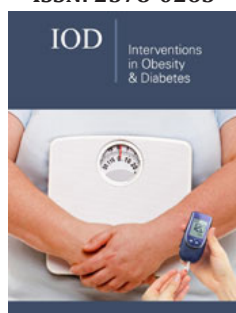


# Iron Deficiency Anemia and Diabetes Mellitus

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## Abstract

Iron deficiency is one of the most common micronutrient deficiencies in the world. Although there are studies showing that iron deficiency treatment has positive effects on diabetes biomarkers in diabetic individuals, there are also studies showing that its effect has not yet been proven. Designing new studies on this subject may provide a better observation of its positive effects.

**Keywords:** Iron deficiency; Metabolism; Cardiovascular complications; Glucose

**Abbreviations:** ID: Iron Deficiency; IDA: Iron Deficiency Anemia; HbA1c: Hemoglobin A1c; T2DM: Type 2 Diabetes Mellitus

## Iron Deficiency

Iron is necessary for various metabolic processes, including oxygen transport and storage, redox reactions, cell signaling and microbial defense. Absorption, transport and storage of iron are carefully regulated, presumably to avert potential toxic effects of free iron [1,2]. Both iron overload and iron deficiency can be detrimental to health, so iron homeostasis is essential. Although many factors that take part in iron homeostasis are known, mechanisms by which the body regulates iron stores are still being elucidated [1-3]. Also, iron absorption and homeostasis are intimately linked to the inflammatory response [4]. Iron deficiency (ID) and iron deficiency anemia (IDA) are prevalent forms of nutritional deficiency. Globally, 50% of anemia is attributed to iron deficiency [5,6]. Since the body has no means of actively excreting excess iron, a sophisticated system for iron homeostasis maintains the optimal balance between adequate dietary iron absorption and iron loss in healthy individuals. Dietary iron is absorbed in a regulated manner from the gastrointestinal tract and transported between cells bound to the protein transferrin. Systemic iron homeostasis is primarily regulated by the liver-derived peptide hormone hepcidin and by the iron exporter protein ferroportin, while intracellular iron homeostasis is regulated by the iron-regulatory protein/iron-responsive element system. The two regulatory systems are finely coordinated [7]. This finely balanced homeostasis, however, can be readily disturbed. Iron deficiency can ensue if dietary iron intake is insufficient or if iron absorption, loss, metabolism, or body distribution become abnormal due to disease or excess blood loss. A group of international experts recently proposed the following comprehensive definition of iron deficiency: “a health-related condition in which iron availability is insufficient to meet the body’s needs and which can be present with or without anemia” [8].

## Diabetes Mellitus

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia, requiring continuous medical care, resulting from insulin deficiency or insulin-effect defects. Genetic, environmental factors and lifestyle changes occur mainly as a result of multifactorial reasons [9]. Type 2 Diabetes Mellitus (T2DM) is the most common type of diabetes, the prevalence of which increases more rapidly than expected and affects millions of people worldwide [10]. Since the early stages of the disease are usually asymptomatic, it causes late diagnosis. In this asymptomatic process, major cardiovascular complications may occur which adversely affect the quality of life and life expectancy of the patients. The risk of these complications increases significantly in individuals with late diagnosis of T2DM [11]. Hemoglobin A1c (HbA1c) level is recommended in the diagnosis and treatment of diabetes and HbA1c > 6.5% is considered sufficient for the diagnosis of DM [12,13]. HbA1c is formed by the nonenzymatic ketoamine reaction between glucose and valine at the N-terminal end of both beta chains of the hemoglobin molecule. When plasma glucose levels increase, non-

enzymatic glycation of hemoglobin increases. HbA1c measurement is the standard method for evaluating long-term glycemic control and shows the blood glucose level in the last 2-3 months [14]. HbA1c levels are affected not only by blood glucose levels but also by the presence of variant hemoglobin affecting erythrocyte survival, hemolytic anemia, uremia, pregnancy and acute and chronic blood loss [15-24].

### IDA and DM

The clinical relevance of the effect of iron deficiency on glucose metabolism is still not clear. Reduced iron stores have been linked to increased glycation of HbA1c. The links between glucose, anemia and HbA1c are complex and not yet fully elucidated. Diabetes may cause to anemia through reducing absorption of iron, gastrointestinal bleeding and through diabetic complications that cause anemia [5,6,25]. In chronic iron deficiency anemia, erythrocyte survival is prolonged, there is a chronic hypoxia and hemoglobin (Hb) cannot be synthesized sufficiently due to iron deficiency. Therefore, nonenzymatic glycosylation is affected and HbA1c percentages increase [26]. Another mechanism responsible for increased HbA1c in iron deficiency anemia is; that iron deficiency disrupts the quaternary structure of Hb, and that this structure causes the glucose to bind more easily to the  $\beta$  globulin chain [27]. Since the serum glucose level is constant in normoglycemic cases, the amount of HbA1c increases and the HbA1c level is detected because Hb amount decreases [28]. The decrease in HbA1c level after iron treatment given to patients with anemia; It is explained by the increase of erythrocyte production in the circulation as a result of iron treatment increases the erythropoiesis in the bone marrow. Because mature erythrocytes have higher HbA1c levels than young erythrocytes. Increased young erythrocytes and mature erythrocytes are diluted and a decrease in HbA1c level is detected [26]. In the first studies investigating the relationship between IDA and HbA1c levels, it was suggested that HbA1c levels were affected in iron deficiency due to the changes in both the structure of Hb and the ratio of old and young erythrocytes [27,29,30]. Later studies reported no difference in HbA1c levels between IDA and control groups [31,32]. In addition, investigations performed on diabetic chronic kidney disease patients, and diabetic pregnant women showed increased HbA1c levels in iron deficiency anemia [33,34]. 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 comorbidities. 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 [35-38]. It has been reported in different studies that HbA1c levels decrease significantly with treatment of iron deficiency in patients with or without type 1 diabetes [27,28].

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 [34-37]. IDA is also associated with oxidative stress and functionally deficient high-density lipoproteins (HDL) particles [38].

### Conclusion

Iron deficiency anemia and DM are common public health problems. It should be remembered that iron deficiency is an important point to be considered in the diagnosis and treatment of diabetes. In addition, studies on the treatment of iron deficiency have a curative effect on complications such as cardiovascular diseases and kidney diseases that frequently accompany diabetes. When planning new studies, more accurate results can be obtained with holistic approach in treatment plans.

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