

Review article

Effect of Iron Deficiency Anemia and Other Clinical Conditions on Hemoglobin A1c Levels

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Abstract

Iron deficiency anemia is the most common type of anemia in the world, the most common form of malnutrition deficit with a prevalence of 50% affecting the developed countries as well as developing countries with a strong influence on social and economic development. According to current guidelines of the American Diabetes Association (2019.) glycated hemoglobin (HbA1c) is a reflection of the patient's glycemic status in the last three months and is used for monitoring of therapeutic effect as well as for diagnostic purposes. Previous studies have proven that not only iron deficiency anemia but also a range of other clinical conditions can affect the level of HbA1c independent of glycemic status. The exact mechanism of the effect of iron deficiency on glycated hemoglobin levels remains unknown and is still at the hypothesis level. Studies have proven that treatment of iron deficiency anemia leads to better control of HbA1c level, regardless of whether the patient is diabetic or not. A small number of studies have noted a correlation between iron deficiency and levels of glycated hemoglobin, thus further research on larger number of patients is certainly necessary in order to improve the therapeutic possibilities for patients with diabetes, more accurately diagnose and understand the pathophysiology of formation and influence on glycated hemoglobin levels.

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Introduction

Iron deficiency anemia in today's modern world is the most common form of malnutrition and the most common form of anemia. Globally, iron deficiency is the cause of 50% of all anemias (1). Hemoglobin A1c (HbA1c) is a glycosylated hemoglobin, which is used to monitor average value of glycemic index of the patient in the last 3 months (2). HbA1c is produced by glycation of the terminal amino acid valine at the β chain of hemoglobin and, unlike other markers for monitoring glycemic status, is less susceptible to daily fluctuations depending on diet, physical activity or disease (3). According to the latest guidelines of the American Diabetes Association (2019), the level of HbA1c $\geq 6.5\%$ is the criteria for the diagnosis of diabetes (3). Various other factors can also affect glycosylated hemoglobin levels such as hemolytic anemia (4), hemoglobinopathies (5), acute blood loss (6), pregnancy (7) and uremia in chronic renal failure (8). What can be concluded is that the level of hemoglobin A1c is not only related to diabetes and glycemic index, but that different factors can affect the level of the same (Table 1).

Table 1. Diseases and clinical conditions affecting hemoglobin A1c level

| HbA1c $\geq 6.5\%$ |
|------------------------|
| Diabetes Mellitus |
| Chronic renal failure |
| Uremia |
| Iron deficiency anemia |
| Hemoglobinopathies |
| Hemolytic anemia |
| Acute blood loss |
| Pregnancy |

Note: Summarized findings from studies to date on the most common diseases and clinical conditions that affect the value of HbA1c levels.

Therefore, it is of the utmost importance to identify comorbidities that may affect the level of glycosylated hemoglobin before its level is taken into account for diagnostic and therapeutic purposes. New studies have provided data on alternative glycemic markers that are not as

susceptible to these comorbidities and that can be used to monitor glycemic status in particular patient populations, but their application has not yet become widely used.

From past to present

Previous studies which examined the correlation of sideropenic anemia and HbA1c levels (depending or independent of the patient's glycemic status) have shown conflicting results. Books and colleagues examined HbA1c values in 35 patients with iron deficiency anemia without proven diabetes, and found significantly elevated levels of HbA1c in patients with iron deficiency anemia and normalization of values after iron substitution therapy (9). Similar results were obtained in the studies of Sluiter et al. (10) and Mitchell et al. (11) who attempted to explain the correlation of HbA1c and sideropenic anemia by alternation of hemoglobin structure and HbA1c levels in old and newly synthesized erythrocytes. According to the conclusion of Sluiter et al., hemoglobin glycation is an irreversible process that is present in accordance with the erythrocyte lifetime.

A prospective study from 2010, on a small sample of patients with proven diabetes mellitus and chronic renal failure (stage IIIB-IV), examined the effect of intravenous iron supplementation and erythropoietin stimulating agents (ESA) on HbA1c values. Both therapeutic choices led to a statistically significant decrease in HbA1c (12). Similar results were obtained in patients with diabetes without developed renal insufficiency (13-16).

CLEVER was the first study to test the hypothesis that intravenous administration of iron carboxymaltosis leads to a reduction in HbA1c levels in patients with type 2 diabetes and sideropenic anemia, thereby improving metabolic status and quality of life. Organized as a randomized, single-blind study, it was conducted on subjects divided into two groups; study group (treated with iron carboxymaltosis) and control group (treated with placebo). The

findings show that iron deficiency is associated with an increased risk of developing insulin resistance and obesity, and iron excess with the development of diabetes (the effect of pancreatic beta-cell stimulation on enhanced insulin secretion) (17).

A 2016. cross-sectional study conducted on 150 patients (75 patients with iron deficiency anemia and 75 patients without anemia) examined HbA1c values relative to the degree of sideropenic anemia. Anemia severity was defined as mild anemia (Hb 120-129 g/L for men and 110-119 g/L for women), moderate anemia (Hb 90-119 g/L for men and 80-109 g/L for women) and severe anemia (Hb <90 g/L for men and <80 g/L for women). An elevated HbA1c was found in the patient with anemia in proportion to the degree of iron deficiency. Upon completion of the study, an increased HbA1c value was observed in a group of patients with iron deficiency anemia that correlated with the severity of the anemia (18). Similar results have been reported in other studies (19-20).

Increased glucose during pregnancy is now a well-known risk factor for the development of perinatal complications of mother and child, so strict control of the glycemic index during pregnancy is of particular importance. Pregnant women with known gestational diabetes have a significantly higher risk of developing type 2 diabetes at the end of pregnancy than pregnant women with normal glucose levels during pregnancy (21). Studies have shown that hemoglobin A1c during pregnancy (the gold standard of glycemic control) is not a true reflection of the glycemic status due to frequent iron deficiency anemia (22-23). Studies also noted that glycated albumin (GA) values were well maintained throughout pregnancy, suggesting that elevated glycated hemoglobin during gestation could be independent of glycemic index and that glycated serum albumin presents more accurate factor for glycemic control in pregnancy.

Furthermore, some studies found no correlation between Hba1c values in patients with iron deficiency anemia and control group (24-25),

other studies have reported lower values of HbA1c in diabetic patients with sideropenic anemia compared to diabetics without anemia (26), while other studies found elevated HbA1c values upon completion of substitution therapy in patients with iron deficiency anemia (unknown variables) (27).

Disclosure

In conclusion, HbA1c is widely used today as a diagnostic tool for diabetes and a means of controlling the patient's glycemic status. Different clinical conditions and diseases may affect the erythropoiesis process with an impact on HbA1c levels. Numerous clinical studies, mostly based on a small number of patients, have confirmed that in the presence of iron deficiency anemia, HbA1c levels are elevated even in non-diabetic patients with normal glycemic status (Table 2).

Table 2. Results of studies examining the association between hemoglobin A1c and sideropenic anemia

| Author and year of the study | No. of subjects | Iron deficiency anemia | Diabetes mellitus | Serum iron ($\mu\text{mol/L}$) / Ferritin (ng/ml) | Hemoglobin (g/l) | HbA1c % (examined group) | HbA1c % (control group) |
|-------------------------------|-----------------|------------------------|-------------------|---|-----------------------------|--------------------------|-------------------------|
| Shanti et al. 2013. | 50 | yes | no | no data / 3.68 | 106 \pm 1.4 | 7.6 \pm 0.5 | 5.5 \pm 0.8 |
| Alap L. Christy et al. 2014.* | 120 | yes | yes | no data / 11.41 | 95.4 (male) / 93.7 (female) | 6.87 \pm 1.4 | 5.65 \pm 0.69 |
| Bhardway et al. 2016. | 50 | yes | no | 2.7 / 7.51 | 61.8 | 6.60 \pm 0.1 | 5.48 \pm 0.56 |
| Rajagopal et al. 2016. | 75 | yes | no | 2.12 / 120.9 | 114.6 | 6.84 \pm 0.07 | 5.12 \pm 0.04 |
| Sinha et al. 2011. | 50 | yes | no | no data / 7.0 | 62 | 4.6 \pm 0.6 | 5.5 \pm 0.6 |
| Solomon et al. 2019.* | 174 | yes | yes | no data / no data | 99.7 | 6.18 \pm 1.57 | 7.74 \pm 1.81 |

* control group; diabetic patients without iron deficiency anemia
All numeric data expressed as mean values

The expected elevated values of glycated hemoglobin in patients with diabetes are well correlated with diabetes control, therefore, in patients with controlled blood glucose levels, HbA1c is expected to be less than 6.5% (3). The initial belief that the level of glycated hemoglobin is proportional exclusively to glycemic status, has been rejected. The mechanism by which iron deficiency anemia affects the level of HbA1c remains unknown, largely based on hypotheses. From the foregoing, it is suggested that the iron status of the patient be taken into account before interpretation of the HbA1c value, with or without proven diabetes. Early diagnosis and treatment of iron deficiency anemia in patients with diabetes may improve glycemic control and delay the onset of complications (28). As there is not enough studies on a large sample from this still-unexplained pathophysiological mechanism, further research is needed in the future to elucidate the correlation of hemoglobin glycation and iron deficiency.

Precisely because the limitations of hemoglobin A1c are known today, there is great interest in the use of alternative glycemic markers. Among the alternative markers that can be used as a complement to hemoglobin A1c is glycated albumin. As the level of glycated hemoglobin is dependent on red blood cell turnover, albumins have a shorter half-life, therefore indicating a glycemic index of the last 2-3 weeks. Postprandial glucose values are also better in states with marked disease progression, such as in type 1 fulminant diabetes mellitus. Restrictions on the use of GA are pathological conditions related to blood albumin levels such as nephrotic syndrome, liver disease, obesity, glucocorticoid administration, Cushing's syndrome and hyperthyroidism. Regardless of the known, routine administration of glycated hemoglobin has not yet taken root in clinical practice, which will require long-term prospective studies (29-31).

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