterized by hyperferritinemia, is also been associated with PCOS.[112] Studies have shown increased serum ferritin levels in patients with overweight or obese patients with PCOS.[113,114] However, in a subsequent study, increase in serum ferritin level was observed in both obese and non-obese patients, suggesting an independent role of PCOS.[115] Increased serum iron, transferrin, TSAT and decreased soluble TfR (sTfR) concentrations have also been noticed in PCOS, indicating iron overload.[112] The mechanisms involved in mild iron overload and PCOS include reduced menstrual loss due to oligomenorrhea or amenorrhea and decreased hepcidin levels due to insulin resistance and androgen excess, which results in increased intestinal iron absorption. The mild iron overload may cause glucose intolerance in PCOS through β cell dysfunction secondary to iron deposition in pancreas and insulin resistance due to oxidative stress. Besides, inflammatory cytokines are also involved in this pathogenesis of T2DM in PCOS.[112]

Iron Overload and Risk of Diabetes

Iron overload, otherwise known as hemochromatosis, can be classified as primary (genetic) or secondary (acquired) form. The primary or hereditary hemochromatosis is a genetic disorder, in which mutation of the genes that are involved in iron homeostasis can cause inadequate hepcidin production, resulting in impaired regulation of iron absorption and increased iron retention. Depending on the gene involved in mutation, the hereditary hemochromatosis is classified as type I (HFE gene mutations – the most common form), type IIA (hemojuvelin [HJV or HFE2] mutation), type IIB (hepcidin antimicrobial peptide [HAMP] or HFE2B mutation), type III (TfR2 or HFE3 mutation), or type IV (ferroportin [SLC40A1] gene mutation). In these conditions, excess iron accumulates in parenchymal cells, particularly in the heart, liver, pancreas, endocrine glands like thyroid and pituitary, and synovium.[89,116]

In secondary (or acquired) hemochromatosis, the iron overload occurs due to multiple blood transfusions in certain anemic conditions (thalassemia, sideroblastic anemia, sickle cell disease, chronic hemolytic anemia, aplastic anemia, pyruvate kinase deficiency) or due to chronic liver diseases (hepatitis C infection, NAFLD, alcoholic fatty liver disease), porphyria cutanea tarda, or other miscellaneous causes. In this type, iron accumulates in reticuloendothelial system in bone marrow, spleen, Kupffer cells, and lymph nodes.[89,116]

Both hereditary and acquired forms of hemochromatosis can affect the progression of several chronic metabolic disorders such as T2DM, obesity, NAFLD, and atherosclerosis. Recent evidences have confirmed that iron overload status, irrespective of the causative factors, is associated with increased risk of T2DM.[116] Although the pathogenesis of T2DM may vary among causes,

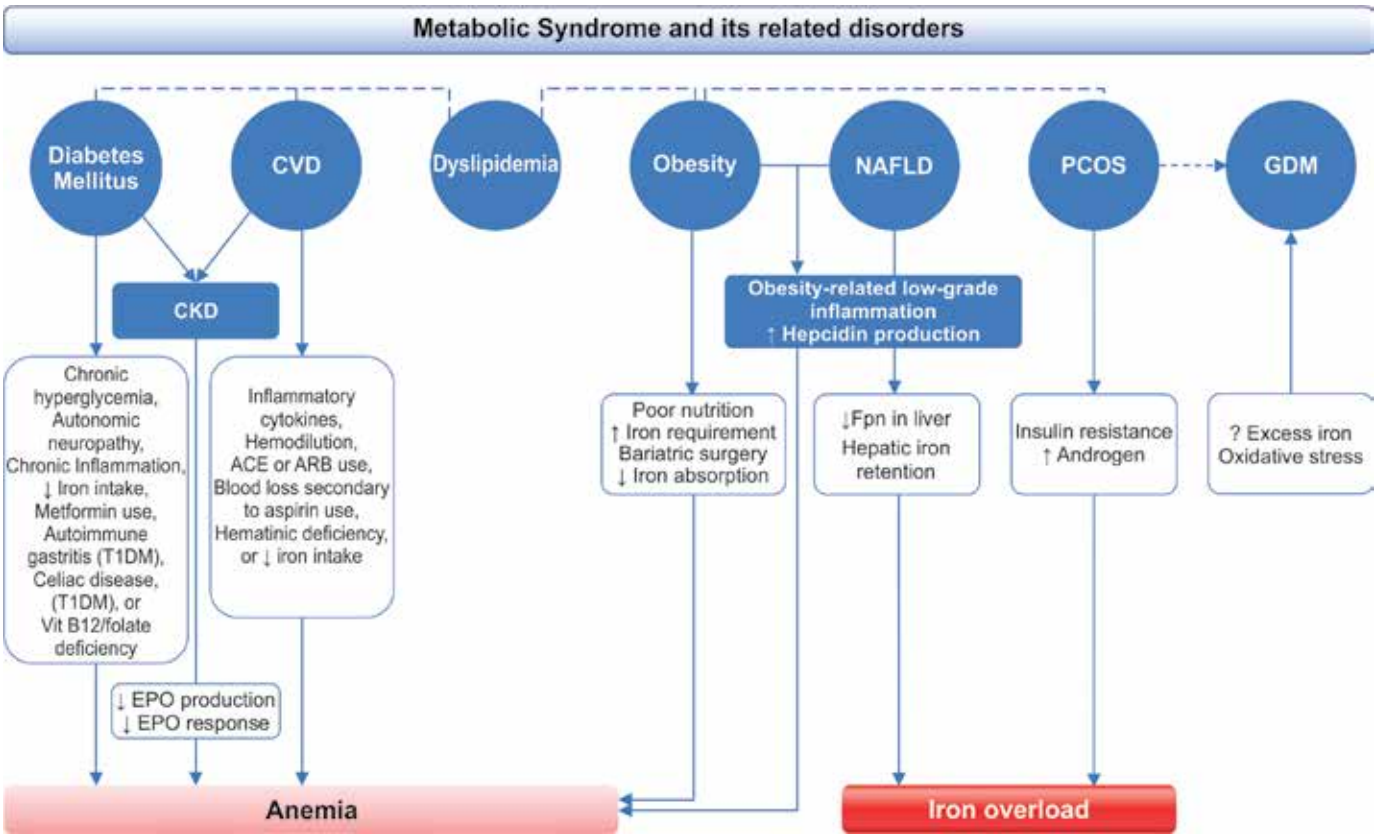

Fig. 2: Mechanism of iron disorders in metabolic syndrome and its component disorders

iron accumulation in β-cell, liver, muscles and adipose tissues and resulting oxidative stress are the key mechanisms involved in the impairment of glucose and lipid metabolism. Excess iron decreases insulin secretion due to damage of pancreatic β cells and cause insulin resistance due to abnormal insulin signaling in muscles, adipose tissues and liver. Impaired insulin action causes increased lipolysis and altered adiponectin secretion in adipose tissues, and reduced glucose uptake in both adipose tissues and muscles. It also impairs the insulin action on inhibiting the hepatic glucose production, causing hyperglycemia, and reduces hepatic insulin clearance, causing hyperinsulinemia.[116]

Screening of Anemia

Patients can be initially diagnosed for anemia based on the WHO criteria (Hb level <13 g/dL for men, <12 g/dL for non-pregnant women and <11 g/dL for pregnant women)[117] and evaluated for comorbid conditions, medication history and clinical status. As per the Indian Council of Medical Research (ICMR) classification, the severity of anemia can be mild (Hb 8-11%), moderate (Hb 5-8%) or severe (Hb <5%). In order to evaluate the type of anemia, complete blood count (CBC) and general blood picture must be assessed. The mean corpuscular volume (MCV) can differentiate the normocytic (80-100 fL), microcytic (<80 fL) or macrocytic (>100 fL) type of anemia. Megaloblastic anemia in macrocytic type can be confirmed based on the peripheral blood smear or bone marrow aspiration (if necessary). In megaloblastic anemia, the possibility of vitamin B12 or folate deficiency can be further determined based on the serum vitamin B12 or folate levels. In patients receiving long-term metformin treatment, serum vitamin B12 levels should be assessed periodically, especially in those with anemia or peripheral neuropathy. Normocytic anemia could be related to malignancy, anemia due to hemorrhage, hemolytic anemia (high bilirubin level), or anemia due to chronic disease or renal failure. In microcytic or normocytic anemia, further evaluation of serum ferritin and TSAT is useful to determine the IDA. Serum ferritin is an iron storage protein and TSAT levels could reflect iron available for erythropoiesis; serum ferritin level <30 μg/mL and TSAT <20% could indicate IDA. In chronic diseases such as CKD, or CHF, the IDA is indicated, if ferritin levels range between 30-100 μg/mL and TSAT <20%.

In CKD, the absolute iron deficiency should be distinguished from functional iron deficiency. In absolute iron deficiency (serum ferritin <100 ng/dL and TSAT <20%), iron levels are inadequate for erythropoiesis. In functional iron deficiency (serum ferritin >100 μg/mL and TSAT <20%), iron levels are adequate; however, there is poor bioavailability of iron for erythropoiesis. In anemia of chronic disease, serum ferritin ranges from 100-500 ng/mL and TSAT 20-30%; however, the presence of IDA can be ruled out with

soluble transferrin receptor (sTfR)/ log ferritin index. The sTfR <1 is observed in anemia due to chronic disease and it is >2 in IDA.[118]

Further evaluation can be conducted to determine the underlying causes: urine or stool examination, colonoscopy or upper endoscopy to determine ongoing blood loss from gastrointestinal or genitourinary tract; non-invasive screening to confirm atrophic gastritis, celiac disease; Hb electrophoresis for sickle cell disease or thalassemia; and C-reactive protein (CRP) for inflammatory conditions. Occasionally bone marrow aspiration may be required for detecting resistant anemia.

Management of Anemia

Evidences clearly support appropriate treatment for anemia in metabolic disorders as it is known to improve the clinical outcomes and overall quality of life.[119] Treating the underlying cause should be the first approach, followed by management of anemia using vitamin B12 or folate supplements, iron preparations (oral or parenteral), or ESAs. The treatment decision should be made based on an individual basis depending on the clinical status, associated disorders like CKD or CHF, and response to treatment (Figure 3).

Dietary management

The dietary sources of iron can help to maintain the iron levels, but it is unlikely to replete iron stores. Hence, it is always advised as an adjunct to iron supplementation. Taking meat, fish and poultry products along with iron supplementation can increase iron absorption. In addition, fruits rich in vitamin C (gooseberries also known as amla), guava and other citrus fruits can improve iron absorption from supplementations as well as from plant foods (green leafy vegetables, legumes and dry fruits).[120] Cooking in iron pots or vessels are also advisable. However, consumption of coffee or tea should be avoided as it can potentially reduce the absorption of iron.

Oral or intravenous iron preparations

There are several oral iron preparations available in the form of ferrous salts (eg. ferrous ascorbate, ferrous fumarate, ferrous gluconate, and ferrous sulphate), in the form of ferric iron salts (eg. ferric citrate) or carbonyl iron (Table 1). Oral iron preparations should be considered in IDA when the intestinal absorption is normal and if the Hb level is between 11-12 g/dL because of slow repletion. Adequate repletion can be achieved with the dose range of 100 to 200 mg elemental iron per day. Gastrointestinal side effects are common with oral iron preparations and may exhibit poor compliance; therefore, to improve the tolerability and adherence, smaller doses ~60 mg of elemental iron per day can be given. The Hb levels should be monitored carefully during the treatment and if the levels do not increase by 2 g/dL within 4 or 8 weeks, treatment should be changed to intravenous iron depending on the cause and severity of the condition.

In addition, the intravenous iron preparations (Table 1) are preferred in anemia that require rapid correction, in conditions associated with diminished iron absorption such as autoimmune gastritis, celiac disease, obesity and bariatric surgery, or in acute or chronic blood loss due to gastrointestinal bleeding, post-surgery, etc. In CKD patients who are non-dialysis dependent, oral or intravenous iron preparation can be used depending upon the clinical profile; however, in dialysis dependent patients, intravenous iron is preferred.

Conditions that require large amount of iron for repletion, use of ferric carboxymaltose, ferumoxytol and iron isomaltoside could be beneficial, as higher doses can be administered per infusion and also it has better tolerability profile in CKD patients. The Hb level and other serum iron markers (ferritin and TSAT) should be carefully monitored every 2 to 3 months to avoid iron overload and patients who do not respond to intravenous iron, treatment with ESAs along with intravenous iron should be considered as they are likely to have anemia of chronic disease.

Erythropoietin and analogues

Several different ESAs are available and can be classified into first generation (Epoetin-alfa and Epoetin-beta), second generation (darbepoetin-alfa) and third generation (continuous erythropoietin receptor activator [CERA). These ESAs are widely used in the management of anemia associated with chronic diseases like CKD and diabetic kidney disease. Treatment with ESA must be individualized based on the Hb levels, previous responses to iron treatment, risk of transfusion, risks related to ESAs, and symptoms attributed to anemia (Table 2).

When and how to start: Before treatment with ESAs, other causes of anemia should be ruled out or treated (including IDA). The time for initiating ESA therapy may vary among patients. The ESA is initiated in iron replete state—in non-dialysis patients when Hb level <11 g/dL and in dialysis patients when <10 g/dL—to reduce the need for blood transfusion, risk of hospitalization and mortality.

The first-generation ESAs, which has a shorter half-life, can be administered up to 3 times/ week to maintain the Hb levels in CKD patients on hemodialysis. In non-dialysis CKD patients, epoetin-alfa can be administered once a week or once every 2 week. The second-generation ESA, darbepoetin-alfa has almost 3 times longer half-life than epoetin, and thus it has advantages of reduced dosing frequency and improved patient compliance when compared with epoetin. Darbepoetin-alfa can be administered once every 2 weeks (dose equivalent to thrice-weekly epoetin) at initiation, however it can be administered once weekly for patients on dialysis. Subsequently, once monthly darbepoetin-alfa can be administered to maintain the adequate Hb levels. The third-generation ESA (CERA) also has longer half-life and can be administered up to once every 2 weeks or once monthly. However, there are limited clinical experience in patients with CKD.

In dialysis patients,

Table 1: Iron preparations for the management of anemia

Oral	Dosage
Ferrous ascorbate	100-200 mg of elemental iron/day
Ferrous sulphate	
Ferrous fumarate	
Ferrous gluconate	
Ferrous bisglycinate	
Ferrous succinate	
Ferric citrate	
Carbonyl Iron	100-200 mg/day
Parenteral	
FCM	15 mg or 20 mg iron/kg (IV administration) or 1000 mg of iron (20 mL FCM)
Iron isomaltoside	100-200 mg IV bolus injection or up to 20 mg iron/kg infusion.
Ferumoxytol	510 mg IV over at least 15 minutes
HMV dextran*	Up to 100 mg of iron IV at ≤50 mg/min
LMW dextran*	Up to 100 mg of iron IV at ≤50 mg/min
Sodium ferric gluconate complex	62.5-125 mg IV during dialysis or infusion over 1 hour
Iron sucrose	100-200 mg IV over 2-5 minutes

IV, intravenous, FCM, ferric carboxymaltose; HMW, high molecular weight; LMW, low molecular weight; *Test dose required.

intravenous ESAs are preferred over subcutaneous due to ease of administration; however, in non-dialysis patients and those on peritoneal dialysis, subcutaneous ESAs have greater advantage.

How to monitor: The Hb levels are monitored every week until the levels reach 11-12 g/dL and subsequently every month. When the Hb level increases by 1 g/dL in a 2-week period or if it is >12 g/dL, the treatment should be suspended and reinitiated with reduced dose (25% below the previous dose) after Hb level declines to <11 g/dL. However, if the increase in Hb level is ≤1 g/dL over 4 weeks, dose of ESA dose should be increased by 25%. If the Hb is inappropriately low after 4 to 6 weeks, causes for ESA hyporesponsiveness should be determined. The possible causes are vitamin deficiency, hemolysis, infection, inflammation, or malignancy; occult blood loss

Table 2: Various types of erythropoietin stimulating agents

ESAs	Dosage
First generation	
Epoetin-alfa	50 to 100 units/kg IV or SC 3 times a week
Epoetin-beta	50 to 100 units/kg IV or SC 3 times a week
Second generation	
Darbepoetin-alfa	0.45 mcg/kg/wk or 0.75 mcg/kg/fortnightly IV or SC
Third generation	
Continuous erythropoietin receptor activator (CERA)	0.6 mcg/kg/fortnightly

ESA, erythropoietin stimulating agents; IV, intravenous; SC, subcutaneous.

or accumulation of aluminium. Targeting Hb >13g/dL is not recommended in patients with CKD and could increase the risk of stroke, vascular thrombosis and hypertension.[11,121] In addition, serum ferritin levels of >200 µg/l and TSAT of >20% are required to be maintained. Upon achieving the target levels, maintenance dose of IV iron (once weekly or monthly) is usually given with ESA therapy to support erythropoiesis. Further, ESAs should be restricted in patients with CHF and should be used if the benefit outweighs the risk of adverse outcomes like stroke or hypertension.[121] The ESA therapy should be carefully monitored for any adverse effects such as headache, shortness of breath, hypertension, tachycardia, hyperkalemia, nausea or vomiting, diarrhea and hypersensitivity reactions such as rash or itching. ESA treatment should be discontinued if patient develops pure red cell aplasia (rare adverse reaction associated with ESA) or severe anaphylactic reactions.

Blood transfusion for anemia

The blood transfusion is generally restricted in order to minimize the associated risk. However, it can be considered if benefit outweighs the risk in patients who have severe life threatening anemia, active bleeding and hemodynamically unstable, failure of other treatments, or anemia associated with cardiovascular disease (Hb level: <7 g/dL).[122,123] Following transfusion, appropriate treatment with intravenous iron or ESAs, should be considered in order to correct and maintain the Hb levels, and to prevent the need for subsequent transfusions.

Conclusions

The co-existence of anemia and metabolic syndrome can be detrimental. Hence, early diagnosis with appropriate clinical evaluation and timely management are required to reduce the risk of morbidity and mortality, and to improve overall quality of life. Available treatment options such as oral or intravenous iron preparations and ESAs for the management of anemia should be considered based on the clinical profile, risk associated with treatment, tolerability, convenience and compliance. Excess correction of anemia associated with iron overload could lead to adverse outcomes. Therefore, treatment of anemia should be carefully monitored along with other metabolic risk factors.

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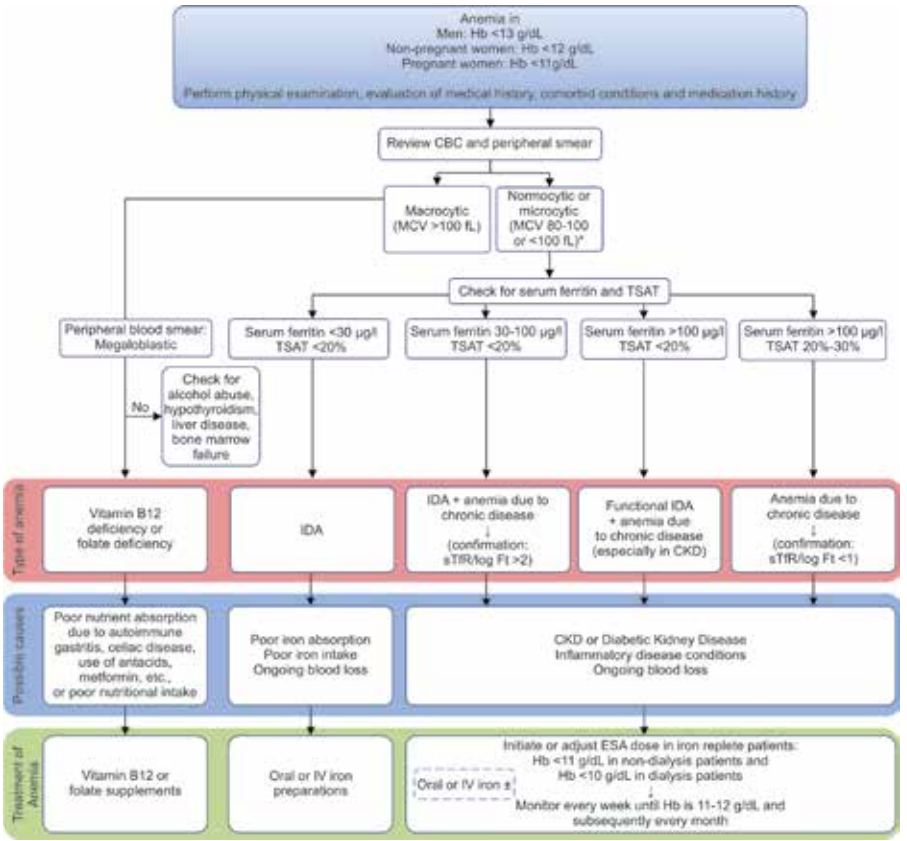

Fig. 3: Screening and treatment strategy for anemia in metabolic syndrome or its component disorder

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