



Effects of Iron Deficiency Anaemia on HbA1c Levels in Non-Diabetics and Diabetics

Ayushi Singh^{1*}, Arvind Bhake¹, Anil Agarwal¹ and Sunita Vagha¹

¹Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Iron deficiency anaemia is one of the most common anaemia striking in our country. The level up to which blood sugar level is regulated is measured by HbA1c. HbA1c represents sugar level in the blood for 120 days. HbA1c could be dependent upon an assemblage of factors like variants of haemoglobinopathies, haemolytic anaemia, other deficiency anaemia, acute loss of blood, uraemia, and pregnancy. Thus, it is crucial to determine the role of HbA1c in iron deficiency anemia in diabetics and non-diabetics before treating the patients.

Methods: Total of 58 articles were collected and based on our study objective total of 19 articles were included in this study. Iron deficiency anaemia, HbA1c, diabetics and non-diabetics has been added in pub med advanced searches and Google scholar. Original articles which compare the correlation between these two were taken. All the information was gathered from original and review articles. Articles which were qualified for review, their inclusion criteria, exclusion criteria, quality of assessment and data collections were taken into consideration. Structure of heme particle, basic mechanism of HbA1c formation in RBCs is elaborated. Review articles which were taken include RCT, retrospective analysis and observational studies. The results were all compared and concluded of each articles. Basic mechanism of formation of HbA1c in RBCs is shown. Also necessary conclusions were derived from each study.

Results: In a wide range of studies, HbA1c was found to be raised in IDA. After iron supplements, studies showed a decrease in HbA1c. Our study showed there is a need to correct anemia in diabetic patients before starting treatment.

Conclusions: Strict HbA1c control is not a prerequisite and prior anaemia correction should be done. Nevertheless, a study which will be conducted in representative population matching to the prevalence and incident of disease in our country also which should be interventional is required for the highest correction value of HbA1c in DM and NDM population.

Keywords: Diabetes mellitus; iron deficiency anaemia; HbA1c.

1. INTRODUCTION

HbA1c has been the benchmark for tracking glycaemic optimization and is useful to anticipate diabetic problems. During the total life span of RBCs, glucose is added to the N - terminal in the β chain of haemoglobin. The addition method is not enzymatic and this depicts glucose estimation of approximately 70 to 90 days. HbA1c is a fast fraction of haemoglobin (HbA1a and A1c), which is eluted before column chromatography along with cation exchange resin. Along with blood glucose level, HbA1c level varies along with various multitudes of factors. They are amended in pregnancy, haemolytic anaemia, internal or external bleeding manifestations, haemoglobinopathies, and uraemia, B12 vitamin, iron deficiency anaemia, as well as folate deficiency, which was shown to affect HbA1c levels[1]. There are 2 factors which have the effect to remodel glycation of these proteins. They are serum glucose level and t1 / 2 of protein[2]. In various literature, glycated states of haemoglobin have shown that HbA1c is noticed higher in pathologies like iron deficiency anaemia. A considerable number of studies have also found that providing after iron supplements, there is decreased glycation of haemoglobin. Also, few studies have shown that serum HbA1c levels in the blood have hyped in iron deficiency anaemia and endeavoured to interpret based on the modified structure of HbA1c and difference in saturation of HbA1c in new and senescence erythroid cells[3]. With this rationale, the objective of the present study was to study the effect of iron deficiency anaemia on glycated haemoglobin (HbA1c) in non - diabetic Indian subjects. And whether there is positive correlation between HbA1c in iron deficiency anemia patients in diabetics and non-diabetics.

2. METHODS

A systemic research has been performed in our study. All the articles were taken from PubMed, PMC, and Google scholar from the last 15 years

of study. Keywords used in different combinations were: "HbA1c", "Diabetes and HbA1c", "Diabetes and Anemia," "HbA1c and Anemia and Diabetes,". All articles published in English between this period were considered for review. Search engines like "Google," "Medscape," "UpToDate" were also used to find the related articles.

All the relevant studies were taken and compared and taken into consideration.

Also results of each study were tabulated comparing correlation between diabetics and non-diabetics iron deficiency anaemia level. On the basis of result of all the studies, formulation of results and conclusion was derived.

2.1 Inclusion and Exclusion Criteria

All the articles relevant to the topic were searched in different databases. Only the studies which were published in English medium with full text between 2011 to 2020 and articles from all the geographical locations were included. All types of studies were included except animal studies.

The database has been searched and identified 58 related articles among of which 39 articles has been excluded on the basis of title or abstract, which were not at all relevant to our study. The pioneer reason for exclusion criteria was incomplete data or not meeting our inclusion criteria. Included article has at least one measurement of the HbA1c and hb by any of the accepted method; however, this rule was not taken into consideration for the review articles.

3. RESULTS AND DISCUSSION

3.1 Iron Deficiency Anaemia

Categories of protein containing iron are:

1. Mononuclear Fe proteins (example: superoxide dismutase),

2. Di iron carboxylate protein (example: ribonucleotide reductase and ferritin),
3. Iron and sulfur protein (example aconitase)
4. Haemoglobin protein (example haemoglobin).

In comparison with all of the haemoglobin is the most abundant type present in the human body. Such that more than half of body stored form of iron is contained within iron stores in the form of ferritin. Based on the location of HB in erythrocytes, anaemia is sub - classified as IDA.

On the contrary to the abundance of iron on our planet iron deficiency anaemia is very commonly found. Iron supply and requirement along with iron production in RBCs is basic to understand the pathogenesis of iron deficiency anaemia. Production of RBCs and their related demand for iron takes place in three steps: requirement of oxygen by tissue, the life span of RBCs, and loss of RBCs in any further complications like bleeding, any pathological state of body, and physiological requirement. All these steps ensure that the haemostasis of body iron remains in the balance. On the daily basis, approximately 20 millilitres of RBCs are senescent, also along with that twenty milligrams of heme iron is again recycled as iron for the formation of new RBCs. A total of about twenty millilitres of dead and recycled erythrocytes are cleared on the daily basis, and twenty milligrams of Fe in the cells are recycled again for producing new erythroid cells. In people having iron - deficiency anaemia, the half - life of RBCs is significantly reduced thus iron from the senescent RBCs is to be regenerated more quickly despite this the quantity of iron in each erythrocyte is significantly diminished. In case of such increased requirement of iron absorption in the diet should be compounded.

The amount of iron required for erythrocytes and their precursors to form heme and haemoglobin is very high. There is low iron saturation present in transferrin in IDA. Stomach, regenerated iron from senescent erythrocytes, and ferritin supplies iron to transferrin and iron is loaded there. Firstly iron stores are depleted before iron deficiency anaemia could be detected in blood in peripheral smear and clinically host to present with IDA. Both irons reabsorbed from the gut and recycled iron from senescent erythrocytes is important for the proper maintenance of iron content in the body. Iron deficiency anaemia does not cause erythroid cell hyperplasia the contrary to thalassemia for the depleted haemoglobin in

RBCs. And thus reticulocytosis is absent in iron deficiency anaemia. If a sudden haemorrhage is not present in the body, IDA develops insidiously in the body over years. Treatment prognosis and results may vary depending upon the quality of dietary iron intake and gastrointestinal reabsorption of iron.

Testing of nutritional deficiency anaemia like IDA and its treatment has been found over decades at very low cost. Regrettably, iron deficiency anaemia continued to be the most common nutritional deficiency anaemia in India and worldwide. Various impediments which include fundable and non - fundable helps, subpopulation believes, and communicable diseases tie up together and make the extermination of disease very strenuous. Supplemental disputes which will come across by a subpopulation in certain geographical areas these if we try to achieve a large scale of global eradication are possible.

3.2 HbA1c

HbA1c at the earlier phase of discoveries approximately 40 years ago was considered to be an abnormal and unusual diseased form of haemoglobin that occurred in the human body [4]. Only after this discovery, many started studies that correlate glucose estimation and helps to correlate HbA1c with glucose for estimation and treatment. The A1C derived sum up a total of glucose study with six hundred and forty - three participants constituted a substantiated link between HbA1C & glucose [5]. In the 1980s HbA1c was introduced into clinical use and then it was taken into practices [6]. Time duration of an average of twelve weeks plasma glucose level is estimated by HbA1c [7]. A random sample could be given at any time and no special preparation is needed like fasting and postprandial. This makes it preferable for diabetes check - up and assessment. In the recent interval of time HbA1c is being used as diagnostic as well as screening tests for people with a high risk of getting diabetes mellitus. Over the large period measurement of fasting for eight hours and measuring blood glucose or performing oral glucose tolerance test, with every day obtaining different values of glucose leading to variability an alternate method to diagnose glucose level in blood was long been sought. HbA1c is recommended by an International Committee and by the ADA for diabetes mellitus diagnosis [8]. The sensitivity and specificity of HbA1c are

very close to the measurement of fasting and post - load glucose measurement in plasma and also depicts the retinopathy risk[9]. 6.5 % of HbA1c is recommended as the standard cut off value for the diagnosis of HbA1c. More than 6.5 % of HbA1c however does not exclude diabetes mellitus. All - embracing effectively of HbA1c is indistinguishable with fasting or 2 - hour blood glucose value. Out of all three measurement criteria for blood glucose value risk factor above which retinopathy is common is unknown. HbA1c, is quite effective in sensitivity and specificity for the measurement of blood glucose level as compared to other methods. Its role in the microvascular lesion is unknown. HbA1c is also not easily available in many parts of the world. A study carried out in Australia showed that in a model taking HbA1c as diagnostic criteria for measuring microvessel damage. It is as good as the other two criteria's of measurement of blood sugar [10]. The expediency of HbA1c avoid everyday uncertainty in glucose measurement values also it circumvents the requirement for a patient to fast and then have foregoing dietary preparation. HbA1c is affected by genetic, ailment related and hematologic factors[11].

HbA1c is formed by the addition of glucose with N - terminal valine group of beta chains, form aldimine linkage which realigns for the formation of the stable ketamine link of HbA1c. American Diabetes Association has made HbA1c significant criteria to recapitulate the prognosis of disease, treatment, and diagnosis. HbA1c in the body is affected by various haematological conditions like bleeding haemorrhage(acute and chronic), and haemolytic anaemia. Pregnancy and uraemia also have a remarkable impact on HbA1c levels[12] [13] [14]. For over a decade, many studies have shown that both in urban as well as rural populations iron deficiency anaemia have been encountered. Also, many studies have shown that treatment of iron deficiency anaemia with supplements has been beneficial for the treatment and maintenance of control of glycated hemoglobin. Significant detrimental in the HbA1c level has been found in patients after the treatment of iron deficiency anaemia even if they are not suffering from diabetes mellitus. In erythrocytes as their age increases, the HbA1 levels also rise. This type of age - associated haemoglobin glycation process is irreversible. With an increase in age, there is a decrease in the production of RBCs and the circulating RBCs have increased concentration of HbA1c in it thus increasing the value of the HbA1c level. Various

studies have shown us that HbA1c is an important prognostic marker in diabetic patients[13]. Iron is mainly stored in our body as ferritin, its storage highly suggests the importance of iron loading status in our body. The increased life span of erythrocytes with increased HbA1c and decreased serum ferritin levels are present in most cases of iron deficiency anemia. Iron supplementation therapy also showed a decrease in HbA1c status which was previously decreased of pregnant women with comorbidities such as diabetes mellitus and diabetic nephropathy like CKD patients who were already suffering from IDA[13], [14]. In recent studies, much is given importance on serum ferritin, acute phase reactant a significant marker of Fe stores in our body and its possible association with the glycemic index. At the same time, HbA1c is also the simplest yet efficient marker for the control and well maintenance of blood sugar value. Various factors which affect or elevate the value of HbA1c should be ruled out before planning the management and course of treatment for diabetes mellitus.

2019, Solomon et al. showed average haemoglobin, haematocrit, and red cells were low in iron deficiency patients [15]. This study concluded that this above - mentioned group has lower HbA1c than the non - IDA group. Hence, monitoring of HbA1c along with iron deficiency anemia patients should be taken with caution.

This finding has come to the same conclusion as an interventional study which included a hundred and twenty people by Kalairajan et al. in 2019[16]. The study concluded that HbA1c levels have decreased in iron deficiency anaemia patients. A positive correlation was noticed in the case of iron deficiency anaemia patients concerning HbA1c and no significant correlation was found after the iron supplements given for three months to the IDA patients. The author has taken the subjects from Indian subcontinents and the IDA was nutritional. Alsayegh et al. in 2017, carried out an observational study that showed that more people are associated with anaemia in diabetic patients and there is also an increase in the number of diabetes - related complications associated with females[17]. However, the HbA1c correlation was not positive. The author also suggested that prior early - stage diagnosis of diabetes and treatment of nutritional deficiency anaemia like IDA will combat the complication of the disease.

In the study conducted by Balasubramanian Shanthy et al, the mean HbA1c of cases was 7.6

$\pm 0.5\%$ in comparison to other it was $5.5 \pm 0.8\%$ in healthy control. Statistical tests showed a difference in HbA1c levels in cases and controls were significant indicating statistically higher HbA1c among the control group[18].

4. CONCLUSION

From the above studies, iron deficiency anaemia might affect the HbA1c levels in diabetic patients thus precautions should be taken and it would benefit patients to treat iron deficiency anemia with iron supplements before diabetes treatment is to be started thus giving it a chance for better judgment and treatment of the disease. This will further reduce the complications which would occur otherwise.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

- Krikorian A. Standards of Medical Care in Diabetes. 2016;61.
- Starkman HS, Wacks M, Soeldner JS, Kim A. Effect of Acute Blood Loss on Glycosylated Hemoglobin Determinations in Normal Subjects. *Diabetes Care*. 1983;6(3):291–4.
- Chowdhury TA, Lasker SS. Elevated glycosylated haemoglobin in non - diabetic patients is associated with an increased mortality in myocardial infarction. *Postgrad Med J*. 1998;74(874):480–1.
- Rahbari S, Blumenfeld O, Ranney HM. Studies of an unusual hemoglobin in patients with diabetes mellitus. *Bio-chem Biophys Res Commun*. 1969;36(5):6.
- Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C Assay Into Estimated Average Glucose Values. *Diabetes Care*. 2008; 31(8):1473–8.
- Massi - Benedetti M. Changing targets in the treatment of type 2 diabetes. *Curr Med Res Opin*. 2006;22(sup2):S5–13.
- Nathan DM, Turgeon H, Regan S. Relationship between glycosylated haemoglobin levels and mean glucose levels over time. *Diabetologia*. 2007;50(11):2239–44.
- The International Expert Committee. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. *Diabetes Care*. 2009;32(7):1327–34.
- Colagiuri S, Lee CMY, Wong TY, Balkau B, Shaw JE, Borch - Johnsen K, et al. Glycemic Thresholds for Diabetes - Specific Retinopathy: Implications for diagnostic criteria for diabetes. *Diabetes Care*. 2011;34(1):145–50.
- Tapp RJ, Tikellis G, Wong TY, Harper CA, Zimmet PZ, Shaw JE, et al. Longitudinal Association of Glucose Metabolism With Retinopathy: Results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study. *Diabetes Care*. 2008;31(7):1349–54.
- Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes: A1c in the management of diabetes. *J Diabetes*. 2009;1(1):9–17.
- Guo W, Zhou Q, Jia Y, Xu J. Increased Levels of Glycosylated Hemoglobin A1c and Iron Deficiency Anemia: A Review. *Med Sci Monit*. 2019;25:8371–8.
- English E, Idris I, Smith G, Dhatariya K, Kilpatrick ES, John WG. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review. *Diabetologia*. 2015;58(7):1409–21.
- Florkowski C. HbA1c as a Diagnostic Test for Diabetes Mellitus – Reviewing the Evidence.:9.
- Solomon A, Hussein M, Negash M, Ahmed A, Bekele F, Kahase D. Effect of iron deficiency anemia on HbA1c in diabetic patients at Tikur Anbessa specialized teaching hospital, Addis Ababa Ethiopia. *BMC Hematol*. 2019;19(1): 2.
- Katwal PC, Jirjees S, Htun ZM, Aldawudi I, Khan S. The Effect of Anemia and the Goal of Optimal HbA1c Control in Diabetes and Non - Diabetes. *Cureus [Internet]*; 2020 [cited 2021 Jun 24]; Available from: <https://www.cureus.com/articles/32895-the-effect-of-anemia-and-the-goal-of-optimal-hba1c-control-in-diabetes-and-non-diabetes>
- Villar E, Lièvre M, Kessler M, Lemaître V, Alamartine E, Rodier M, et al. Anemia normalization in patients with type 2 diabetes and chronic kidney disease: results of the NEPHRODIAB2 randomized trial. *J Diabetes Complications*. 2011;25(4):237–43.

18. Shanthi B. Effect of Iron Deficiency on Glycation of Haemoglobin in Nondiabetics. J Clin Diagn Res [Internet]; 2013. [cited 2021 Jun 24]. Available: http://www.jcdr.net/article_fulltext.asp?issn=0973-709x&year=2013&month=January&volume=7&issue=1&page=15-17&id=2659

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