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Influence of Iron Deficiency Anemia on HbA1c: A Review



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Abstract

Hemoglobin A1c (HbA1c) is widely used as a diagnostic tool for diabetes. Many clinical conditions affect erythrocyte turnover which influence HbA1c levels. These levels are lowered by different forms of anemia, but reverse is the case in iron deficiency anemia (IDA). This is suggested by various studies which propose an increase in HbA1c levels in patients with IDA. However, there are studies which negate any influence of IDA over HbA1c levels. In both cases the clinical data is not sufficient to confirm or nullify the role of IDA in increasing HbA1c levels.

Introduction

Hemoglobin A1c (HbA1c), a glycosylated hemoglobin is formed by an irreversible, slow non-enzymatic catalysis of the β chain of globin in mature hemoglobin (Hb) [1,2]. It is used as a gold standard for monitoring glycemic status for the previous three months (the life span of a red blood cell) in patients with diabetes [3]. HbA1c provides an integrated measure of glycemia which is less susceptible to short-term modulation than blood glucose levels. Also, it helps to keep a track of diabetic therapy within individuals suffering from diabetes. WHO and ADA have approved the use of HbA1c determination for diagnosis of type 2 diabetes [4,5]. The normal range of HbA1c in a healthy person is 4 to 6% [6].

Clinically there are three major factors on which HbA1c levels depend.

- HbA1c in reticulocytes when released from the bone marrow;
- Hb glycation rate as red blood cells (RBCs) become older, a function of glucose concentration to which Hb is exposed; and
- The mean age of RBCs in the circulation [7].

HbA1c levels can be affected by number of factors such as structural hemoglobinopathies, thalassemia syndrome, and alteration in quaternary structure of Hb [8]. Also, HbA1c levels can be changed by different types of anemia [9]. Anemia is the most prevalent form of nutritional deficiency both in developed

and developing countries. Globally, 50% of anemic burden is contributed alone by Iron deficiency [10,11]. The clinical profile of many systemic diseases is regulated by the iron [12], which is involved in most important metabolic processes viz. transportation of oxygen, regulation of cell growth and differentiation, deoxyribonucleic acid (DNA) synthesis, and electron transport [13,14].

Iron deficiency anemia (IDA) can increase the red blood cell turnover which can increase glycation of Hb leading to higher HbA1c values as observed in blood loss, hemolysis, hemoglobinopathies, red cell disorders and myelodysplastic disease [15]. There are studies to support the idea that diabetes is influenced by changes in the iron level in a body [16]. Lower levels of serum iron or serum ferritin have been linked with increased glycation of HbA1c [17,18]. It has been reported that there is a bidirectional relationship between iron metabolism and glucose homeostasis, higher iron levels modulate both the action and secretion of insulin [12]. Thus, lower the iron levels, higher is the glycation of HbA1c, leading to its false-high values in diabetic as well as non-diabetic individuals [19].

Brooks et al. [20] reported that a relative absence of iron results in the alteration of quaternary structure of the Hb molecule leading to excessive glycation of the beta globin chain. In another study by Sluiter et al. [21] it was reported that glycation of Hb is an irreversible process thus, with the aging of a cell there is a linear increase of HbA1c in the erythrocyte. El Agouza et al.

[22] reported that at a constant glucose level, lower levels of Hb can lead to an increase in the glycated fraction because HbA1c is measured as a percentage of total HbA. These studies report relationship between IDA and HbA1c on the basis of structural modification of Hb and HbA1c levels in old and new red blood cells [20]. Coban et al. [19] in his studies showed that patients with IDA had higher HbA1c levels and on treatment with iron these levels significantly decreased. A case study by Mudenha et al. [23] reported that HbA1c levels significantly decreased with correction of IDA. Furthermore, Silva et al. [24] and Rajagopal et al. [7] reported difference in HbA1c levels among diabetic as well as non diabetic patients with mild, moderate, and severe IDA.

On the other hand, Heyningen et al. [25] and Hansen et al. [25] reported that there was no difference between HbA1c levels in patients with IDA and control. These findings gather support from study by Rai et al. [26], who reported no difference in HbA1c levels with respect to IDA using different methods to assay HbA1c. Thus these conflicting reports are enough to create a stir in the minds of clinicians regarding a successful therapy in diabetic patients with IDA. Hence the effect of IDA on HbA1c needs to be evaluated at mechanistic level, so as to be assured about the outcome of the therapy. Iron replacement therapy in diabetic patients with IDA needs to be considered.

Conclusion

IDA is the commonest nutritional deficiency worldwide but the prevalence is higher in developing countries, and most vulnerable groups to IDA are women, children and adolescents [27]. Also, in low and middle income countries diabetes too is increasing and the mostly affected age group is 45-64 years [28]. So, determination of HbA1c levels has increased for both screening and diagnosis of diabetes. Clinicians need to evaluate the nonglycemic factors that could affect the HbA1c levels of a patient [29,30]. Different types of anemia can have a negative effect on HbA1c levels, some investigators have shown that IDA increases the HbA1c levels independent of fasting glucose level [16] whereas others have negated these findings. In either case the clinical data is not sufficient and further studies are required to identify the role of erythrocyte indices in modulation of HbA1c levels. Studies with large population need to be conducted to evaluate the difference between severity and effects of IDA on HbA1c values.

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