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Study of Level of Glycated Hemoglobin (Hba1c) In Patients of Type 2 Diabetes Mellitus Associated With Iron Deficiency Anemia and Without Iron Deficiency Anemia in Rural Population in Jharkhand

Dr. Avinash Kumar[1], Prof. (Dr) Santosh Kumar[2]
JRA III Department of Biochemistry[1], Professor &HeadDepartment of Biochemistry[2]
RIMS, Ranchi, Jharkhand

Abstract
Introduction:*Glycated Hemoglobin (HbA1c) is the predominant hemoglobin found in HbA1 fractions. It is used as a gold standard for measuring glycemic control.Iron deficiency anemia (IDA)is one of themost prevalent formof malnutrition in rural population.Any condition that alters red cell turnover like, iron deficiency anemia, will lead to changes in HbA1c levels. The present study was aimed at determining the effect of IDA on HbA1c in type 2 diabectes mellitus (DM) patients in rural population.****Methods:****The present study was ancross sectional study conducted on 100 type 2 diabetic patients (50 with IDA and 50 without IDA) at RIMS Ranchi, Jharkhand. Hematological investigations, HbA1c, Serum Ferritin and FPG were analyzed.****Result:*** *The mean HbA1c level (7.48±0.580)in patients with IDA and type2 DM was higher than that in the patients without IDA(5.98± 0.141).****Conclusion :****Present study shows IDA spuriously elevates HbA1c levels. It is therefore very important to rule out IDA especially in rural populationbefore making a therapeutic decision solely based on HbA1c level.*
Keywords: *HbA1c , Iron Deficiency Anemia (IDA), Type 2 Diabetes Mellitus (DM)*

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I. Introduction :

Glycated Hemoglobin (HbA1c) is the predominant hemoglobin found in HbA1 fractionsand it is formed by the glycation of terminal valine at the β-chain of hemoglobin[1]. It is used as a gold standard for measuring glycemic control over the previous three months and American Diabetes Association has recently endorsed HbA1c ≥ 6.5% as a diagnostic criterion for diabetes mellitus [2]. However HbA1C levels can be influenced by a variety of other factors affecting erythrocyte turnover and glucose homeostasis.[3-6] One such condition affecting erythrocyte turnover is anemia. Anemia may be associated with rapid erythrocyte turnover conditions like acute or chronic blood loss, hemolytic anemia, sickle cell anemia, vitamin B12 deficiency, pregnancy that lower HbA1C levels (or) with slower erythrocytes turnover conditions like Iron deficiency anemia (IDA), alcoholism that increases HbA1C levels. Iron deficiency anemia (IDA) is one of themost prevalent formof malnutrition in rural population.Any condition that alters red cell turnover such as, iron deficiency anemia, will lead to changes in HbA1c levels.Most epidemiologic studies suggest thatiron-deficiency anemia (IDA) can result in spuriously high HbA1c values,[7,8,9,10]though some suggest there is lower HbA1c among individuals with IDA[11] or anemia[12].The present study was aimed at determining the effect of IDA on HbA1c in type 2 diabectes mellitus (DM) patients in rural population.

Due to the variation in the results of multiple studies, we decided to investigate and conducted a study in iron-deficient individuals with type 2 DM patients with normal fasting blood sugar (FBS) and iron-sufficient individuals to assess whether anemia has any effect on HbA1c levels, and anemia can be considered before making any therapeutic decisions based solely on HbA1c levels[13].

II. Material & Methods:

The present study was an observational study conducted on 100 type 2 diabetic patients (50 with IDA and 50 without IDA) at RIMS Ranchi, Jharkhand over a period of one year(2018-19). Both groups after taking their consent were subjected to a questionnaire. After exclusion of individuals with prefixed exclusion criteria such as Type 1 DM, patients with uncontrolled blood sugar, severe systemic illness, any hemoglobinopathies, a total of 100 patients were finalized for our study. There after sample of venous blood was taken for analysis and biochemical investigation was done. The instrument used for biochemical analysis was Beckman coulter AU480 Biochemical auto analyzer. Serum Ferritin was estimated on ARCHITECT i1000SR, fully automated Immunoassay analyzer. HbA1c was estimated on Bio-Rad D 10 analyzer. Red cell indices was estimated on

SYSMEX XT-2000i haematology analyser . Patients with IDA were chosen by their hemoglobin level (Hb < 13 gm% in males and <12 gm% in females)based on WHO definition of IDA. Also various Red cell indices along with peripheral smear done to confirm IDA as per WHO definition. Data was analyzed using SPSS version22 software. Pearson's correlation, chi square and student t tests were calculated. The data were presented as mean± SD. A p value of <0.05 was taken as statistically significant.

III. Results

The Meanage ±SDinpatients of type2 diabetes mellitus associated with iron deficiency anemia (DM + IDA)was 51.5±9.96 and in patients of type2 diabetes mellitus without iron deficiency anemia (DM – IDA) was 53.9 ±9.61 .Minimumage:19years,Maximum age:75years. [table I].

The majority ofthe study subjects in patients of type2 diabetes mellitus associated with iron deficiency anemiawerefemales(72%)whilethe remaining 28%weremales. It confirmsthe factthat iron deficiency anemiaismorecommoninfemales in rural population.Overall participation of females in the study is 53.33% and males is 46.66%.[Table II]

The Mean ±SD haemoglobin in patients of type 2 DM with IDA was : 7.90 ±1.66 gm/dl and in patients of type 2 DM without IDA was 13.36 ±0.52 . Also the Mean ±SD of glycated haemoglobin (HbA1c) in patients of type 2 DM with IDA was : 7.48 ± 0.580 % and in patients of type 2 DM without IDA was 5.98 ± 0.141 %. This result shows that the mean HbA1c was higher in patients of type 2 DM associated with IDA than in those type 2 DM patients without IDA which was statistically significant (p< 0.001) in both groups. [Table III]

The present study showed that the mean ±SD of haemoglobin inpatients of type2 diabetes mellitus associated with iron deficiency anemia ,among females is : 7.19 ±1.14 gm/dl and among males is 9.71± 1.43 gm/dl which shows that females are more anemic than males in rural population. Also the mean ±SD of HbA1c in patients of type2 diabetes mellitus associated with iron deficiency anemia among females is : 7.50 ± 0.60 % and among males is 7.43± 0.51 . The above data indicates that as level of haemoglobin decreases the level of HbA1c increases. [Table IV]

Inpatients of type2 diabetes mellitus associated with iron deficiency anemia ,Hb&HbA1c showedPearson's correlationwhich was statistically significant (p=<0.001). It signifies that both the variables i.e,Hb and HbA1c ,inpatients of type2 diabetes mellitus associated with iron deficiency anemiabears statistically highly significant difference. It signifies that if one variable decreases the other one increases.

Table No : I

DISTRIBUTION OF STUDY POPULATION ACCORDING TO AGE IN BOTH GROUPS

AGE(in years)	GROUPS	
	DM + IDA	DM - IDA
Mean ± SD	51.58± 9.967	53.92± 9.610

Table No : II

SEX DISTRIBUTION AMONG BOTH GROUPS

GENDER	GROUPS	
	DM + IDA	DM - IDA
MALE	14	30
FEMALE	36	20
TOTAL	50	50

Table No : III

Mean , SD of Hemoglobin and HbA1C Both Groups

	GROUPS	
MEAN±SD	DM+IDA	DM - IDA
Hb(gm/dl)	7.90 ± 1.66	13.36 ± 0.525
HbA1c(%)	7.48 ± 0.580	5.98 ± 0.141
P value	< 0.05	< 0.05

Table No : IV

Distribution of Hb and HbA1cin patients of type2 diabetes mellitus associated with iron deficiency anemia(DM + IDA)on the basis of Gender

	Males	Females
No. of cases	14	36
Haemoglobin(Hb)	9.71±1.43	7.19±1.14
HbA1c (%)	7.43± 0.514	7.50 ± 0.609

IV. Discussion :

Ourresultssuggestedthatpatients with Type2 diabetes mellitus associated with iron deficiencyanemia wasassociatedwith higherconcentrationsof HbA1c.Theearlieststudy toinvestigatetheeffectsof irondeficiencyanemia onHbA1clevelswasconductedbyBrooksetal.[14] who assessedHbA1clevelsin35nondiabeticpatientshaving irondeficiency anemiabothbeforeandaftertreatment withiron.TheyobservedthatHbA1clevelswere significantly higherinirondeficiency anemiapatients anddecreasedaftertreatmentwithiron.Themechanisms leading to increased HbA1clevels were not clear. It was proposedthat,inirondeficiency,thequaternarystructure oftheHbmoleculewasaltered,andthatglycationof theglobin chain occurredmorereadilyintherelative absenceofiron.[14]

The results of this study show that HbA1c levels are spuriously elevated in the presence of IDAirrespectiveof controlledplasma glucoselevels . Our finding confirms the study results of Tarim et al, who reported HbA1c level is elevated in diabetics with IDA than with iron-sufficient controls. This may be explained by iron deficiency related changes in the quaternary structure of hemoglobin molecule increasing the glycation of globin chain.[15]

Similar to this study, a study done by Alap L. Christy et al[16] concluded that iron deficiency anemia elevates HbA1c levels in diabetic individuals with controlled plasma glucose levels. They postulated that iron deficiency anemia has a positive correlation with increased HbA1c levels.

A study done by Catherine Kim et al[17] concluded that iron deficiency shifted the HbA1c slightly upwards independent of fasting glucose level.

Our study results are also consistent with the study done by El-Agouza et al in non-diabetics who reported that a decline in the Hb level might lead to increase in the glycated fraction at a fixed glucose level, because HbA_{1C} is measured as a percentage of total Hb.[18]

Our results were also in concordance with the study results of Shanthi et al[19], Coban et al [20], and Silva et al[21].Coban et al showed a very large difference between HbA1clevels in non-diabetic patients with and without IDA.Shanthi et al conducted study in non –diabetics and reported that iron deficiency was associated with higher proportions of HbA1c and suggested that iron status must be considered during the interpretation of the HbA1c concentrations in Diabetes mellitusSilva et al reported that IDA affects HbA1c levels and causes spurious increase in their results. Although these upward changes in HbA1cvalues are statistically significant, they may be not clinically relevant when the overall variability of the HbA1c test is considered. This effect is dependent on anaemia degree and the presence of mild anaemia is likely to have a minor effect on HbA1c levels.

Sluiteretal.[22] triedtoprovideanexplanationforthe abovefindings.Theyproposedthattheformation of HbA1cisanirreversibleprocessandhence, theconcentrationof HbA1cinerythrocytewill increaselinearlywiththecell'sage.Forexample,they found that in patientswith normal blood glucose levels, but with very young red cells, as would be foundaftertreatmentofirondeficiencyanemia, HbA1c concentration was reduced. However, if irondeficiency has persisted fora long time, the red cellproduction ratewould fall,leadingnot only to anemiabutalsotoahigher-than-normalaverageage ofcirculatingerythrocytesand, therefore, increased HbA1clevels.[22]

Studies by Ford ES et al reported no significant difference in mean HbA1c concentration according to the IDA status as well as before and after iron treatment.[23]Sinha et al [24]and Kalaskar et al [25] contradicts with our results reporting that HbA_{1C} levels are lowered in IDA.

Also Saudek et al suggested that red cell age was unlikely to be a significant factor in explaining the changes in HbA1c levels during the treatment of IDA and believed that the reported differences in HbA1c concentrations before and after iron supplementation were due to differences in the laboratory methods used for measuring HbA1c.[26]Ferritin is a storage form of iron, and it reflects the true iron status . In our study, serum ferritin level was indirectly proportional to HbA1c. As explained previously, in IDA, ferritin is decreased with increase in the red cell life span which is associated with increased HbA1c. This goes in hand with other study results of Shanthi et al[19] and Raj et al.[27]

Our results contradicts with the study results of Sharifi et al [28], who reported that there was no correlation between serum iron , serum ferritin and HbA1c in diabetic patients of either sex.

In these studies, the probable explanation of elevated HbA1c in iron deficiency-anaemia at baseline is that, if serum glucose is accepted to remain constant, a decrease in the hemoglobin concentration might lead to an increase in the glycated fraction but the exact mechanism still remains elusive.

Different studies have been carried out inboth diabetic and non-diabetic groups; however, its distributionin well-controlleddiabeticswhoareon regular therapy is inadequately studied. Although diabetes itselfcanelevatethe HbA1c levels,ithasbeen proven that controlled plasma glucose levels for 3 monthscorrelatesvery wellwithcontrolledHbA1c. Hence, patientswithcontrolled plasma glucose levels areexpectedtohave HbA1cbelow6.5%

Asshownintheresults,therewasa significant elevationin HbA1clevelsin iron-deficientanemic individuals with FPGless than 126. Therefore, westudied HbA1c distribution in these individuals accordingly. In this study group, Hb& HbA1c showed positive correlation in a negative direction means which was also statistically very significant ($p<0.001$).

That is, in patients with Type 2 DM when the hemoglobin decreases the HbA1c will increase and vice versa.

V. Conclusion:

HbA1cwas higherin patients with Type 2 Diabetes Mellitus associated with iron deficiency anemia comparedtopatients with Type 2 Diabetes Mellitus not associated with iron deficiency anemia . This study showsthatwheneverHbA1c iscalculatedto detecttheglycemic statusof a patient,factors otherthanglucosealsoplay apartinits calculated value, which should be kept in mind beforeatherapeutictreatment isgiven. If we cannot rule out the different influences for HbA1c then it may result in unnecessary hypoglycemia in patients as they are over-treated to try to bring down the HbA1c to within set targets. Also, we must be cautious while treating any diabetic patients from a rural population especially females , keeping in mind that IDA is very common in female population of rural origin.

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