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Impact of iron deficiency anemia on HbA1c level in non-diabetic children

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Abstract

Background and objective: HbA1c has been endorsed by the American Diabetes Association and World Health Organization to diagnose and monitor diabetes mellitus. Its value is directly proportional to the blood glucose level. However, besides the blood glucose level, other factors like iron deficiency anemia can affect HbA1c level. We conducted this study to reveal the impact of iron deficiency anemia on HbA1c level and to assess whether HbA1c result changes after the correction of iron deficiency anemia.

Methods: Twenty five non-diabetic children who were confirmed to have iron deficiency anemia were enrolled. HbA1c, hemoglobin, serum iron, and ferritin were measured and compared at baseline and post-correction of iron deficiency anemia with a three-month age-appropriate dose of iron therapy. The baseline results were compared with 25 age- and sex-matched normal controls.

Results: Children with iron deficiency anemia had significantly higher HbA1c level (6.144±0.6312, *P* <0.001) than the control group (5.032±0.5558, *P* <0.001). After three months of treatment of iron deficiency anemia, HbA1c significantly dropped (from 6.144±0.6312, *P* <0.001 to 5.604±0.51, *P* <0.001).

Conclusion: This study concluded that HbA1c is inversely proportional to iron deficiency anemia in non-diabetic children, and treatment of iron deficiency anemia led to a drop in HbA1c level. Due to this false elevation of HbA1c by iron deficiency anemia, iron deficiency anemia should be considered and excluded before making the diagnosis or deciding on any therapeutic change in diabetic children.

Keywords: Iron deficiency anemia; HbA1c; Non-diabetic children.

Introduction

HbA1c or glycated hemoglobin is formed by the attachment of glucose to the hemoglobin inside erythrocytes. HbA1c test measures the amount of blood glucose attached to hemoglobin in red blood cells over the past three months related to the lifespan of red blood cells, which is about 120 days.[1,2] HbA1c is directly proportional to good glycemic control. One of the primary goals in the management of diabetic patients is to have good glycemic control to decrease the potentiality of diabetes-related complications.[3,4] Since 2010, both American Diabetes Association and World Health Organization have endorsed the HbA1c test as a diagnostic tool for diabetes mellitus. Levels below 5.7% are normal, values of 5.7%-6.5% are suggestive of pre-diabetes, and any results equal to or above 6.5% establish the diagnosis of diabetes mellitus.[5-7] However, it is not only the glucose level that affects the HbA1c test. It will be influenced by hemolytic anemia, hemoglobinopathies, acute and chronic blood loss, and uremia. Furthermore, vitamin B12, folate, and iron deficiency anemia (IDA) have also been shown to alter HbA1c level.[8-14]

Iron deficiency is the commonest nutritional deficiency worldwide and is a major public health issue globally.[15] According to the World Health Organization, IDA affects about 30% of the global population and is

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more prevalent among children in developing countries.[16] The most common type of anemia in children is microcytic anemia due to iron deficiency.[17] Hemoglobin values two standard deviations below the mean for age and sex are regarded as anemia. The cutoff level of hemoglobin to decide on having anemia for children aged 6-59 months is 11 g/dl, for 5-11 years is 11.5 g/dl, and it is 12 g/dl for 12-14 years.[18-20] IDA decelerates erythrocyte turnover leading to increased mean survival of erythrocytes which affects glycation of hemoglobin and thereby might alter HbA1c level.[13] There is no consensus on how IDA affects HbA1c value. Studies done by Brooks et al. and Sluiter et al. found out an elevation of HbA1c level in IDA. On the other hand, Heyningen et al. and Hansen et al. revealed that IDA exerts no impact on HbA1c level.[8-14] Furthermore, a study by Nitin Sinha, et al. reported that HbA1c level increased after treatment of IDA with iron therapy.[10]

The results from these studies are inconsistent about the relation between IDA and HbA1c level. Therefore, we conducted this study to determine the influence of IDA on the HbA1c level. This study aimed to measure HbA1c level in non-diabetic children with IDA, assess the effect of IDA on HbA1c level, and see whether HbA1c level is altered after correcting IDA.

Methods

This non-randomized controlled trial (quasi-experimental) study has been carried out at Raparin Pediatric Hospital and Nanakaly hospital for hematological and oncological diseases in Erbil city, Kurdistan Region, Iraq, over six months from November 1, 2019, to May 1, 2020. The data involved in this study were taken from two groups. Group A (study group) consisted of 25 children who had IDA and group B (control group), who were 25 children but had no IDA. Children from group B were matched for the same age and sex with group A. Inclusion criterion for the study group was any non-diabetic children below the age of 18 years who had IDA. Children who had a history of diabetes mellitus or had fasting blood glucose >100mg/dl even in the absence of a history of established diabetes mellitus were excluded from this study. Other exclusion criteria were anemia other than IDA, those with acute febrile illness, and children who had any chronic illness. Participants from both groups, after fulfilling the inclusion criteria, were enrolled in the study. All of them were subjected to a full history taking and thorough physical examination. The following investigations: complete blood count to measure hemoglobin (gm/dl), mean corpuscular volume (80-100 fl) and mean corpuscular hemoglobin (25.4-36.4 pg/cell),[21] serum ferritin (12-300ng/mL), serum iron (60-170 mcg/dl),[22] and HbA1c level had been done for group A both at baseline and three months after treatment of IDA with weight appropriate dose of iron therapy at a dose of 3-6 mg/kg of elemental iron for three months duration.[16] The same investigations were done for the control group once at baseline. The baseline results of HbA1c level in IDA group (group A) were compared with that of group B. Likewise, the baseline and at three months (post-correction of IDA) HbA1c level results of group A were compared with each other to observe any potential change in HbA1c level after IDA had been corrected.

Laboratory tests

Fasting blood glucose level was checked using (Accu-Check® Active Model: GU, Ser. No. GU03560779 Roche Germany) glucometer. Complete blood count was performed with Medonic M-series (Boule Medical AB, Stockholm, Sweden). Serum ferritin and serum iron were determined by COBAS INTEGRA 400/800 Chemistry analyzer. HbA1c value was measured by Gesan 400 device (Gesan production S.r.1. Campobello di Mazara, Italy). All the investigations were done with the same devices using the same methods throughout the study.

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Ethical consideration

The ethical approval of this study was granted by the Research Ethics Committee of the Kurdistan Board of Medical Specialties before conducting the study. Informed consent (both verbal and written) was obtained from parents of enrolled children.

Data analysis

The data were recorded on a specially designed questionnaire, collected and entered in the computer via Microsoft Excel worksheet (Excel 2010) and then analyzed using the statistical package for the social sciences, version 24 (SPSS, IBM Company, Chicago, USA). Pearson correlation coefficient (*r*) was calculated to assess the correlation between two numerical variables. Paired student *t*-test was applied to compare variables among the study group before and after treatment. The independent samples *t*-test was used to compare variables between study and comparison groups. *A P* value of <0.05 was considered statistically significant.

Results

A total of 50 children were enrolled in the current study. They were divided equally into two groups -case and control - each of 25 children. The two groups were matched for gender (14 males and 11 females) and age (mean ± SD of 2.104±0.95 years), 60% of the children were from urban settings, and 40% were from rural areas.

The findings from Table 1 illustrate a statistically significant difference in all measures between case and control groups. At the start of the study, the average baseline readings, including Hb, MCH, MCV, serum iron, and ferritin, were higher among the control group in comparison to cases, except for HbA1c, which was lower in the control group compared to the study group participants. *T*-test was performed to compare the averages of the two groups, and *P* values were less than 0.05.

Table 1 Comparison between case and control groups regarding hematological indices

Variables	Study group	N	Mean	(±SD)	*P* value
Hb baseline	Group A	25	9.47	(±1.05)	<0.001
	Group B	25	12.56	(±0.84)	
MCV baseline	Group A	25	60.44	(±4.71)	<0.001
	Group B	25	85.00	(±6.37)	
MCH baseline	Group A	25	19.40	(±2.55)	<0.001
	Group B	25	28.00	(±1.65)	
Serum iron baseline	Group A	25	29.84	(±10.15)	<0.001
	Group B	25	82.80	(±17.45)	
Serum ferritin baseline	Group A	25	10.04	(±2.50)	<0.001
	Group B	25	140.72	(±81.26)	
HbA1c baseline	Group A	25	6.14	(±0.63)	<0.001
	Group B	25	5.03	(±0.55)	

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The results of Table 2 reveal a significant statistical difference in hematological measures of cases before and after receiving the treatment. Generally, all hematological indices increased after three months of receiving treatment for IDA. The only measure that decreased after treatment was HbA1c. All these differences were statistically significant. The mean Hb at the start was 9.47 gm/dl, which increased to 12.72 gm/dl after therapy. The MCV at baseline was 60.44fl, then became higher after three months to reach 80.44fl. Similarly, MCH rose from 19.40pg/cell to 26.88pg/cell upon completion of therapy. The serum iron also increased dramatically from 29.84mcg/dl to 82.00mcg/dl. The serum ferritin at the baseline was 10.04ng/mL, which also increased to a great extent to reach 98.76ng/mL. The only measurement that decreased was HbA1c; it was 6.14% originally, then dropped to 5.60%. Paired *t*-test was done to compare the average readings of the two occasions, and in all conditions, the *P* value was <0.001.

As depicted in Figure 1, there was a significant inverse correlation between HbA1c reading and serum ferritin level (r: -0.494 and *P* <0.001), with an increase in serum ferritin level, HbA1c dropped.

Table 2 Difference in hematological measures before and after treatment

Variables	N	Mean	(±SD)	*P* value
Hb baseline	25	9.47	(±1.05)	<0.001
Hb 3 months	25	12.72	(±0.87)	
MCV baseline	25	60.44	(±4.71)	<0.001
MCV 3 months	25	80.44	(±6.90)	
MCH baseline	25	19.40	(±2.55)	<0.001
MCH 3 months	25	26.88	(±1.92)	
S. Iron baseline	25	29.84	(±10.15)	<0.001
S. Iron 3 months	25	82.00	(±14.56)	
S. Ferritin baseline	25	10.04	(±2.51)	<0.001
S. Ferritin 3 months	25	98.76	(±62.51)	
HbA1c baseline	25	6.14	(±0.63)	<0.001
HbA1c 3 months	25	5.60	(±0.51)	

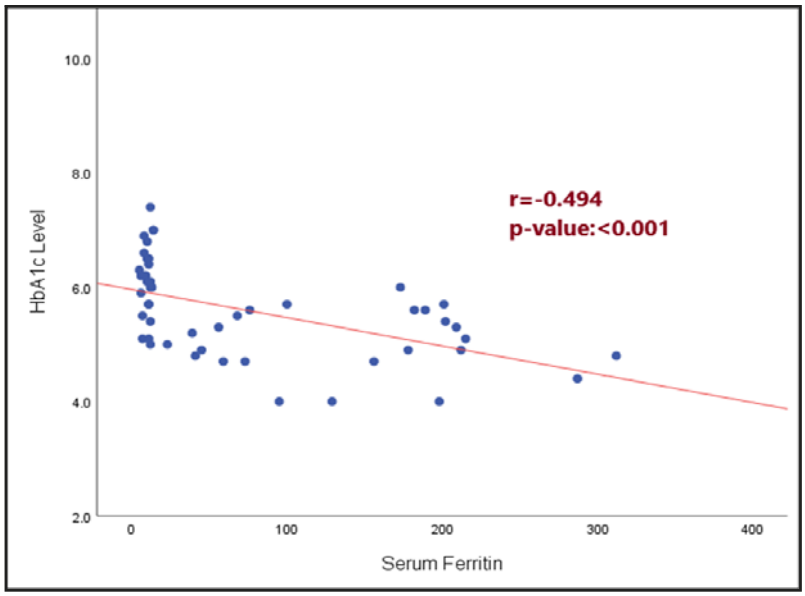

Figure 1 Correlation between HbA1c level and serum ferritin level

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Discussion

HbA1c test has been accepted as a screening tool to diagnose diabetes mellitus and as a marker of glycemic control as it is affected by blood glucose level.[12] However, besides blood glucose, various other factors like physiological, genetic, and hematological factors may alter HbA1c value.[23] Anemia including IDA may falsely increase or decrease HbA1c value depending on the type of anemia. Multiple studies have been done to know the effect of IDA on the HbA1c level. The results were contradictory.

In this study, we observed that HbA1c levels were significantly higher in non-diabetic children who had IDA compared to HbA1c levels of age- and sex-matched children who were free from IDA (P <0.001). We treated the IDA group with an age-appropriate dose of iron therapy for three months. Then we compared pre- and post-IDA HbA1c measurements among the IDA group. We noticed that with the increase of hemoglobin and serum ferritin, the HbA1c level significantly dropped (P <0.001).

The results of our study are similar to the results of many other studies like Christy et al. and Rajagopal et al. that revealed HbA1c levels were higher among the IDA group, and the level decreased significantly after treatment and correction of IDA.[11,14] This study results are also consistent with studies done by Bhardwaj et al. and Hong et al.,[10,13] who reported an inverse correlation between HbA1c level and IDA and a decline in HbaA1c level following correction of anemia due to iron deficiency. The exact mechanism of how IDA exerts its effect on HbA1c remains unclear. It has been speculated that the quaternary structure of the Hb molecule may be changed, and glycation of beta-globin chain occurs more easily in the relative absence of iron. Another reason that has been proposed is that glycation of Hb is an irreversible process, and therefore, the concentration of HbA1 in one erythrocyte will increase linearly with the cell's age.[10]

The results of some studies contradict this study's results. Solomon et al. found that the HbA1c result is significantly lower in IDA patients than non-IDA diabetic patients.[12] In contrast to what we observed, Sinha et al. concluded that treatment and correction of IDA led to an increase in HbA1c level. They suggested that lower HbA1c is due to the severity of anemia in the study participants.[24]

Limitations to this study included enrolling a small number of children, and including only two hospitals in Erbil city. Studies involving larger populations of children and in multiple centers needed to be conducted to better reveal the influence of IDA on HbA1c modulation.

Conclusion

In this study, we concluded that HbA1c is inversely proportional to IDA in non-diabetic children, and treatment of IDA led to a drop in HbA1c level. The false elevation of HbA1c level in IDA children independent of blood glucose level should make physicians and health care providers not depend solely on HbA1c value both for diagnosis or monitoring of diabetic patients. Hence, IDA should be considered and excluded before making the diagnosis or deciding on any therapeutic change in diabetic children.

Funding

None.

Competing interests

None declared.

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