Iron deficiency anemia and glucose metabolism

Ashraf T. Soliman[1], Vincenzo De Sanctis[2], Mohamed Yassin[3], Nada Soliman[4]

[1] Department of Pediatrics, Alexandria University Children Hospital, Elchatby, Alexandria, Egypt; [2] Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; [3] Department of Hematology, Hamad Medical Center, Doha, Qatar; [4] Primary Health Care, Ministry of Health, Alexandria, Egypt

Summary. Iron deficiency anemia (IDA) is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It occurs at all stages of the life cycle, but is more prevalent in pregnant women and young children. IDA appears to be more common in diabetic patients compared to non-diabetic population. Iron deficiency (ID) and IDA can impair glucose homeostasis in animals and human and may negatively affect glycemic control and predispose to more complications in diabetic patients. On the other hand diabetes and its complications are associated with anemia and its correction improves diabetes control and may prevent or delay the occurrence of complications. Physicians treating this form of anemia should be aware of its negative effect on glycemic control in normal and diabetic patients (both type 1 and type 2). They should prevent ID and treat early all those with IDA. This brief review aims to enlighten the different effects of IDA on glucose metabolism in normal and diabetic patients. (www.actabiomedica.it)

Key words: iron, iron deficiency anemia (IDA), glycated hemoglobin (HbA1c) , insulin, glycemic control, diabetes type 1 and type 2

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) (1-3). 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 (1-3).

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.

The present review focuses on the current knowledge on the different effects of IDA on glucose metabolism in normal and diabetic patients.

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 (4-7).

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 (4-9).

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 (9-12).

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 (10, 11-15).

On the other hand, Márquez-Ibarra A et al. (16) 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 (16).

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 (16, 17-22).

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 (23-28).

OhiraY et al. (29) 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

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

carboxykinase 1 (Pck1) 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 (30-31).

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 (HbA1c), leading to false-high values of HbA1c in non-diabetic individuals. HbA1c is the most predominant fraction of HbA1, 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. HbA1c is widely used as a screening test for diabetes mellitus, and American Diabetes Association has recently endorsed HbA1c ≥6.5% as a diagnostic criterion for diabetes mellitus (32-36). Some studies investigated the relation between ID and IDA and changes in blood glucose concentration, HbA1c level and insulin secretion.

1. Non-diabetic patients with ID

Ozdemir A et al. (37) 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. (35) 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. (34) measured HbA1c values in 35 non-diabetic 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.(38) showed normal HbA1c concentrations in iron deficiency, which dropped to subnormal levels after iron supplementation.

Coban E et al. (39) 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. (40) 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. (2) 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. (3) 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. (41) 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 and glycemic control in patients with Type 2 DM

Christy et al.(1) 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 (42-45).

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 (45-48). 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 NIDDM at increased risk for progressive renal disease (44).

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 (44-48).

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).(48,49)

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. (50-54)

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

Tarim et al. (55) 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 ± 2.7% to a mean of 8.2 ± 3.1% (P<0.05). Additionally, HbA1c in ID non-diabetic patients decreased from a mean of 7.6 ± 2.6% to 6.2 ± 1.4% after iron therapy (P<0.05).

In support with this finding, El-Agouza et al.(56) studied 47 students with IDA (Hb <12 g/dl). After treatment with oral iron for 20 weeks their HbA1c significantly decreased from 6.2 ± 0.6% to 5.3 ± 0.5 % .

In conclusion

These studies thus suggest that among non-diabetic and diabetic individuals IDA is associated with higher concentrations of HbA1c.

Iron replacement therapy decreases HbA1c in both diabetic and non-diabetic individuals. This implies that the iron states must be considered during the interpretation of HbA1c concentrations in diabetic or non-diabetic patients. Early diagnosis and treatment of ID in diabetic patients can improve their glycemic control and may prevent or delay complications.

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