# Interventions That Decrease Anemia Development in Diabetic Patients

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**Abstract.** In our research, we try to explore the relationship between diabetes mellitus and iron deficiency anemia. Anemia can lead to a false elevation in HbA1c in non-diabetic people. In addition, patients with diabetes who had anemia have an unfavorable effect on the quality of life and affect disease progression which increases the risk of micro and macrovascular complications. We searched in PubMed electronic database and included articles only that were published as a full free-text in the last six years and we excluded the articles that were written in languages other than English. We reviewed the articles and found there is a relation between D.M in developing IDA, Studies showed that controlling blood glucose with insulin shows more benefits than oral antidiabetics in reducing the possibility to develop and progress micro and macrovascular complications especially IDA by decreasing the rate of developing chronic kidney diseases. Also, RAS inhibitors (ACE inhibitors and ARBs) reduce the prevention and reduce the progression of renal complications development in diabetic patients.

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## 1. Introduction & Background

Diabetes mellitus (D.M) is a developing global health concern with the highest prevalence expected to occur in the Middle East and North Africa because of many factors involving rapid economic development, living in urban areas, and lifestyle changes. In 2000, Diabetes affected 171 million individuals worldwide; this number is increased to more than 366 million in 2011 and expected to exceed 552 million by 2030 (Atlas, 2015).

Anemia definition established by WHO according to hemoglobin level. In 2010, statistics from WHO show that one-third of the global population had anemia, and Iron deficiency anemia (IDA) was the case in about one-half of these people. Iron deficiency can be attributed to increasing iron demands, decrease iron absorption, or increased blood losses (Murphy, 2002).

Diabetes mellitus can happen due to impaired insulin secretion or impaired insulin effect or both. There are many types of D.M: type 1, type 2, Gestational, Latent Autoimmune Diabetes in Adult (LADA), Maturity Onset Diabetes of the Young (MODY) (Petersmann et al., 2019).

Anemia means Hemoglobin (Hb) level below the lower limit of the normal range and iron deficiency represents the most common micronutrient deficiency worldwide (Goddard et al., 2011).

Some studies showed that there is a relationship between iron store reduction and increased level of glycated hemoglobin HbA1C, this leads to a false elevation in HbA1c in non-diabetics. Glycated hemoglobin is formed by the glycation of terminal valine at the β-chain of hemoglobin and it reflects glycemic control last three months, so it's used as a screening test for diabetes. American Diabetes Association recently take the HbA1c level of greater than 6.5% as diagnostic criteria for diabetes mellitus (Brooks et al., 1980). In the state of anemia, the erythrocyte has a short life span which leads to reduced hemoglobin concentration and the result of this reduction will lead to compensatory hyperplasia of the erythrocyte (Gallagher et al., 2009).

Diabetic patients who had anemia have an unfavorable effect on life quality and effect on the progression of the disease and may lead to the appearance of co-morbidities The risk of renal disease increase with a decrease in the level of hemoglobin. Anemia is closely associated with macro and microvascular complications in a patient with diabetes mellitus (Ueda et al., 2003). Renin-Angiotensin system inhibitors, iron supplements, and erythropoietin have a role in preventing and decreasing the development of complications in diabetic patients.

In this project, we collected our data from the PubMed database. We searched the databases by using keywords: diabetes mellitus, iron deficiency anemia, glycated hemoglobin, chronic renal diseases, and inflammatory process. We reviewed free full-text studies,

and used the studies published in the last five years, we followed ethical and legal protocols while collecting our data.

## 2. Discussion

### *2.1. Glycated Hemoglobin and Iron Deficiency Anemia*

HbA1c is a subtype of hemoglobin A (HbA) identified by electrophoresis and its result from glycosylation of hemoglobin β-chain N-terminal proline (Kim et al., 2010). HbA1c is an important test to reflect the average blood glucose level in the previous three months and many factors affect the level of HbA1c, one of these factors is anemia (Eberentz-Lhomme et al., 1984). The mechanism of this effect is not clear till now, but IDA prolongs the lifespan of red blood cells (RBCs) and cause falsely elevated level of HbA1c; so because of prolongation of lifespan of (RBCs), the red cell turnover is low which result in disproportionate number of older red blood cells and lead to elevation HbA1c. While in hemolytic anemia, there is a rapid red cells turnover that leads to falsely reduced HbA1c level. Iron defeciency is not affecting Hb level only, it also may affect multiple enzymes activity, which include lipid peroxidation. Lipid peroxidation is the oxidative degradation of lipids occur by increase peroxidation of polyunsaturated fatty acids, this process create unstable lipid radicles that interact with oxygen to form free radicles that cause cell membrane damage (oxidative stress). Iron supplement used for treatment IDA and also observed to have an effect on the level of the oxidative stress, and HbA1c reduction (Sinha et al., 2012; Del Rio et al. 2005). Iron defeciency associated with elevation of HbA1c independently regardless the plasma level of glucose and severity of anemia. Several studies showed that non-diabetic persons with IDA had elevation in HbA1c level in compare with non-diabetic non-anemic person (Brooks et al., 1980; Madhu et al., 2017; Selvaraj et al., 2006; Zaka-Ur-Rab et al., 2016; Del Rio et al. 2005; Coban et al., 2004).

### *2.2. Iron Deficiency Anemia as a Result of Diabetes Mellitus Complications*

Patients with diabetes who have uncontrolled blood glucose will suffer from developing micro and macrovascular complications and it is the major cause of chronic kidney diseases (CKD). The inflammatory process had a role in developing CKD by increasing pro-inflammatory cytokines that affected insulin resistance and that lead to the macro-and microvascular complications. Anemia is considered to be one of the causes that increase Interleukin-6 that reduces the sensitivity of progenitor of erythropoietin in kidneys that lead to apoptosis of immature erythrocyte. Diabetic Nephropathy will decrease the production of erythropoietin which leads to anemia development. So in an inflammatory state due to renal disease activate pro-inflammatory cytokines is considered the main factor in the reduction of hemoglobin levels in diabetic patients (Angelousi & Larger, 2015; Fava et al., 2001; Jha at al., 2013; Escorcio et al., 2010; Weiss & Goodnough, 2005). Another cause of iron deficiency in patients with diabetes is malnutrition and malabsorption. And it is important to ensure patients' intake of healthy food and encourage exercise. Ferritin is a special intracellular protein that store iron and release it in a control way, and contribute to insulin resistance mostly in patients with type 2 D.M. Inflammation cause alteration of systemic iron metabolism and this increase the susceptibility of iron deposition in β cells of pancreas lead to insulin deficiency and alter metabolic state, so will decrease in plasma iron level due to decrease intestinal absorption and increase intracellular sequestration of iron lead to iron deficiency (Milto et al., 2016; Fernández-Real et al., 2002; Hosseini et al., 2014; Thomas et al., 2005; Cherayil, 2015; Wang et al., 2013). Patients with diabetes and kidney disease had higher risk to develop anemia. Some researches show the potential role of iron in the pathogenesis of type 2 D.M, obesity, and metabolic syndrome by generating reactive oxygen species and increasing the oxidative stress. One American study showed that obese patients with diabetes had significant elevation of ferritin level than those obese without diabetes (Jehn et al., 2004; Dinneen, 1994; Gillum, 2001).

### *2.3. Management of Diabetes Mellitus and Iron Deficiency Anemia*

Generally, treatment for diabetes is determined based on the type, patient compliance, patient health status, and cost. Two treatment options are commonly used, insulin or oral antidiabetic agents (Girardot, 2020). Patients with type 2 diabetes mellitus who were treated with insulin had an elevation in the level of transferrin receptors (sTfR); which is a membrane glycoprotein that had a role in cellular uptake of iron from plasma glycoprotein transferrin, so insulin promotes erythropoiesis and iron uptake by the fat cell. Because of the insulin effect, the sTfR will be rearranged from the internal membrane to the cell surface. About 84.7% of patients on insulin had an increase in the expression of sTfR for adequate use of iron in circulation for erythropoiesis (Fernández-Real et al., 2007; Hernández et al., 2005; Clairmont & Czech, 1990; Kurtz et al., 2003; Miyagawa et al., 2000; Davis et al., 2006; Ponka & Lok, 1999 ). sTfR levels have a relation to insulin resistance, especially in patients on hemodialysis. However conflicting results exist regarding the association between sTfR and type 2 D.M (Manolov et al., 2017; Van der Weerd et al., 2012; Fernández-Real et al., 2015; Suárez-Ortegón et al., 2016; Orban et al., 2014). Patients with diabetes develop an inflammatory process that leads to the release of cytokines that will increase the number of transferrin receptors (TfRs) on the cell surface, in the same time the release of inflammatory cytokines also lead to an increase in hepatic production of Hepcidine. that lead to endocytosis and proteolysis of ferroportin and will be

trapping the iron in absorbing enterocyte and this process will be lead to iron deficiency anemia (Milto et al., 2016; Fernández-Real et al., 2002; Hosseini et al., 2014) (Figure 1). So diabetic patients on insulin treatment had higher levels of TfR than diabetic patients on oral antidiabetic agents this led to reducing the probability to developed iron deficiency anemia. The prevalence of anemia in diabetic patients is about 10% to 30%, one-third of them due to iron deficiency (Cherayil, 2015).

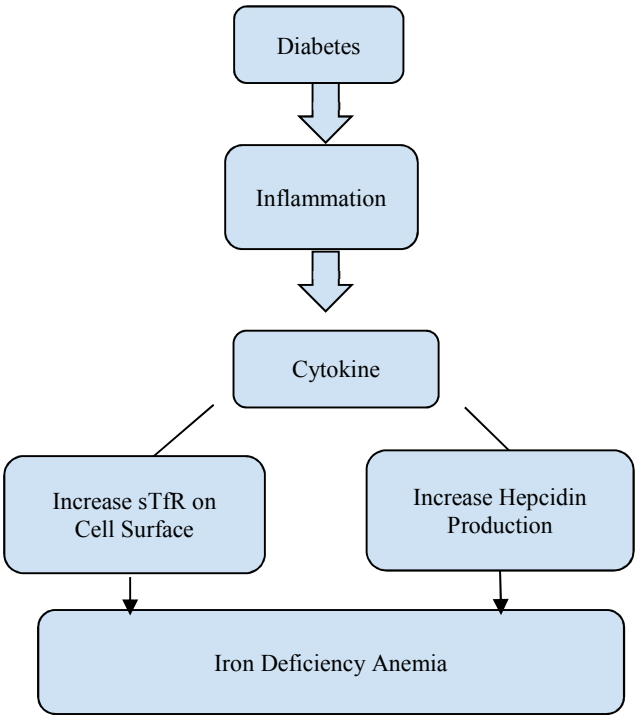


**Figure 1.** Summarize the Pathophysiology of Iron Deficiency in Diabetic Patients.

*2.4. Prophylaxis of Iron Deficiency Anemia in the Diabetic Patients*

Diabetes is the most common leading cause of chronic kidney disease (CKD) worldwide and CKD is the most common cause of anemia in uncontrolled diabetic patients. The mechanism of diabetic kidney disease (DKD) is not clear yet but in general, it is developed by glomerular damage. As a result of CKD, patients will suffer from cardiovascular diseases also, So, there are associations between DKD and mortality, morbidity, and cost. therefore, the prevention and early treatment had good clinical care results and public health outcomes. The use of RAS inhibitors including Angiotensin-Converting Enzyme inhibitors (ACEI) and Angiotensin Receptors Blockers (ARBs) agents had a good benefit to decrease the progression of DKD and decrease Coronary Artery Diseases (CAD) and End-Stage Renal Diseases (ESRD), thus reducing the possibility to develop IDA (Haller et al., 2011; de Boer et al., 2011; Foundation, 2012). RAS inhibitors are recommended for diabetic patients to reduce the progression of CKD by adding a mineralocorticoid receptors antagonist (MRA ) to reduce protein urea (Bisson et al., 2013). Diabetic patients who suffer from albuminuria that means start the early stage of renal impairment, to protect those patients from developing CKD and its complications and one of them is anemia. Based on the above, we prefer to use ACE inhibitors and ARBs agents to reduce the risk to develop CKD by improving the hemodynamics of the kidneys, reducing the doubling of serum creatinine that occur in ESRD. Patients with diabetes and albuminuria preferred use ARBs rather than ACE inhibitors (Wang et al., 2018; Reidy, 2014). Iron supplements are used to prevent and treat IDA. Many ways are used for iron status improvement including (dietary improvement, fortification of food with iron, iron supplements, and other health measures such as helminth control) the most effective measure used is iron supplements, the prophylactic dose of elemental iron used in adults is 60 mg and the preferred rout is oral rout rather than iv to avoid infection (Stoltzfus & Dreyfuss, 1998). Patients who had CKD or were on hemodialysis had iron deficiency and were unable to stimulate the kidneys to produce erythropoietin, which leads to more exaggeration for anemia, In those patients, erythropoietin derivative agents can be used as prophylaxis against IDA in patients with diabetes mellitus. On the other hand, some patients with type 1 D.M may suffer from other autoimmune malabsorption diseases such as (Whipple disease, Small intestinal bacterial overgrowth (SIBO), Celiac disease, and Pernicious anemia) they also may suffer from iron deficiency (Zimmermann, & Hurrell, 2007). so we prefer to use prophylactic agents to protect patients from micro and macrovascular complications.

## 3. Conclusions

Diabetes mellitus and iron deficiency anemia are common problems worldwide. In our research, we tried to highlight the relation between D.M and IDA. depending on the pathophysiology, IDA can elevate glycated hemoglobin levels. Also, uncontrolled Diabetes and its complications can lead to anemia, especially IDA. Patients on insulin have more control of blood glucose and have a low risk to develop CKD and then a lower risk of IDA. Then we searched for the ways to prevent developing IDA in diabetic patients by using medications including Renin-

Angiotensin system inhibitors (RAS inhibitors), iron supplementation, and erythropoietin derivative agents. In this research, we hope reached the point to prevent and decrease the progression of diabetes mellitus complications and improve the public health for diabetic patients, and in the same time, this research aims to encourage future researchers to improve the current intervention and invent new interventions to decrease the rate of mortality and morbidity from diabetes.

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