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Effect of Iron Deficiency Anemia on Glycated Albumin Levels: A Comparative Study in Nondiabetic Subjects with Iron Deficiency Anemia

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Abstract

Objective Glycated hemoglobin A1c (HbA1c), used for monitoring glycemia control, is altered in iron deficiency anemia (IDA). Glycated albumin (GA) is considered an alternate biomarker to HbA1c. However, effect of IDA on GA needs to be studied.

Materials and Methods Thirty nondiabetic cases with IDA and 30 healthy controls were included. Fasting plasma glucose (FPG), creatinine, urea, albumin, total protein, ferritin, iron, unsaturated iron binding capacity, hemoglobin (Hb), HbA1c, complete hemogram, and GA were estimated. Transferrin saturation and total iron binding capacity (TIBC) were calculated. Statistical analysis was done using unpaired two-tailed *t*-test/Mann–Whitney *U*-test and Pearson's correlation/Spearman-rank correlation, as appropriate.

Results Total protein, albumin, Hb, iron, ferritin, and transferrin saturation were significantly lower while FPG, GA, TIBC, and HbA1c were significantly higher in cases compared to controls. HbA1C and GA have a significant negative correlation with iron, transferrin saturation, and ferritin. Significant negative correlations of GA with albumin ($r = -0.754$; $p < 0.001$) and Hb ($r = -0.435$; $p = 0.001$) and that of HbA1c with albumin ($r = -0.271$; $p = 0.03$) and Hb ($r = -0.629$; $p < 0.001$) while significant positive correlation of Hb with albumin ($r = 0.395$; $p = 0.002$) and HbA1c with FPG ($r = 0.415$; $p = 0.001$) were observed.

Conclusion Low albumin levels increase plasma protein glycation, including albumin. Hence, elevated GA levels indicate false elevation of GA in scenario of lowered albumin observed in IDA, similar to HbA1c. Thus, using GA in diabetes mellitus with IDA should be avoided or used with caution to prevent potentially inappropriate treatment intensification and risk of hypoglycemia.

Keywords
- glycated albumin
- HbA1c
- iron deficiency anemia
- albumin
- hemoglobin

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Introduction

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India.[1] Hence, it is very important to maintain glucose hemostasis to avoid complications of diabetes mellitus. For decades, glycated hemoglobin A1c (HbA1c) has remained the standard biomarker for monitoring glycemic control.[2] Because of HbA1c's integral role in diagnosis and monitoring treatment, it is important to recognize the various clinical scenarios and physiological conditions that may give rise to abnormal HbA1c results. There are many factors like anemia, hemoglobin (Hb) variant, analytical interference, or drugs that affect the HbA1c measurement. Of all the factors affecting HbA1c, iron deficiency anemia (IDA) is reported to alter the Hb levels.[3,4] Glycated albumin (GA), which was reported not to be influenced by gender, erythrocyte life span, and erythropoietin therapy, is considered as a measure of short-term glycemic control of 2 to 3 weeks in IDA.[5,6]

As GA is proposed to be a promising alternate to HbA1c, a case-control observational study was undertaken to study the effect of anemia on GA levels and the association of GA with iron indices and albumin levels. In order to avoid confounding effect of diabetes mellitus and treatment effects on HbA1c and GA, the study was conducted on nondiabetic subjects with and without IDA. By these selection criteria of subjects, it was aimed to study only the effect on anemia of GA levels. Associations of GA with HbA1c, iron indices, albumin, and plasma glucose were analyzed.

Materials and Methods

A case-control study was undertaken with sample size calculated from similar studies using the formula $n = 2/d^2 \times Cp$, power, at 80% power and 0.05 alpha error. A total of 100 subjects attending Medicine and Hematology outpatient department of Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India, were recruited into the study and screened for IDA. Among the subjects screened, 30 cases diagnosed with IDA during the period of December 2019 to January 2020 were included into the study. Inclusion criteria for cases (IDA) were low transferrin saturation less than 15%; serum ferritin levels less than 12 µg/L; and Hb concentrations less than 12 g/dL in women aged 20 to 69 years, less than 11.8 g/dL in women aged 70 years, less than 13.7 g/dL in men aged 20 to 49 years, less than 13.3 g/dL in men aged 50 to 69 years, and less than 12.4 g/dL in men aged 70 years.[7] Cases with diabetes mellitus (fasting plasma glucose [FPG] >126 mg/dL) on treatment; with other forms of anemia; on iron and multivitamin supplements; with liver, kidney, and thyroid disorders; with inflammatory diseases; with acute illness; alcoholics; smokers; and pregnant and lactating women were excluded from the study. Thirty healthy controls were included from the subjects accompanying the patients and from the working staff of the hospital. Subjects with IDA, or metabolic diseases such as diabetes, hypertension, hyperlipidemia, and obesity were excluded from the study. The study was approved by the institutional ethics committee and was conducted after obtaining written informed consent from the study subjects. The study was conducted in accordance with the principles of Declaration of Helsinki.

Sample Collection

Peripheral venous blood was collected from all the study subjects who were fasting for 8 to 10 hours. Then, 2 mL of blood was transferred to sodium fluoride and potassium oxalate anticoagulant-containing tubes and 2 mL of blood was transferred into sodium ethylene diamine tetra acetic acid anticoagulant-containing tubes that were centrifuged immediately, and the plasma separated and analyzed for plasma glucose, HbA1c, and complete hemogram. Also, 2 mL of blood was transferred into additive free tubes that were allowed to stand for 30 minutes for clotting and serum was separated by centrifugation at 2,000 rpm for 15 minutes. Serum was stored in appropriately labeled vials at –80°C in deep freezer until further analysis.

Methods

HbA1c was measured by ion-exchange high-performance liquid chromatography method and complete hemogram profile obtained by electrical impedance principle using Hematology analyzer (Mindray, Shenzhen, China). Serum GA was estimated by enzyme linked immunosorbent assay (ELISA) method (Human GA ELISA kit, Elk Biotechnology, Hubei, P.R.C) and measured using Erba ELISA reader Spectrophotometer (United States). Serum urea, creatinine, albumin, total protein, iron, ferritin, and unsaturated iron binding capacity (UIBC) were estimated by commercially available kits using standard methods on Beckman coulterAU480 Auto analyzer (Brea, California, United States). Total iron binding capacity (TIBC) was calculated as Iron + UIBC and transferrin saturation as Iron/TIBC × 100.

Statistical Analysis

Data distribution was studied using Kolmogorov–Smirnov test. Data obtained were expressed as mean ± standard deviation for data with normal distribution, and median (interquartile range) for data that showed nonnormal distribution. Comparison between means of biomarkers of the two groups was done using unpaired *t*-test for data with normal distribution and Mann–Whitney *U*-test for data with nonnormal distribution. Correlation between the biomarkers was studied using Pearson's correlation analysis for data with normal distribution and Spearman-rank correlation for data with nonnormal distribution. A *p*-value less than 0.05 was considered as statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, United States) for Windows, version 16.

Table 1 Clinical and biochemical characteristics of the study participants

Baseline parameters	Group 1: Controls ($n = 30$)	Group 2: Cases ($n = 30$)	*p*-Value
Age (years)	32.36 ± 8.94	43.80 ± 17.88	0.030[a]
Males: number (%)	13 (46)	16 (53)	–
BMI (kg/m^2)	22.54 ± 1.74	21.57 ± 1.94	0.051
FPG (mg/dL)	82.3 ± 9.9	90.2 ± 8.5	0.002[a]
Urea (mg/dL)	17 (6.25)	20 (7.25)	0.119
Creatinine (mg/dL)	0.71 (0.14)	0.67 (0.21)	0.195
Total protein (g/dL)	7.6 ± 0.43	7.2 ± 0.79	0.022[a]
Albumin (g/dL)	3.95 (0.23)	3.7 (0.50)	0.002[a]
GA (%)	9.0 (1.0)	11.0 (1.0)	< 0.001[a]
Hb (g/dL)	13 (1.27)	7.1 (2.2)	< 0.001[a]
HbA1c (%)	4.9 (0.55)	5.8 (0.40)	< 0.001[a]
Iron (µg/dL)	72 (24)	13 (7.2)	< 0.001[a]
TIBC (µg/dL)	313 (37.2)	478 (34.7)	< 0.001[a]
Ferritin (ng/mL)	63 (15.4)	12 (2)	< 0.001[a]
Transferrin saturation (%)	22.5 (8.25)	3 (1.25)	< 0.001[a]

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; GA, glycated albumin; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c; TIBC, total iron binding capacity.
Note: Data presented as mean ± standard deviation for data with normal distribution and median (interquartile range) for data with nonnormal distribution.
[a]$p < 0.05$ is statistically significant.

Results

►**Table 1** depicts the clinical and biochemical characteristics of the study participants. Among control subjects, 13 were males and 17 were females; in cases, 16 were males and 14 were females. The levels of total protein, albumin, Hb, iron, ferritin, and transferrin saturation were found to be statistically significantly lower while FPG, GA, TIBC, and HbA1c levels were found to be statistically significantly higher in cases when compared to controls.

►**Table 2** depicts the correlation analysis of HbA1C, albumin, and GA with iron indices. HbA1c has statistically negative correlation with serum iron, serum transferrin saturation, and serum ferritin. GA has statistically negative correlation with serum iron, serum transferrin saturation, and serum ferritin. Albumin has statistically significant positive correlation with serum iron and serum transferrin saturation and serum ferritin.

►**Table 3** depicts the correlation analysis between HbA1c, GA, albumin, and Hb. Statistically significant negative correlations of albumin with GA and HbA1c and Hb with GA and HbA1c, and a significant positive correlation of Hb with albumin were observed.

►**Table 4** depicts the correlation analysis of HbA1c and GA with FPG. HbA1c had a significant positive correlation with FPG, but GA did not have significant correlation with FPG.

Discussion

There has been a switch in the past decade to diagnosing the presence of diabetes mellitus and its severity through measurement of blood glycated proteins such as HbA1c and GA.[8] Glycated proteins provide a measure of glycemic control over a period of time and the measurements are used in diabetes management and progression.[9] HbA1c is considered an important marker of glycemic control as it estimates average blood glucose of the previous 3 months, hence providing a better estimate of average blood glucose than measurement of blood glucose directly. Hence, as HbA1c monitors long-term glycemic control, the utility of HbA1c over discrete

Table 2 Correlation of HbA1c, albumin, and GA with iron, transferrin saturation, and ferritin

Parameter	Iron		Transferrin saturation		Ferritin	
	r-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value
HbA1c	−0.682	< 0.001[a]	−0.681	< 0.001[a]	−0.45	< 0.001[a]
Albumin	0.337	0.008[a]	0.318	0.01[a]	0.281	0.02[a]
GA	−0.373	0.003[a]	−0.356	0.005[a]	−0.367	0.003[a]

Abbreviations: GA, glycated albumin; HbA1c, glycated hemoglobin A1c.
[a]$p < 0.05$ is statistically significant.

Table 3 Correlation between HbA1c, GA, albumin, and Hb

Parameter	Albumin		GA		HbA1c	
	r-Value	*p*-Value	*r*-Value	*p*-Value	*r*-Value	*p*-Value
Albumin	–	–	–0.754	< 0.001[a]	–0.271	0.03[a]
Hb	0.395	0.002[a]	–0.435	0.001[a]	–0.629	< 0.001[a]
GA	–	–	–	–	0.224	0.08

Abbreviations: GA, glycated albumin; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c.
[a]$p < 0.05$ is statistically significant.

Table 4 Correlation of HbA1c and GA with fasting plasma glucose

Parameter	GA		HbA1c	
	r-Value	*p*-Value	*r*-Value	*p*-Value
FPG	0.122	0.349	0.415	0.001[a]

Abbreviations: FPG, fasting plasma glucose; GA, glycated albumin; HbA1c, glycated hemoglobin A1c.
[a]$p < 0.05$ is statistically significant.

blood glucose measurement was also accepted for diabetes screening and diagnosis.[10,11]

Many previous studies have shown that various factors affect the HbA1c levels; for example, the age and lifespan of erythrocytes; intracellular glucose in erythrocytes; conditions like anemia, splenomegaly, and pregnancy; ethnicity and gender; estimation methods; antiglycation drugs such as aspirin; and iron-containing diet and supplements.[12] In the presence of comorbid conditions such as IDA, which is most prevalent in India, an elevation of HbA1c has been observed.[3,4] Studies done in nondiabetic subjects with IDA have reported higher HbA1c values.[13,14] The earliest study to investigate the effects of IDA on HbA1c levels was conducted by Brooks et al,[15] who assessed HbA1c levels in 35 nondiabetic patients having IDA both before and after treatment with iron. They observed that HbA1c levels were significantly higher in IDA patients. However, in their study, following treatment with iron supplementation and with improvement in Hb levels, a decrease in HbA1c levels was observed. Other studies have also evaluated HbA1c levels in nondiabetic anemic patients before and after treatment, with oral iron replacement therapy for anemia with period of treatment ranging from 9 to 20 weeks.[9,16–18] These studies reported higher HbA1c levels in iron deficiency, which showed a significant fall in HbA1c levels after treatment with iron replacement. The common condition of IDA can lead to rise in HbA1c levels of up to 2% that can be reversed by iron treatment.[9,15,19,20] It has been suggested that IDA by itself does not affect or influence the glycemic status, but the decrease in Hb in anemia may give rise to apparently higher HbA1c. It was proposed that, in iron deficiency, the quaternary structure of the Hb molecule was altered, and that glycation of the globin chain occurred more readily in the relative absence of iron. The hypothesis was that the formation of HbA1c is an irreversible process and hence, the concentration of HbA1c in one erythrocyte will increase linearly with the cell's age.[21] If iron deficiency has persisted for a long time, the red blood cell production rate would fall, leading not only to anemia but also to a higher-than-normal average age of circulating erythrocytes and therefore increased HbA1c levels. In patients with normal blood glucose levels, but with very young red blood cells, as would be found after treatment of IDA, HbA1c concentration was reduced. Any condition that prolongs the life of the erythrocyte or is associated with decreased red blood cell turnover exposes the cell to glucose for a longer time, resulting in higher HbA1c levels. Similarly, the present study found significantly higher HbA1c levels in nondiabetic subjects with IDA compared to normal healthy controls (►**Table 1**). The lowered Hb levels were associated with elevated HbA1c levels in the present study (►**Table 3**), reinforcing the fact that in IDA a false elevation in HbA1c levels is present.

With regard to evaluating GA as a marker of glycemic status, albumin levels were also measured. Though the albumin levels were within the reference range (3.5–5.0 g/dL) in both groups, the albumin levels in IDA were significantly lower when compared to controls (►**Table 1**). Correlation analysis done to evaluate the association of iron indices of IDA with albumin levels found serum albumin to have significant positive associations with serum transferrin saturation, iron, ferritin levels (►**Table 2**), and Hb (►**Table 3**) indicating that IDA is associated with lowered albumin levels. The association of iron indices with glycated proteins revealed significant positive association of iron, transferrin saturation, ferritin, and Hb with GA and HbA1c (►**Tables 2** and **3**). Plasma albumin level has been shown to be negatively associated with HbA1c in a large cohort of diabetic subjects.[22–24] Similarly, we found albumin to have negative association with both GA and HbA1c (►**Table 3**). There are numerous potential effectors on GA measurements such as liver cirrhosis, emaciation, thyroid disorders, use of glucocorticoids, Cushing's syndrome, nonalcoholic fatty liver disease, hyperuricemia, hypertriglyceridemia, obesity, smoking, and nephrotic syndrome. It is suggested that GA is an inaccurate marker in diseases affecting albumin metabolism, as low GA values were observed in patients with increased albumin metabolism such as in hyperthyroidism and nephrotic syndrome.[6,25,26] Conversely, patients with decreased albumin metabolism such as that observed with low thyroid function or liver cirrhosis have higher GA values. Studies suggest that higher serum albumin levels may decrease HbA1c levels and that lower serum albumin levels may raise HbA1c levels.[22] It was speculated that this could be due to higher albumin levels competing with

Hb to get excessively glycated.[23] Furthermore, it has been demonstrated in vitro that albumin can protect glycation of other less abundant proteins such as insulin and apomyoglobin by the mere abundance of plasma albumin levels that competitively inhibit the glycation of the other proteins.[27] Additionally, low albumin levels were associated with increased plasma protein glycation including albumin, fibrinogen, apolipoproteins, and haptoglobin. It was hence suggested that GA should be used cautiously in the above conditions.[25] Similarly, in the present study, both albumin and Hb have significant negative association with GA and HbA1c levels (►**Table 3**).

Studies showed that HbA1c level correlates with average plasma glucose and the progression of diabetes complication.[28,29] Similarly, in the present study, a significant positive correlation between HbA1c and FPG (►**Table 4**) was observed. On the other hand, no significant correlation between GA and FPG was observed (►**Table 4**). However, it may be prudent to observe that the association between GA and FPG is positive though not significant, which may be due to the small sample size of the present study. Hence, it is proposed that studies with larger sample size may be required to study the significance of association between GA and FPG. The association of both glycated proteins with each other revealed no significant correlation between HbA1c and GA (►**Table 4**). Further, we would like to draw attention to certain observations in the present study, with regard to the fact that though subjects in both groups were nondiabetic with FPG values within the reference range (70–110 mg/dL), in IDA the FPG was significantly higher compared to controls. Similarly, the albumin levels were within the reference range (3.5–5.0 g/dL) in both groups, but the albumin levels in IDA were significantly lower when compared to controls (►**Table 1**). These findings indicate that given the function of albumin to prevent glycation of proteins, even a subtle lowering of albumin levels can bring about glycation of proteins including albumin leading to increased GA and also maybe HbA1c. The albumin had significant positive association with Hb. Hence, it can be proposed that IDA is associated with lowered albumin levels. Low serum albumin is considered as an indicator of nutritional status, as a negative acute phase protein that is found to be decreased in inflammatory conditions, and hence albumin is considered as a component of malnutrition–inflammation complex.[30] Hence, IDA and low albumin status can coexist in the scenario of nutritional disorders. This interaction between anemia and albumin is supported in the present study as a positive correlation of Hb with albumin levels.

In diabetic patients, measured GA values can be three to four times higher than in nondiabetic individuals.[29] However, GA, a proposed alternative index of glycemic control, is also observed to have its own confounding factors such as effect of changes in circulating albumin levels as observed in this study. While the various potential effects on GA measurements need to be considered when evaluating GA levels in patients, there is currently not enough information available to systematically correct GA measurements.

This study is limited by the sample size and the results need to be validated by larger studies. The study was undertaken to observe solely the effect of anemia on GA levels as IDA is prevalent in Indian population.

Hence, from this study findings we would like to propose that when requesting for a laboratory panel having HbA1c and GA, it is very essential to have Hb and albumin measurements, to confirm that the changes in HbA1c and GA are reflective of the glycation status and are not due to changes in Hb and albumin levels. Due to the changes in GA being associated with anemia, as was observed in this study, the GA results should be given with a notation indicating that the GA may be unreliable in certain conditions and not be reflective of the patient's true level of average glycemia.

These approaches serve to avoid potentially inappropriate treatment intensification and hence minimize the risk for hypoglycemia in a diabetic subject.

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Conflict of Interest
None declared.

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