Positioning of Ferrous Ascorbate in Indian T2DM Patients

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Background and Objective of the Survey

Ferrous ascorbate, a combination of iron and vitamin C, holds a unique position in the management of type 2 diabetes mellitus (T2DM) among Indian patients. While primarily recognized for its role in treating iron deficiency anemia, its relevance in the context of T2DM stems from the high prevalence of both conditions in India and their intricate interplay.

In Indian T2DM patients, iron deficiency is a common comorbidity, often exacerbated by poor dietary intake, malabsorption, and chronic inflammation associated with diabetes. Ferrous ascorbate addresses this dual burden by providing supplemental iron in a form that enhances its absorption due to the presence of vitamin C.

Moreover, iron plays a crucial role in glucose metabolism and insulin action, with iron deficiency potentially contributing to insulin resistance and impaired glycemic control in diabetic individuals. By replenishing iron stores, ferrous ascorbate may help optimize metabolic parameters and improve overall diabetes management.

Furthermore, the antioxidant properties of vitamin C in ferrous ascorbate may confer additional benefits by mitigating oxidative stress, a hallmark of diabetes complications.

The objective of the survey is:

To evaluate the of positioning of ferrous ascorbate in Indian T2DM patients

Methodology of the Survey

A survey was conducted to evaluate the of positioning of ferrous ascorbate in Indian T2DM patients. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Animal studies
- Gene expression regulating glucose homeostasis during ID
- Human studies
- Management of iron deficiency anemia
- Ferrous Ascorbate

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) are prevalent forms of nutritional deficiency. Globally, 50% of anemia is attributed to iron deficiency. Reduced iron stores have been linked to increased glycation of hemoglobin A1C (HbA1c). In addition, the prevalence of IDA is considerably significant in patients with type 2 diabetes mellitus especially those with nephropathy. The clinical relevance of the effect of iron deficiency on glucose metabolism is still not clear. The links between glucose, anemia and HbA1c are complex and not yet fully elucidated. Diabetes can contribute to anemia through reducing absorption of iron, gastrointestinal bleeding and through diabetic complications that cause anemia.

Studying the effect of ID and IDA on glucose metabolism in experimental animals and in human subjects revealed some important consequences of both on glucose levels, HbA1c and insulin secretion. In addition, some of the possible mechanisms that mediate these effects have been investigated.

Animal studies

In animal models, responses to ID include alterations in glucose and lipid metabolism. ID animals display signs of disrupted metabolic homeostasis, including alterations in insulin signaling, as evidenced by hyperglycemia, hyperinsulinemia, and hyperlipidemia. Decreased oxidative capacity leads to a shift in preferential fuel utilization from fat to glucose.

Some studies measured serum glucose concentrations in ID animals using a laboratory animal diet in which the primary carbohydrate source was sucrose and using formula (AIN-93) with a major change being the substitution of cornstarch for sucrose. These studies reported elevated serum glucose levels in severely iron-deficient (hemoglobin <60 g/L) rodents fed on both diets. However, the lipid abnormalities (increased triglyceride) occurred in the rats fed AIN-76A diets. The mechanisms contributing to these metabolic responses were not the primary focus of these investigations.

The metabolic response to ID is correlated to the severity of these consequences (hyperglycemia and hyperlipidemia) and appeared to be a graded response associated with a reduction in hemoglobin. However, less severe reductions in hemoglobin are not as highly correlated with hyperglycemia and hyperlipidemia.

These findings suggest a certain threshold exists in order to develop these potentially negative metabolic consequences.

However, in other studies, even a moderate induction of iron deficiency appears to contribute to is sufficient to disrupt normal glucose homeostasis in rodents and to elevations in both steady-state levels of serum glucose and insulin regardless of basal diet formulation. This relative hyperglycemia was associated with a relative hyperinsulinemia in the ID animals.

Hyperglycemia was associated with a relative decrease in cortisol in the ID groups signifying that high cortisol secretion (secondary to the stress of anemia) is not responsible for the presence of hyperglycemia.

On the other hand, Marquez-Ibarra A et al. showed that low levels of dietary iron reduced levels of serum triglycerides, hemoglobin, and cholesterol, and significantly improved insulin, and glucose tolerance in healthy rats.

Gene expression regulating glucose homeostasis during ID

Some studies examined the hepatic expression of genes involved in maintenance of glucose homeostasis during ID. These studies have shown that dietary intervention(s) tend to elicit biologically meaningful, transcriptional responses. The ID rats in each group showed significant alterations in the expression of genes representative of glucose metabolism.

Distinguished changes in gene expression include those genes associated with metabolic pathways including both glycolysis and gluconeogenesis.

The significant increase in the glucokinase (Gck) expression is likely due to the relative increase in circulating insulin levels observed in the ID groups, as insulin is a known inducer of hepatic Gck mRNA expression. Increased expression of Gck could potentially be very important as ID animals have been shown to have an increased reliance on glucose as a metabolic substrate, and Gck is able to rapidly increase the rate of glucose phosphorylation in the liver in response to the elevations in blood glucose levels. Furthermore, as Gck catalyzes

the first step in hepatic glucose utilization it can contribute multiple pathways including glycogen synthesis, glycolysis, and de novo lipogenesis which could explain the enhanced glucose utilization and hyperlipidemia reported in response to dietary ID.

Previous observations suggest that alterations in metabolic gene expression are indicative of an impaired hepatic insulin response wherein ID animals exhibited a form of mixed insulin resistance. Chronic hyperinsulinemia may contribute to a combination of hepatic insulin resistance in which the insulin-dependent activation of lipogenic gene expression remains intact, but gluconeogenic gene expression is inadequately repressed. In this model of mixed insulin resistance, insulin acts through the mammalian target of rapamycin complex 1 to activate lipogenesis via a sterol regulatory element (SRE) -binding protein)-1c-dependent increase in lipogenic gene expression, whereas insulin-induced phosphorylation of the transcription factor forkhead box protein O1 is diminished such that gluconeogenic gene expression remains inappropriately active. Thus, mixed insulin resistance remains a candidate mechanism explaining the relative hyperglycemia and hyperlipidemia reported in ID animals.

OhiraY et al. revealed that ID led to upregulated expression of genes encoding gluconeogenic enzymes as well as increased serum glucose levels. Glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase 1 (Pckl) were among the upregulated genes involved in carboxylic acid metabolic processes. These genes encode the rate-limiting enzymes for gluconeogenesis. In addition, serum insulin levels also increased. This increase is consistent with a report that under hypoxic conditions in iron-deficient rats with lactate accumulation which activates gluconeogenesis. Despite changes in hepatic insulin signaling, peripheral tissue insulin sensitivity as assessed by glucose clearance appears to be enhanced with ID.

Table 1. Summary of tissue changes in gene expression in response to iron deficiency in rats

Upregulated genes	**Downregulated genes**	**Increased changes in serum**	**Decreased changes in liver or serum**
Lipogenesis (SREBF1) - liver and muscle	B-oxidation (FASN,CPT1A) in liver	Glucose Pyruvate	Triglycerides Cholesterol (serum and liver)

	and muscle Lactate (serum)		
Glycolysis (PFKL) - liver and muscle	Ketogenesis (HMGCS2)	Insulin	Cortisol
Gluconeogenesis (PDK4) - liver	TCA cycle (ACO20) in liver and muscle Gluconeogenesis (PDK4) muscle		

Human studies

Iron deficiency remains the most common micronutrient deficiency in the world. Symptoms of ID include weakness, fatigue, impaired immune function, and reduced cognitive function in children. Serum ferritin is the storage form of iron, and it reflects the iron status fairly accurately.

An earlier study showed that reduced iron stores have a link with increased glycation of hemoglobin A1C (HbAlc), leading to false-high values of HbAlc in non-diabetic individuals. HbAlc is the most predominant fraction of HbAl, and it is formed by the glycation of terminal valine at the β-chain of hemoglobin. It reflects the patient's glycemic status over previous three months. HbAlc is widely used as a screening test for diabetes mellitus, and American Diabetes Association has recently endorsed HbAlc ≥6.5% as a diagnostic criterion for diabetes mellitus. Some studies investigated the relation between ID and IDA and changes in blood glucose concentration, HbAlc level and insulin secretion.

1. Non-diabetic patients with ID

Ozdemir A et al. evaluated the effects of correction of ID anemia (from Hb: 9.9 ± 1.8 g/dL to Hb: 13.1 ± 1 g/dL) on insulin secretion in 54 non-diabetic premenopausal women with IDA. A statistically significant decreases were found in fasting insulin levels and homeostatic model assessment (HOMA) scores following correction of anemia in women <40 years and normal body mass index (BMI <27 kg/m^2) but not in older patients >40 years or those with high BMI

(>27 kg/m^2). Post-treatment fasting insulin levels were positively correlated both with post-treatment hemoglobin levels.

Kim C et al. studied 913 women who had ID and 266 patients with IDA. Anemia was defined as hemoglobin <13.5 g/dl in men and <12.0 g/dl in women. Among women, iron deficiency was associated with a greater odds of HbA1c ≥5.5% (odds ratio 1.39; 95% CI 1.11-1.73) after adjustment for age, race/ethnicity, and waist circumference but not with a greater odds of HbA1c ≥6.5% (0.79; range 0.33-1.85). Brooks et al. measured HbA1c values in 35 nondiabetic patients with IDA before and after treatment with iron. They significantly observed elevated HbA1c values in IDA patients before treatment with significantly decreased levels after treatment with iron.

Gram-Hansen et al. showed normal HbA1c concentrations in iron deficiency, which dropped to subnormal levels after iron supplementation.

Coban E et al. studied 50 non-diabetic patients (30 women, 20 men, mean age 35.7 ± 11.9 years) with IDA and 50 healthy controls. All patients with IDA were treated with iron 100 mg/day for 3 months. Before iron treatment, the mean HbA1c 7.4 ± 0.8% level in patients with IDA(Hb:10.8 ± 1.2 g/dL) was higher than in a healthy group (5.9% ± 0.5) (Hb: 13.6 ± 0.9 g/dL) ($p<0.001$). In patients with IDA, HbA1c decreased significantly after iron treatment to 6.2% ± 0. 6 ($p<0.001$), when Hb raised to 12.7 ± 0.97 g/dL).

Rafat D et al. studied 30 pregnant non-diabetic women with IDA before and after 3 months of iron therapy. In their patients, anemia was defined as Hb levels <12 g/dl in males and <11 g/dl in females. They reported significant decrease of HbA1C after iron supplementation and observed significant correlation between erythrocyte indices, iron metabolic indices and HbA1c.

Hashimoto et al. demonstrated that the HbA1c, but not serum glycated albumin, is elevated in late pregnancy in 47 nondiabetic pregnant women not receiving iron supplementation, mean corpuscular hemoglobin (MCH) decreased from 29.9 ± 1.8 pg to 28.7 ± 2.7 pg, due to iron deficiency. Their Hb A1C levels showed a negative correlation with mean corpuscular hemoglobin (MCH), serum transferrin saturation, and serum ferritin.

Koga M et al. reported that in 180 premenopausal women with normal glucose tolerance, hemoglobin, mean corpuscular volume (MCV) and MCH showed a negative association with HbA1c.

Bhardwaj et al. reported that the mean baseline HbA1c level in anaemic patients (Hb: 6.8 g/dl) (Hb A1c: 6.6 %) was higher than that of non anemic controls (Hb: 13.2 g/dl) (HbA1c: 5.4%). However, after 3 months of treatment, a significant decline of HbA1C (from 6.6 to 5.7%) with the rise of Hb (12.2 g/dL) was recorded.

2. ID and IDA andglycemic control in patients with Type 2 DM

Christy et al. found a positive correlation between IDA (patients with Hb: = 9.4 ± 1.3 g/dL) and increased A1C levels, especially in the controlled diabetic women and individuals having FPG between 100-126 mg/dl.

In addition, investigations performed on diabetic chronic kidney disease patients, and diabetic pregnant women showed increased HbA1c levels in iron deficiency anemia (Hb ≤10.5 g/dl), which was reduced following iron therapy and improvement of Hb level.

Anemia in diabetic patient appears to have a remarkable unfavorable effect on quality of life and is associated with disease progression and the development of co-morbidities. Reduced hemoglobin (Hb) levels, even to a limited degree, can identify patients at increased risk of progressive renal disease. Although anemia is clearly associated with both micro- and macrovascular complications in patients with type 1 diabetes, it remains to be established what role anemia may have in the development or progression of these complications. There is a direct relationship between anemia and diabetic kidney disease, A number of studies, including the reduction on endpoints in non-insulin-dependent diabetes mellitus (NIDDM) with angiotensin II antagonist losartan (RENAAL) trial, have suggested that reduced Hb levels, even within the normal range, identify patients with NID-DM at increased risk for progressive renal disease.

Anemia may play a direct role in this process through direct mitogenic and fibrogenic effects on the kidney and the heart, associated with expression of growth factors, hormones, and vasoactive reagents, many of which are also implicated in the diabetic microvascular disease. Anemia is also correlated with oxidative stress, because erythrocytes represent a major antioxidant component of the blood.

IDA is associated with oxidative stress and functionally deficient high-density lipoproteins (HDL) particles. Women with IDA have higher triglycerides and cholesteryl ester transfer protein (CETP) activity and lower HDL-C than controls ($p<0.001$). Arylesterase activity of

paraoxonase-1(PON-1) was significantly lower in IDA patients than controls (-16%, $p<0.05$). The intravenous administration of iron was associated with a decrease in malondialdehyde levels and an increase in arylesterase activity of PON-1 (-22% and +18%, respectively, $p<0.05$).

3. Diabetes effect on anemia

The elevation of proinflammatory cytokines plays an essential role in insulin resistance and induces the appearance of cardiovascular complications diabetic micro- and macrovascular, kidney disease and anemia. By increasing especially IL-6. IL6 decreases the sensitivity of progenitors to erythropoietin (erythroid growth factor) and promotes apoptosis of immature erythrocytes. During the development of diabetes mellitus, nephropathy may arise, which further undermines the renal production of erythropoietin, positively contributing to an deterioration of anemia. According to Escorcio et al. approximately 40% of diabetic patients are affected by kidney diseases. The decreased renal function and proinflammatory cytokines are the most important factors in determining reduction of hemoglobin levels in those patients. Moreover, the inflammatory situation created by kidney disease also interferes with intestinal iron absorption and mobilization of iron. Therefore, diabetic patients with kidney disease have the highest risk for developing anemia.

4. IDA and glycemic control in patients with Type 1 DM

Tarim et al. performed a prospective study including 37 patients with type 1 diabetes (11 patients were ID and the remaining 26 were iron sufficient). Patients with ID had higher levels of HbA1c than patients without iron deficiency. After iron supplementation for three months, these patients showed a significant decrease in HbA1c levels. In patients with Type 1 DM, HbA1c decreased from a mean of $10.1 \pm 2.7\%$ to a mean of $8.2 \pm 3.1\%$ ($P<0.05$). Additionally, HbA1c in ID non-diabetic patients decreased from a mean of $7.6 \pm 2.6\%$ to $6.2 \pm 1.4\%$ after iron therapy ($P<0.05$).

In support with this finding, El-Agouza et al. studied 47 students with IDA (Hb <12 g/dl). After treatment with oral iron for 20 weeks their HbA1c significantly decreased from $6.2 \pm 0.6\%$ to 5.3 ± 0.5 %.

Management of iron deficiency anemia[2]

There is clear evidence to support prompt treatment in all patients with iron deficiency anemia because it is known that treatment improves quality of life and physical condition as well as alleviates fatigue and cognitive deficits.[-] Although clear evidence is lacking, iron deficiency without anemia is associated with RLS and chronic fatigue, and treatment alleviates these symptoms.[,-] In CHF, iron replacement therapy has been shown to be beneficial, even when anemia is not present.[,-] Thus, the decision to treat iron deficiency in a patient without manifest anemia must be made on an individual basis.[,] The treatment of iron deficiency anemia in patients with CKD, CHF, or cancer should be undertaken in conjunction with the appropriate specialists because different guidelines may apply.

Oral iron[2]

Intestinal iron absorption is limited. The maximum rate of absorption of 100 mg of oral iron is 20% to 25% and is reached only in the late stage of iron deficiency. Latent iron deficiency and iron deficiency anemia correspond to mean absorption rates of 10% and 13%, respectively, whereas healthy males absorb 5% and healthy females 5.6%. Iron that remains in the intestinal lumen may cause mucosal injury,[,] and studies in animal models suggest an exacerbation of disease activity and the induction of carcinogenesis in IBD. Furthermore, dose-dependent gastrointestinal side effects hinder compliance and result in nonadherence in up to 50% of patients. Thus, it is reasonable to adjust the dosage to improve tolerability. Although doses typically range from 100 to 200 mg of elemental iron per day, successful repletion can be achieved with doses as low as 15 to 30 mg of elemental iron daily.[-] Several formulations are available over the counter and are typically composed of ferrous iron salts (eg, ferrous sulfate, ferrous gluconate, and ferrous fumarate).

Oral iron supplementation is effective when intestinal uptake is intact. However, its use should be limited to patients with mild anemia (Hb, 11.0-11.9 g/dL in non-pregnant women and 11.0-12.9 g/dL in men) because repletion occurs slowly. When faster repletion is desired, intravenous administration is the preferred route. Nevertheless, oral iron is readily available, inexpensive, and convenient, making it a viable treatment option.

The response to therapy should be carefully monitored. The Hb level should increase by 2 g/dL within 4 to 8 weeks, although some patients may report an improved sense of well-being after

a few days. If the Hb level does not respond appropriately within this time frame, treatment should be modified (changed to intravenous iron) and the cause of the lack of response evaluated. Depending on the severity of the deficiency and underlying cause, normalization of the Hb level may take up to 3 months, and it may take longer to replace iron stores (ferritin >100 µg/L).

Intravenous iron[2]

Intravenous iron is very effective in the treatment of iron deficiency anemia and should be considered when oral iron is ineffective. The efficacy of oral iron is diminished when uptake through the gut is impaired (eg, in celiac disease, autoimmune gastritis, ACD, or post-gastric or duodenal resection) or when iron losses are large and/or continuous (eg, with menorrhagia, gastrointestinal bleeding, or postsurgery). Diminished patient compliance due to side effects also limits the efficacy of oral iron. In these situations, intravenous iron therapy is preferred because the gut is bypassed, allowing faster repletion. Ferritin expression increases shortly after administration and reaches higher levels than with oral iron, which can diminish the recurrence of iron deficiency anemia in the long term.

Table 2. Oral Vs Intravenous Iron

Oral Iron	
Pros	***Cons***
• Available over the counter • Convenient • Inexpensive • Effective when intestinal absorption is not impaired	• Limited daily intestinal absorption results in slower iron repletion. • Dose-dependent gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation) may limit patient compliance. • Uptake is impaired in the setting of disease (eg, celiac disease, anemia of chronic disease, autoimmune gastritis).

	• Mucosal injury and/or potential exacerbation of disease activity may occur in inflammatory bowel disease. • Alteration of microbiota and tumorigenic potential have been observed.
Intravenous Iron	
Pros	***Cons***
• Fast repletion of iron stores • Safe if formulations with dextran are avoided • Effective even when intestinal absorption is impaired	• Requires administration by a health care professional, with associated increased costs • Potential for iron overload and transient increase in oxidative stress • Potential for anaphylactic reactions with dextran-containing formulations

The main disadvantage of intravenous iron is the necessity for administration by a health care professional, with the associated costs. Safety was an issue in the past because of an increase in serious adverse events noted with high-molecular-weight iron dextran (HMWID). This was generalized to include all intravenous formulations; however, a review of the US Food and Drug Administration database from 1998 to 2000 showed that the cumulative rate of serious adverse events for all intravenous formulations excluding HMWID (ie, low-molecular-weight iron dextran, iron sucrose, and ferric gluconate) is low (<1:200,000). Furthermore, a study of ferric carboxymaltose and HMWID revealed similar efficacy, with fewer hypersensitivity reactions for ferric carboxymaltose. Few studies have directly compared the intravenous formulations in terms of efficacy to recommend the most effective one, but it is advisable to avoid HMWID because of the potential risk of anaphylactic reactions. In the United States and Europe, HMWID has been taken off the market. A test dose is required for all dextran-containing compounds, and if sensitivity to dextran is known, it is also prudent to include a test dose for iron sucrose and iron gluconate.

The required dose of parenteral iron was historically calculated with the Ganzoni formula, in which total iron deficit in mg = [body weight in kg x (target Hb — actual Hb in g/dL) x 0.24s + 500. However, this formula is inconvenient and inconsistently used, and it underestimates iron requirements.' The FERGIcor (FERinject in GI Disorders to Correct Iron Deficiency) trial compared a simpler dosing scheme with Ganzoni-calculated dosing and found better efficacy and compliance for the simpler regimen. Although this study was conducted in patients with IBD, it can be used as a reference point for general treatment. Patients with more severe anemia (<7.0 g/dL) may require an additional 500 mg of iron. The treatment of iron deficiency without anemia can be undertaken with 500 to 1000 mg. When large amounts of iron are required, ferric carboxymaltose and low-molecular-weight iron dextran are advantageous because higher doses can be administered per infusion,"" whereas other formulations (iron sucrose and ferric gluconate) require multiple infusion schedules with increased associated costs.

Ferrous Ascorbate[3]

Chemistry Ferrous ascorbate is a synthetic chelate of iron in the ferrous state with ascorbic acid. The unique chemistry of ferrous ascorbate includes a high content of iron and its coexistence with ascorbate in the same compound. Ascorbic acid, in quantities greater than 200 mg, increases the absorption of medicinal iron by at least 30%. Ferrous ascorbate has a high iron content (12–15%) and ascorbic acid.

Ferrous ascorbate has a quick response as improvement in Hb can be seen as early as 15 days after the initiation of supplementation with ferrous ascorbate. The evident good efficacy and excellent safety and tolerability of ferrous ascorbate can be explained by advantages of the chemical state including a better bioavailability and utilization of iron.

The chemical state of ferrous iron in oral supplements has a distinct advantage over iron in the ferric form. Given the high effectiveness, acceptable tolerability, and low cost of ferrous preparations, these are preferred over ferric preparations of oral iron supplementation.

Pharmacokinetics[3]

Iron in conventional ferrous salts is subject to oxidation by the alkaline milieu in the gastrointestinal tract and by food constituents. In the ascorbate preparation, iron is maximally absorbed due to: (i) Inhibition of conversion of ferrous into ferric iron, leading to better absorption, (ii) inhibition of the effect of phytates, phosphates, and oxalates on iron absorption, and (iii) inhibition of formation of insoluble iron complexes that interfere with absorption. Ferrous ascorbate has some inherent features that facilitate its absorption. Ferrous ascorbate dissociates to monomeric cations in aqueous solutions. Between pH of 6 and 8, ferrous ascorbate shows a solubility-enhancing effect of ascorbate. Some distinctive manufacturing process including advanced coating technology (ACT) adds stability to the ferrous ascorbate chelate and prevents it from dissociating in the presence of inhibitors in the stomach leading to higher absorption.

Bioavailability[3]

Ferrous ascorbate has a high bioavailability. In a study in 45 healthy males, the National Institute of Nutrition, Hyderabad, reported absorption of 8.3, 6.3, and 0% iron from ferric orthophosphate, sodium iron pyrophosphate, and ferric pyrophosphate, respectively, and 30.6% from ferrous ascorbate. Several studies have reported a similarly high absorption (39–43.7%) of iron from ferrous ascorbate and absorption as high as 67% is reported in the state of irondeficiency with anemia. In a bioavailability assessment of iron compounds, the geometric mean absorption from ferrous sulfate, ferrous ammonium phosphate, and ferric pyrophosphate was 10.4, 7.4, and 3.3%, respectively. The greater absorption of iron from ferrous ascorbate when compared to ferrous sulfate is explained by the prevention or retardation of oxidation of ferrous iron by ascorbate and the existence of ferrous iron as a chelate with ascorbate.

In a comparative study for ferric and ferrous preparations of oral iron, there was a significant difference in the bioavailability of 59Fe III hydroxide polymaltose compared to that of 59Fe labeledbivalent iron preparations like ferrous ascorbate or a quick-release ferrous sulfate. Intestinal iron absorption in the fasting state was low for the Fe III complex (1.2 ± 0.1%) as compared to ferrous ascorbate (43.7 ± 7.1%). After a meal, the absorption of the ferrous preparation was not affected, whereas that of the ferric preparation increased to 8.8 ± 4.7%. After an equivalent therapeutic dose of 100 mg elemental iron over 28 days, daily rise in Hb concentration was greater for the ferrous preparations (1.1 ± 0.3 g/L) compared to the Fe III

hydroxide-polymaltose complex (0.68 ± 0.2 g/L).24,25 Only about 1–8% of iron is absorbed from the available preparations of oral iron.

Regardless of the iron status, ferrous ascorbate has the highest percent uptake when compared to the uptake from other forms of iron. Yeung et al. compared the iron uptake from radiolabeled ferrous sulfate, ferrous ascorbate, ferrous bisglycinate, ferric chloride, ferric citrate, and ferric EDTA by Caco-2 cells with different iron status to mimic iron-deficient and iron overload and in the presence of divalent metal cations. When compared to cells receiving no supplemental iron, cells receiving supplemental iron showed significant reductions in uptake from radiolabeled ferrous ascorbate and ferrous bisglycinate, but not from ferric compounds. Ferrous ascorbate had the greatest percent reduction (−90%). Ferrous form of the iron has the highest absorption efficiency.

Efficacy of Ferrous ascorbate[3]

Ferrous ascorbate is widely used in clinical practice. In a retrospective analysis of hospital records of 250 patients with anemia (15–35 years of age) being treated in a teaching hospital in India, ferrous ascorbate was most commonly prescribed (69.2%), followed by ferrous sulfate (13.6%), ferrous fumarate (9.6%), and ferric ammonium citrate (7.6%).

Ferrous ascorbate has shown good efficacy in an open-label, prospective study in clinical settings in India. Oral once daily administration of a fixed-dose combination tablet (Orofer-XT) of ferrous ascorbate (equivalent to 100 mg iron) and folic acid (1.1 mg) for 45 days showed a rapid rise in Hb (mean: 2.37 g/ dL; 95% CI: 2.25–2.49) in 1,461 women (IDA without pregnancy: 508; anemia during pregnancy: 613; pregnancy with IDA: 204; not specified: 136) who had a mean baseline Hb of 8.53 ± 1.46 g/dL (95% CI: 8.45–8.61) and mean age of 27 ± 8 years. In this study, ferrous ascorbate was well tolerated, and a significant improvement in Hb was reported as early as 15 days (mean: 1.67; 95% CI: 1.56–1.78). The largest rise in Hb (3.60 g/dL) was seen in women with Hb less than 6 g/dL at baseline followed by those with baseline Hb of 6–8 g/dL (2.91 g/dL), 8.1–10 g/dL (2.23 g/dL), and greater than 10 g/dL (1.25 g/dL). In addition, there was a marked improvement in fatigue and pallor.

In an open-labeled, randomized study, ferrous ascorbate (n = 30) was compared to carbonyl iron (n = 30) for IDA. Patients received the two preparations in doses equivalent to 100 mg elemental iron for 60 days. The mean rise in hemoglobin was significantly greater with ferrous

ascorbate (5.03 ± 1.81 g/dL) than with carbonyl iron (2.82 ± 1.43 g/dL). The responder rate was higher with ferrous ascorbate as 93.33% patients were rendered nonanemic as compared to 46.66% by carbonyl iron [absolute risk reduction:46.67%; (99% CI = 17–76.2%); relative risk reduction: 88%; number needed to treat: 2.1]. The rise in serum ferritin was better with ferrous ascorbate (53.20 ± 13.35 vs 38.22 ± 15.21 µg/L; p = 0.0002).

Ferrous ascorbate has also been used in the prophylaxis of anemia in surgical patients. In a prospective study in 68 patients who underwent orthopedic surgery and autotransfusion, prophylaxis with ferrous ascorbate (99 mg elementary iron) starting 1 week before their first blood donation and up to 2 months after surgery restored Hb levels and ferritin levels.

Comparison of ferrous ascorbate with other oral iron preparations[3]

When compared to other iron salts, ferrous ascorbate has been shown to have better efficacy in children. In a comparative study of ferrous ascorbate and iron polymaltose complex (IPC) (dose of 6 mg/kg) for the treatment of IDA in children, there was a significant improvement in Hb at 12 weeks compared to baseline in both the groups. The rise in Hb was 4.88 + 1.28 g/dL and 3.33 + 1.33 g/dL with ferrous ascorbate and IPC, respectively, and the improvement in Hb was significantly higher for ferrous ascorbate (p <0.001). There is mixed evidence for the efficacy of IPC in the treatment of IDA. Some studies report its efficacy for raising Hb to be as good as ferrous sulfate or other salts and others report no significant differences.

Better efficacy has been reported for ferrous ascorbate compared to colloidal iron preparation. In an open-labeled, randomized, parallel-group comparison of ferrous ascorbate (n = 41) and colloidal iron (n = 39) in children (6 months to 12 years in age) with IDA (Hb <10 g%), ferrous ascorbate resulted in a significantly higher rise in Hb at 12 weeks when compared to colloidal iron (3.24 ± 1.66 g% vs 1.42 ± 2.04 g%; p <0.01). In this study, children received elemental iron in doses of 3 mg/kg/ day for 12 weeks. Responder rate (Hb ≥ 11.5 g%) after 12 weeks of therapy was also significantly higher for ferrous ascorbate (53.57 vs 10.34%; p<0.01).

In an open-label, randomized, comparative study of ferrous ascorbate (n= 30) and carbonyl iron (n= 30) in the treatment of IDA, ferrous ascorbate showed a significantly (p <0.05) greater increase in Hb (5.03 ± 1.81 vs 2.82 ± 1.43 g/dL above baseline).

Ferrous ascorbate is more effective than ferrous sulfate for the treatment of IDA. In a prospective, randomized, comparative clinical study, Singhal et al. reported a significant and

comparable rise in Hb on days 30 and 60 with ferrous sulfate (100 mg), fumarate (100 mg), ascorbate (100 mg), sodium feredetate (33 mg), and ferrous bisglycinate (30 mg) in the treatment of IDA in 250 antenatal women with Hb between 7 and 10 g%.40,41 At day 60, the rise in Hb was significantly more with ferrous ascorbate (1.13 ± 0.35; p = 0.024) and ferrous bisglycinate (1.11 ± 0.27; p = 0.014) as compared to ferrous sulfate.

Newer generation iron preparations, such as sucrosomial, are currently available. These preparations are said to have a higher absorption rate, better tolerability, better compliance, and better clinical outcomes. It may be noteworthy that these preparations are currently approved for food supplementation in India and contain only 30 mg of elemental iron. This sets in limitations for therapeutic use in the management of IDA. There are no data from human studies to support the high bioavailability of sucrosomial iron. These preparations have limited clinical evidence, and most of the studies have a small sample size. One study has reported a rise in Hb with 120 mg dose and at expense of gastrointestinal side effects in 26% of patients. Published evidence highlighted that frequency and number of pills can lead to noncompliance with iron deficiency treatment that may be critical in the management of IDA. Similarly, multiple daily dosing of sucrosomial iron may adversely impact compliance with therapy.

Safety of ferrous ascorbate[3]

Safety is a key concern in oral iron supplementation as up to 50% of patients develop gastrointestinal adverse events that lead to reduced compliance. The tolerability of oral iron supplementation is influenced by factors such as age, body mass, and genetic variants for tolerance in the patient. Ferrous ascorbate has a good safety profile and tolerability. Ferrous ascorbate delivers the maximum amount of ferrous iron to the duodenal brush border and reduces possible gastrointestinal adverse events.

In a real-world experience, ferrous ascorbate was well tolerated in 1,461 pregnant and nonpregnant women. Gastrointestinal AEs were reported in 7.05% (95% CI: 5.79–8.49%) of women, which included acidity, loose stools, constipation, gastritis, nausea, vomiting, and black stools. In general, gastrointestinal upset with iron supplemental preparations is minimal if the daily doses do not exceed 180 mg elemental iron and when given with food.

Ferrous ascorbate is also well-tolerated in children. In a comparative study of ferrous ascorbate and colloidal iron supplementation in doses of 3 mg/kg/day for 12 weeks in 80 children aged

6 months to 12 years, ferrous ascorbate was well accepted and there were no reported side effects.

In a comparative evaluation of ferrous sulfate (100 mg), fumarate (100 mg), ascorbate (100 mg), sodium feredetate (33 mg), and ferrous bisglycinate (30 mg) in antenatal women, maximum side effects were reported with ferrous fumarate (51 AEs) followed by ferrous sulfate (40 AEs), ferrous bisglycinate (26 AEs), ascorbate (18 AEs), and sodium feredetate (10 AEs). None of the iron preparations were associated with treatment discontinuations.

References:

1. Soliman AT, De Sanctis V, Yassin M, Soliman N. Iron deficiency anemia and glucose metabolism. *Acta Biomed*. 2017;88(1):112-118.
2. Jimenez K, Kulnigg-Dabsch S, Gasche C. Management of Iron Deficiency Anemia. Gastroenterol Hepatol (N Y). 2015 Apr;11(4):241-50. PMID: 27099596; PMCID: PMC4836595.
3. Kriplani, Alka & Malhotra, Narendra & Pal, Bhaskar & Bhat, Vidya & Swami, Onkar. (2021). Ferrous Ascorbate: Current Clinical Place of Therapy in the Management of Iron Deficiency Anemia. Journal of South Asian Federation of Obstetrics and Gynaecology. 13. 99-105.

Survey Form

1) Do you measure the iron levels of a patient with T2DM?

a. Yes

b. No

2) In your clinical practice, which tests are routinely done to assess ID?

a. Serum ferritin

b. Hemoglobin

c. Transferrin saturation

d. Peripheral smear

3) In your clinical practise, what percent of patients with T2DM have Irondeficiency?

a. <10%

b. 10-20%

v. 20-30%

d. 30-40%

e. >40%

4) Would correcting iron deficiency in a T2DM patient result in better outcomes for patients with T2DM?

a. Yes

b. No

5) At what Hb level do you consider initiating therapy for Iron Deficiency in T2DM patients in men?

a. 11–12.9 g/dl

b. 8–10.9 g/dl

6) At what Hb level do you consider initiating therapy for Iron Deficiency in T2DM patients in women?

a. 11–11.9 g/dl

b. 8–10.9 g/dl

7) Which is your preferred oral iron supplementation?

a. Ferrous Ascorbate

b. Ferrous Fumarate

c. Ferrous Gluconate

8) In what percentage of your T2DM patients have you observed vitamin B12 deficiency?

a. <25%

b. 25-50%

c. >50%

9) What could be the advantage that you perceive by correcting ID in T2DM patients?

a. Better HbA1c reduction

b. Improvement in immune status

c. Lesser occurrence of infections

10) In your opinion, what are the benefits of Ferrous Ascorbate over other oral iron supplements?

a. More ferritin content

b. Better compliance

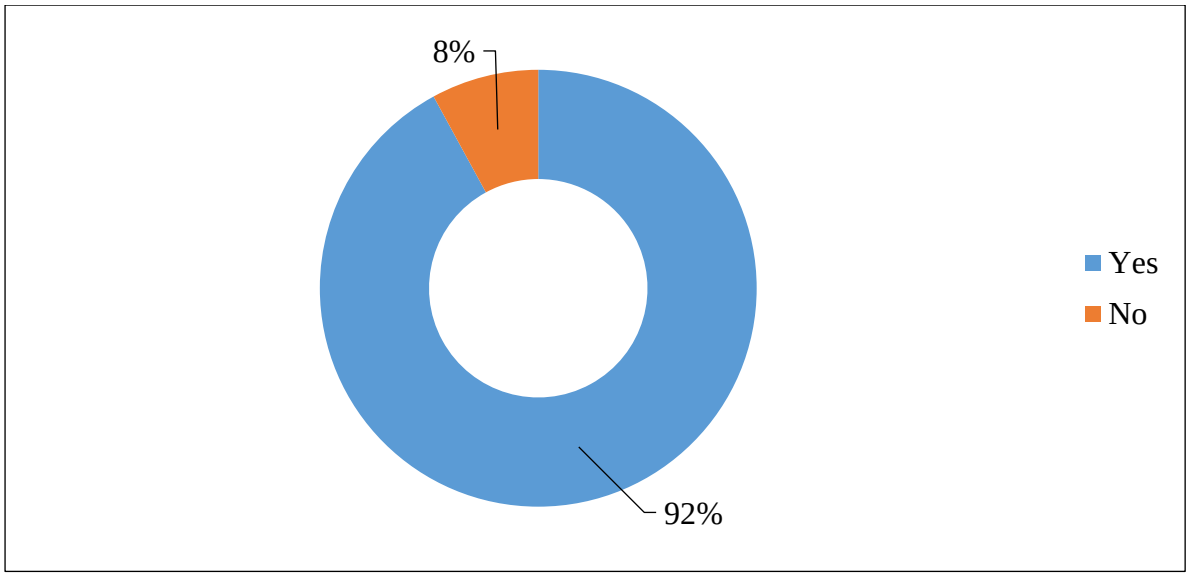
c. Lesser Side effects

Survey Findings

1) Do you measure the iron levels of a patient with T2DM?

a. Yes

b. No



According to 92% of doctors, they do measure the iron levels of a patient with T2DM.

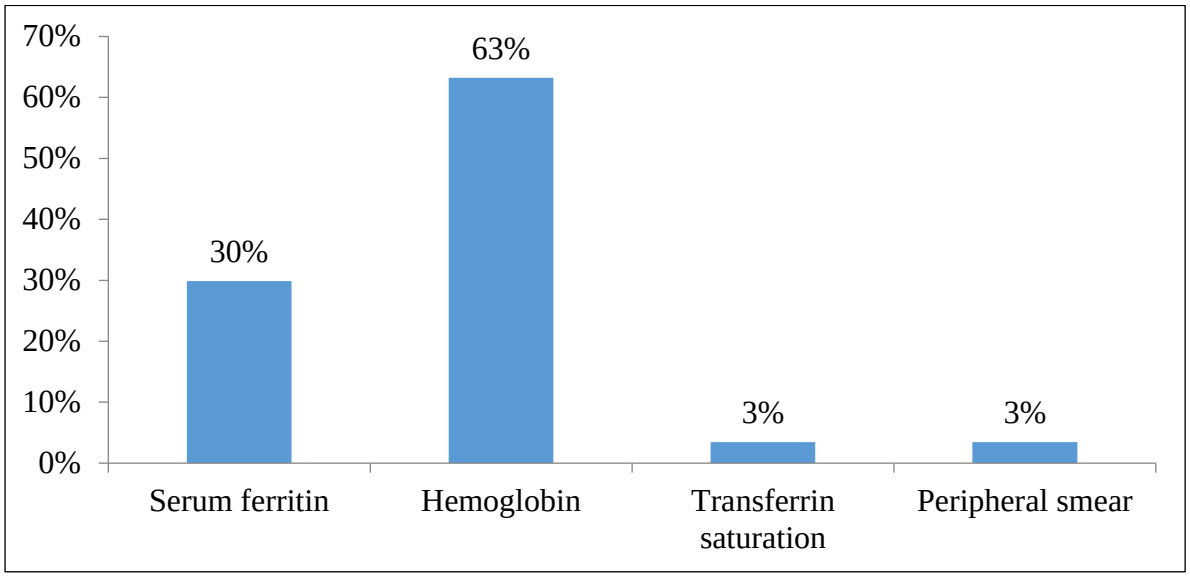
2) In your clinical practice, which tests are routinely done to assess ID?

a. Serum ferritin

b. Hemoglobin

c. Transferrin saturation

d. Peripheral smear



As per 63% of doctors, they routinely perform hemoglobin to assess ID.

3) In your clinical practise, what percent of patients with T2DM have Iron deficiency?

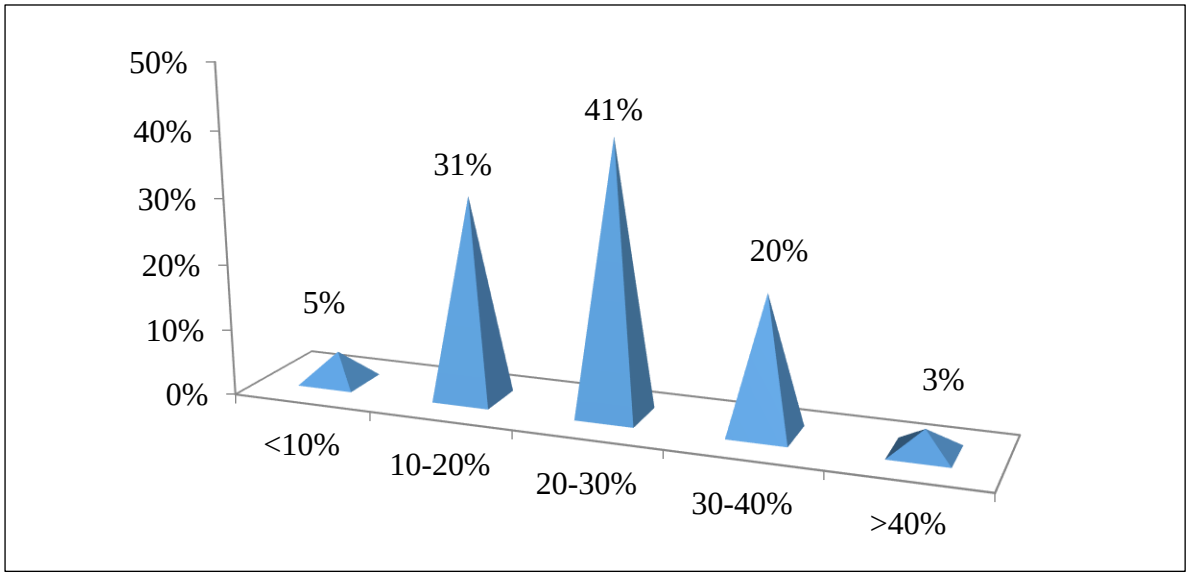
a. <10%

b. 10-20%

v. 20-30%

d. 30-40%

e. >40%

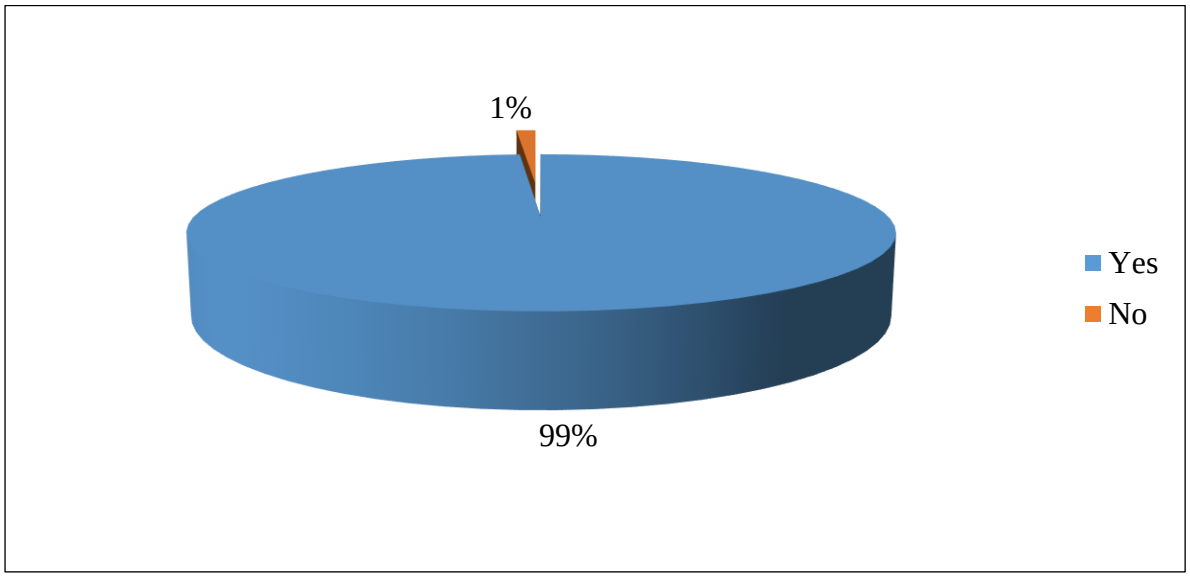


According to 41% of doctors, 20-30% of patients with T2DM have iron deficiency.

4) Would correcting iron deficiency in a T2DM patient result in better outcomes for patients with T2DM?

a. Yes

b. No

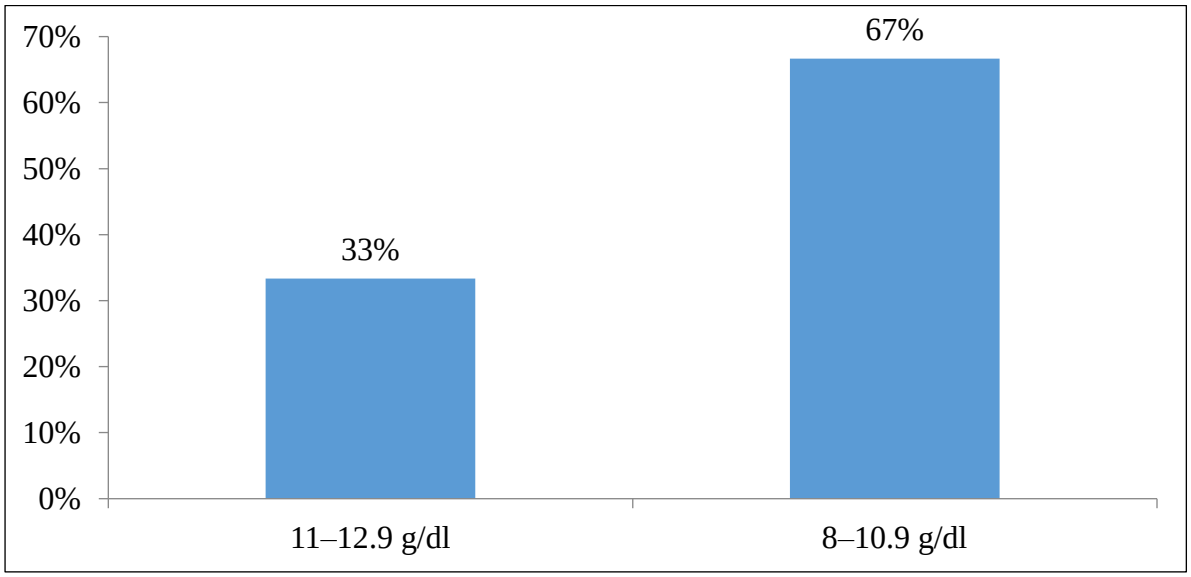


According to 99% of doctors, correcting iron deficiency in a T2DM patient result in better outcomes for patients with T2DM.

5) At what Hb level do you consider initiating therapy for Iron Deficiency in T2DM patients in men?

a. 11–12.9 g/dl

b. 8–10.9 g/dl

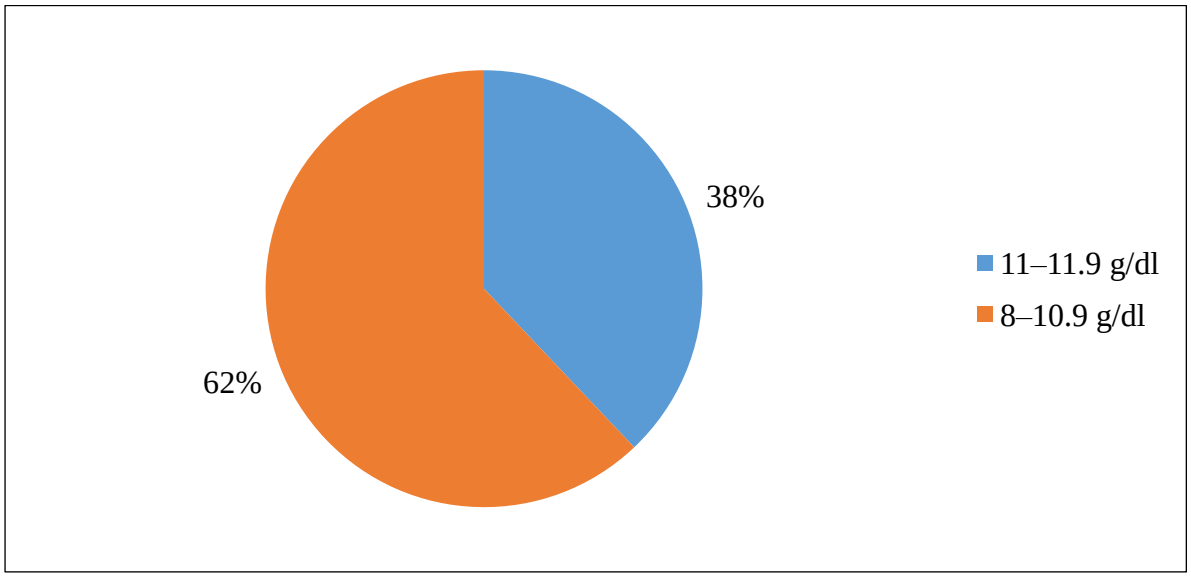


As per 67% of doctors, they consider initiating therapy for iron deficiency in T2DM patients in men at Hb level of 8–10.9 g/dl.

6) At what Hb level do you consider initiating therapy for Iron Deficiency in T2DM patients in women?

a. 11–11.9 g/dl

b. 8–10.9 g/dl



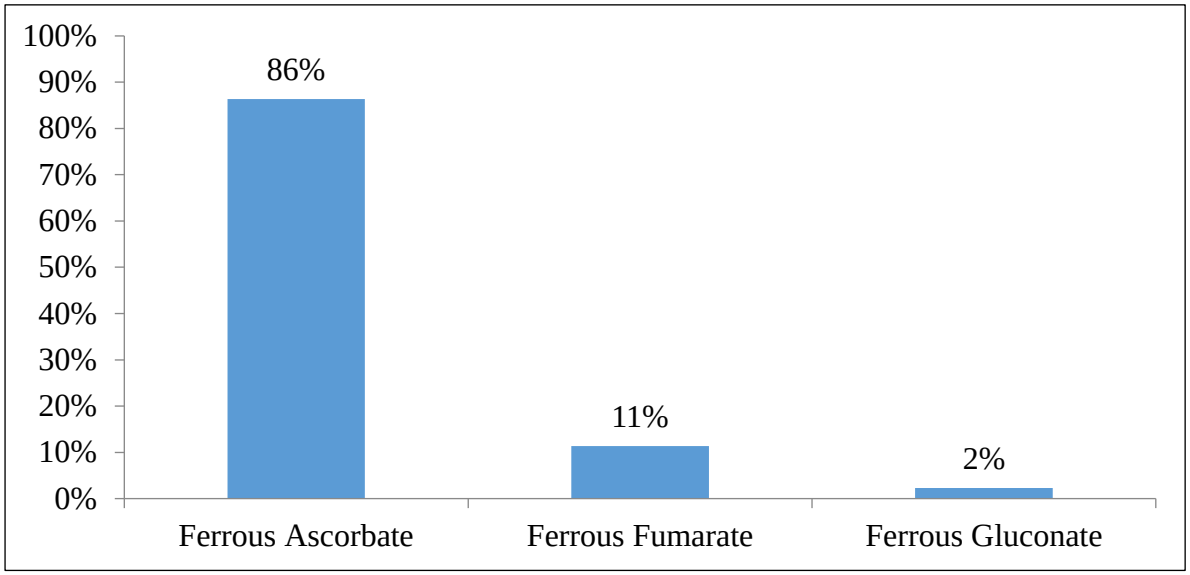
According to 62% of doctors, they consider initiating therapy for iron deficiency in T2DM patients in women at Hb level of 8–10.9 g/dl.

7) Which is your preferred oral iron supplementation?

a. Ferrous Ascorbate

b. Ferrous Fumarate

c. Ferrous Gluconate



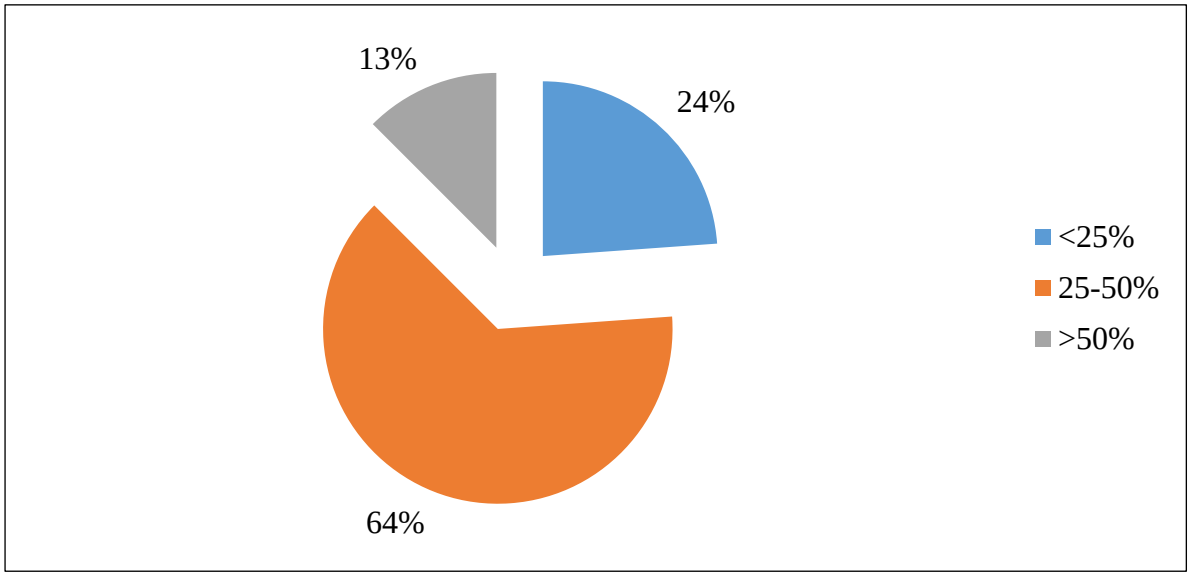
As per 86% of doctors, ferrous ascorbate is the preferred oral iron supplementation.

8) In what percentage of your T2DM patients have you observed vitamin B12 deficiency?

a. <25%

b. 25-50%

c. >50%



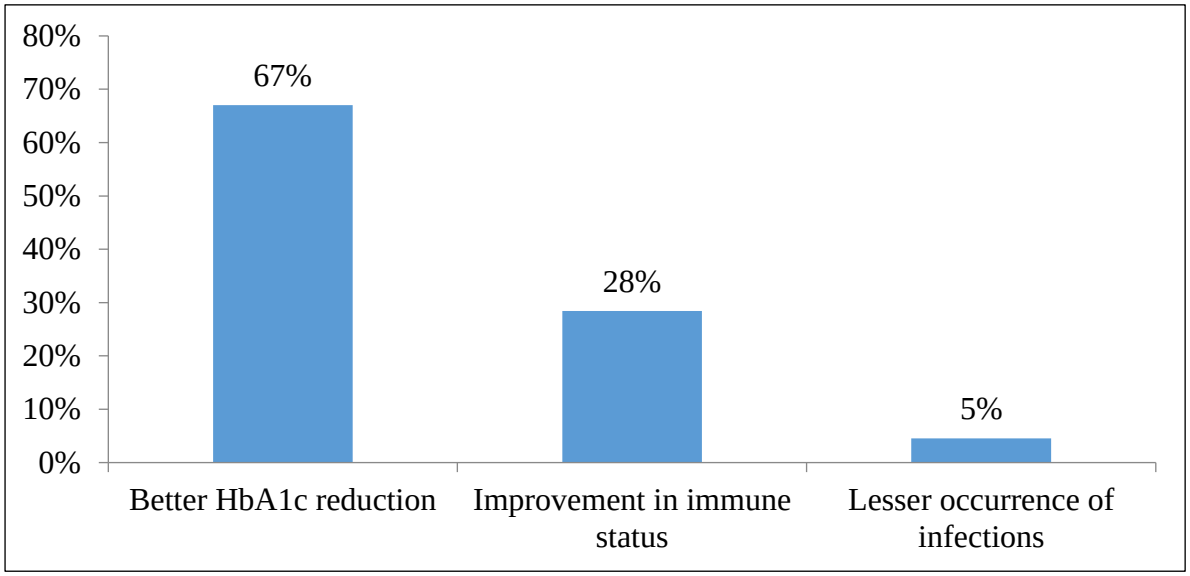
As per 64% of doctors, they have observed vitamin B12 deficiency in 25-50% of their T2DM patients.

9) What could be the advantage that you perceive by correcting ID in T2DM patients?

a. Better HbA1c reduction

b. Improvement in immune status

c. Lesser occurrence of infections



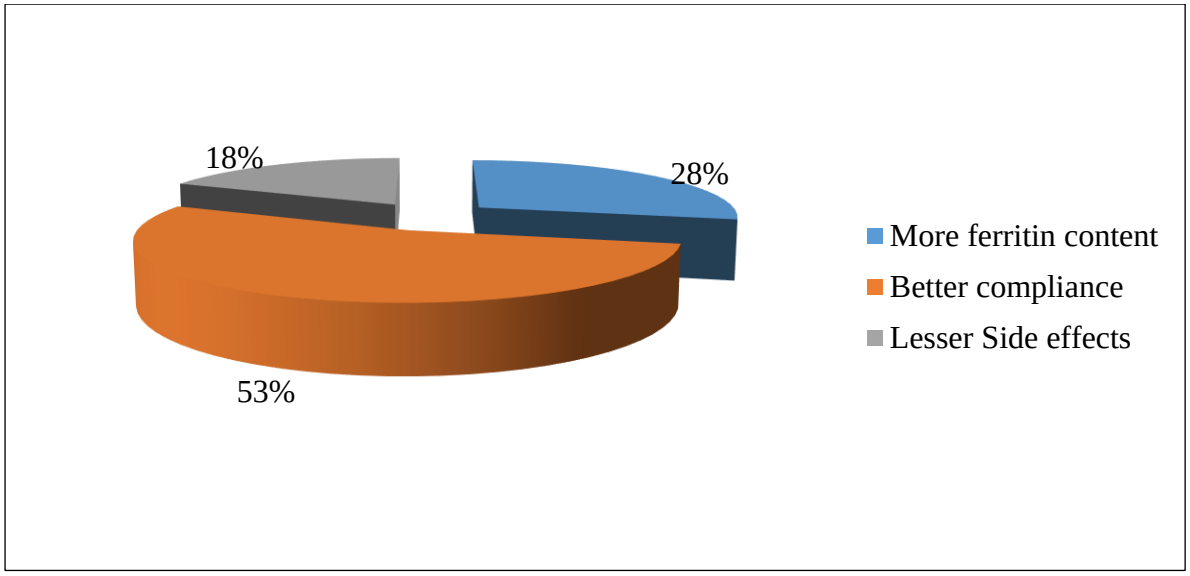
According to 67% of doctors, the advantage perceived by correcting ID in T2DM patients is better HbA1c reduction.

10) In your opinion, what are the benefits of Ferrous Ascorbate over other oral iron supplements?

a. More ferritin content

b. Better compliance

c. Lesser Side effects



As per 53% of doctors, better compliance is the benefit of Ferrous Ascorbate over other oral iron supplements.

Summary

- According to 92% of doctors, they do measure the iron levels of a patient with T2DM.
- As per 63% of doctors, they routinely perform hemoglobin to assess ID.
- According to 41% of doctors, 20-30% of patients with T2DM have iron deficiency.
- According to 99% of doctors, correcting iron deficiency in a T2DM patient result in better outcomes for patients with T2DM.
- As per 67% of doctors, they consider initiating therapy for iron deficiency in T2DM patients in men at Hb level of 8–10.9 g/dl.
- According to 62% of doctors, they consider initiating therapy for iron deficiency in T2DM patients in women at Hb level of 8–10.9 g/dl.
- As per 86% of doctors, ferrous ascorbate is the preferred oral iron supplementation.
- As per 64% of doctors, they have observed vitamin B12 deficiency in 25-50% of their T2DM patients.
- According to 67% of doctors, the advantage perceived by correcting ID in T2DM patients is better HbA1c reduction.
- As per 53% of doctors, better compliance is the benefit of Ferrous Ascorbate over other oral iron supplements.

Consultant Opinion

Market Opportunities:

There is an opportunity for the development of convenient and accessible tools for measuring iron levels in T2DM patients, considering that 92% of doctors measure iron levels in these patients. Such tools can facilitate early detection and management of iron deficiency.

Value for Healthcare Professionals:

Pharmaceutical companies can collaborate with healthcare professionals to develop standardized diagnostic protocols for routinely assessing iron levels and hemoglobin to evaluate iron deficiency in T2DM patients, as recommended by 63% of doctors.

Adverse Effect Management:

Given that 86% of doctors prefer ferrous ascorbate as the oral iron supplementation, pharmaceutical companies can focus on optimizing the formulation and delivery of ferrous ascorbate to enhance its effectiveness and tolerability, ultimately improving patient compliance and outcomes.

Market Positioning:

Pharma companies can launch educational initiatives targeting healthcare professionals to raise awareness about the prevalence of iron deficiency in T2DM patients (reported by 41% of doctors) and the benefits of correcting it, which can help position their iron supplementation products as essential components of T2DM management.

Personalized Treatment Decisions:

Collaborating with healthcare professionals, pharma companies can develop gender-specific guidelines for initiating iron deficiency therapy in T2DM patients based on hemoglobin levels, as suggested by 67% of doctors.

Improving Patient Outcomes:

Pharma companies can highlight the advantages of ferrous ascorbate, such as better compliance (as reported by 53% of doctors), in their marketing strategies to encourage its use and improve patient adherence to iron supplementation regimens, thereby enhancing outcomes in T2DM patients.

NOTES

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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