Ministry Of Higher Education And Scientific Research-Diyala University College of Medicine

Iron deficiencyAnemia in patient with type 1diabetes

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Done by

Zainab Waleed Hassan

Supervised by

Dr.Hella Othman Habeeb

قال تعالى: بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ)، «سورة المجادلة: الآية 11».

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Abstract

Aim: The aim of this study is to determine how common iron deficiency anemia among children with type 1 diabetes for early adequate treatment aiming for improving their quality of life.

Objectives: To find out a relationship between hemoglobin concentration and HbA1c and any correlation between HbA1c, serum ferritin and serum level. To detect a correlation between serum ferritin and duration of diabetes.

Methods: This study is an observational cross sectional study, carried out on 100 children aged from 3 to 17 years old, already diagnosed

by type 1 diabetes, according to diagnostic criteria of American Diabetes Association. Hb A1c ≥ 6.5% Detailed medical history

and full clinical examination were done , Investigations included complete blood picture, Hba1c and serum ferritin.

Results: Prevalence of iron deficiency anemia among type 1 diabetic children was 52%. The mean of HbA1c is 11.25% in anemic

diabetic patients while the mean is 10.885% in non anemic diabetic patients and there is a significant difference between them.

There is a statistically significant correlation between HbA1c and Hb and serum ferritin levels in type 1 diabetic patients.

There was a weak positive correlation between duration of diabetes and mean Hb levels and serum ferritin levels.

Conclusion: The prevalence of iron deficiency anemia was high among type 1 diabetic children, and value of HbA1c was higher among severe iron deficiency anemic patients than moderately iron deficiency anemic patients.

Introduction

The term diabetes mellitus DM is a complex metabolic disorder characterized by persistent hyperglycemia that occurs because of deficiency in insulin secretion, insulin activity, or both. That prompts variations from the normal blood glucose with profound impacts on carbohydrate metabolism It is a rapidly developing non-communicable disease all over the world and is one of the most well-known endocrine disease in children around the world (1).

Long-term diabetic complications are classified into microvascular (microangiopathy of micro vessels) and macrovascular (macroangiopathy of macro vessels). Microvascular complications include the eyes (retinopathy) resulting in visual impairment or even loss, the kidneys leading to Diabetic Kidney Disease and nerves (neuropathy) leading to diabetic foot a consequent of peripheral arterial disease with extreme ischemia with potential amputation. Macrovascular complications include diabetic cardiomyopathy in addition to increased risk of infections that may be complicated by , for example, respiratory failure, strok and periphreral arterial disease.

Diabetes does not directly cause anemia, but certain complications and conditions related to diabetes can contribute to it as nephropathy and neuropathy (2). Diabetes frequently leads to nephropathy and this will cause anemia as the kidneys secret a hormone called erythropoietin (EPO), which stimulates the bone marrow to generate red blood cells. Diabetic kidneys don't secret sufficient EPO to keep up with body needs (3).

Autonomic neuropathy in diabetic patients hinders the body's capacity to legitimately stimulate the kidneys to create more erythropoietin in reaction to anemia(4).

Iron deficiency is characterized by decreased red blood cell (RBC) mass transporting oxygen and carbon dioxide which disables the body's capacity for gas exchange (5). Among the conceivable components that decline kidney function, is renal ischemia caused by a decreased oxygen supply due to decreased levels of Hb and diabetic

cardiomyopathy (4). Diabetic nephropathy is rare among young type 1 diabetic children.

Iron deficiency anemia is the foremost common type and is effectively treatable by dietary changes and oral or parentral iron and other supplements. It is an important public health problem in the Eastern Mediterranean countries. It is estimated that more than one third of the population in Middle East have iron-deficiency anemia. Pregnant ladies and young children are at utmost risk; approximately 50% of pregnant ladies and 67.4% of children under-5 and 15.5% school adolescents have iron deficiency anemia. Iron plays an essential role in hemoglobin (Hb) synthesis, electron transport for cellular respiration, DNA synthesis, and other vital enzymatic reactions (6).

As iron deficiency anemia in patients with type 1 diabetes leads to fatigue and impairs cognitive function as well as the ability to work, thus influencing the psychosocial development of children with type 1 diabetes. So early detection and treatment of it improves quality of life among children (7). The use of HbA1c for diagnosing and controlling glycemia in type 1diabetic children is controversial and has pitfalls spectacularly in low-diagnostic threshold. The relationship between anemia and HbA1c is complicated and further studies are needed to resolve that issue.

Addi- tionally, adequate interpretation of the HbA1c measurement

that is routinely performed during diabetes control visits, requires also to know the patient's serum iron concentration, because the presence of iron deficiency anemia correlates with higher HbA1c values (8). It is interesting that even though the value of a performed blood count is well known as well as the multiplicity of information it gives, there are no recommendations whether and when it should be carried out in T1D patients—neither in the guidelines published by Diabetes Poland (2018) nor those of the International Society for Pediatric and Adolescent Diabetes (9,10). Until present, there have been a few publications assessing the blood count, iron metabolism parameters, and vitamin B12 levels in chil- dren with T1D, which most often use other T1D individuals as a control group. To our knowledge comparisons to healthy peers are lacking.

Aim: The aim of this study is to determine how common iron deficiency anemia among children with type 1 diabetes for early adequate treatment aiming for improving their quality of life

Patient and method

This is cross-sectional study conducted in Al-Batool teaching hospital for pediatrics and gynecology. A sample of 100 children was enrolled in this study with age ranged from 3 years to 17years. We collected the sample by filling a prepared written questionnaire in the period from october 2022 to December 2022.it contained questions name ,age ,gender,height,weight,BMI,family history of DM,duration of type 1DM,age at type 1 DM diagnosis,we take the blood sample from children to measure complete blood picture,Hba1c and serum ferritin, measure random blood sugar .

Results

Demographic data

Table 1 comparison between anemic and non-anemic diabetic children according to gender, residency and age.it showed that there were 54.2% males who were non-anemic compared to 48.1% males who were anemic while there were 45.8% females non anemic and 51.9% of females were anemic with no significant difference between them.

It shows that there were 91.7% urban diabetic children were non-anemic and 73.1% were anemic while there were 8.3% rural diabetic children were found non-anemic and 26.9% were anemic with no significant deference between them. This subclassification was made due to differences in sociodemographic conditions between urban and rural children.

It was found that the mean age in non-anemic patents was 9.96 while mean age in anemic patients was 9.88, with no significant deference between them.

Iron deficiency anemia was more prevalent among age 7-14 years old diabetic children as it represents 42.3%

Table 1: demographic baseline of the diabetic under the study

Title		Anemic		Non anemic		P value
		No	%	No	%	
Gender	Male	25	48.1%	26	54.2%	0.556¥
	Female	27	51.9%	22	45.8%	
Residence	Urban	38	73.1%	44	91.7%	0.009¥
	Rural	14	26.9%	4	8.3%	
Age (Years)	2-6	9	17.3%	3	6.3%	0.0038¥
	7-10	21	40.4%	31	64.6%	
	11-14	22	42.3%	14	29.2%	
	15-18					
		Mean	SD	Mean	SD	0.722€
		9.88	3.335	9.96	1.948	

Table 2 shows that the prevalence of iron deficiency anemia among type 1 diabetic children was 52%

Table 2: The prevalence of iron deficiency anemia

Title	Anemic(n=52)		Non anemic (n=48)	
	No	%	No	%
Total prevalence	52	52%	48	48%

Table 3 shows that the mean of HBA1c is 10.885% in non-anemic diabetic patients while the mean is 11.25% in anemic diabetic patients and there is no significant difference between them.

Table 3: Difference of HBA1c regarding presence of anemia in the sample under the study.

Title	Anemic(n=52)		Non anemic (n=48)		P value
	Mean	SD	mean	SD	
HBA1C%	11.25	2.04	10.885	3.194	0.115€

Table 4 shows that there is no significient correlation between HBA1C and serum ferritin.

Table 4: correlation between HbA1c,Hb and serum ferritin.

	HbA1c	
	Pearson correlation coeffective	Pvalue
HB(g\dl)	0.998	0.000
Serum ferritin(go\dl)	0.018	o.859

Table 5 shows that there was a weak positive correlation between duration of diabetes and Hb, and serum ferritin levels p ≤0.567 and 0.485respectively.

	Duration of diabetes	
	Pearson correlation coeffective	P value
HB(g\d)	0.058	0.567
Serum ferritin (go\dl)	0.071	0.485

Discussion

This study was carried out to determine the prevalence of iron deficiency anemia in children with type 1 diabetes as it is one of the most common and preventable disease aiming to improve their quality of life.

As shown in table 1, iron deficiency anemia among type 1 diabetic children was more prominent among age group 11-14 years 42.3% the mean of age in iron deficient diabetic patients was 9.88years and that 51.9% of anemic patients were female while 48.1% were male this probably may be due to the menstruation in pubertal females.further more,inadequate iron intake is the most common causes of IDA in children especially in rural areas where poor socioeconomic condition ,parasitic infection ,ignorance and neglect of dietary requirements.

Tarim and his colleges studied the effects of iron deficiency anemia ,on hemoglobin A1c in type 1diabetic children in Uludağ University Bursa, Turkey that study included 37 patients with type 1 DM, 11 non-diabetic subjects with iron deficiency anemia and 20 completely healthy subjects and found that the prevalence of iron deficiency among diabetics was 29.7% this prevalence was lower than our study as it was done in Turkey with different study population and use different classification to the subject included in the study (11). Interpretation of increased HbA1c in this study was made in the context of decreased serum iron concentration which was markedly decreased in type 1 diabetic children.

Current study has shown that the mean of HbA1c in the anemic

patients was 7.81% which was statistically significant compared to non-anemic patients which was 7.4% and that there was a negative correlation between hemoglobin, and both of serum iron and serum ferritin. However, serum ferritin may increase due to inflammatory disease and other stimuli and its elevation does not exclude iron deficiency .so it has limited diagnosis utility in this setting.

It was recommended to test hs-CRP in inflammatory bowel disease to confirm the diagnosis of iron deficiency anemia. However, no consensus for adding hs-CRP in the diagnosis of IDA in the presence of increased serum ferritin. Moreover, hs-CRP is not included in all available guidelines to measure it in case of iron deficiency anemia with inflammatory diseases. That meant that the presence of iron deficiency anemia led to higher levels of HbA1c in diabetic children. Iron deficiency accelerates glycation of hemoglobin by changing the its molecular structure through increased peroxidation in diabetics. This may be a consequence of chronic low-grade inflammation in diabetics. Furthermore, it increases the life span of red blood cells. Patients with type 1 diabetes with IDA have a restricted availability of iron that is necessary for erythropoiesis due to increased hepcidin expression (12).

In a systematic review that included 47 students with iron deficiency anemia it was found that the mean HbA1c level decreased significantly from 6.15% ± 0.62 to 5.25% ± 0.45 after treatment with oral iron supplement for 20 weeks These results demonstrated

,that iron deficiency is associated with higher levels of HbA1C which could cause problems in the interpretation and diagnosis of uncontrolled diabetes mellitus in iron deficient anemic patients(13).

Madhu S., et al. studied the effect of iron deficiency anemia and iron supplementation on HbA1c levels for diagnosis of prediabetes and diabetes mellitus in Asian Indians, the subjects were clustered in 2 groups, iron deficient anemia (IDA) and healthy controls (HC) and found that the mean levels of RBC Indices and iron study parameters were significantly higher ($p < 0.001$) in IDA group as compared to HC and the mean glycated hemoglobin % levels in the pre-intervention arm in the IDA subjects were significantly higher by 0.66% ($p < 0.001$) as compared to the healthy controls (14).

Intra., et al. studied the effects of iron deficiency anemia on HbA1c values among subjects without diabetes in University of Milano-Bicocca, Desio, Italy. Results showed that non-diabetic individuals with iron deficiency anemia presented significantly higher HbA1c measurements when compared to those obtained in non-anemic subjects (15). Solomon., et al. studied the effect of iron deficiency anemia on HbA1c in diabetic patients at Tikor Anbessa specialized teaching hospital, Addis Ababa, Ethiopia among a total of 174 diabetic patients (87 with IDA and 87 without IDA) participated in the study and they found that HbA1c was significantly lower in IDA group (6.18 ± 1.57) compared to the control group.

This difference might be due to different population (adults) and the different working definition by investigators who used different methods in detecting the level of HbA1c (by COBAS C 111 analyzer as well as serum ferritin (16). This study found a statistically significance correlation between duration of diabetes and Hb while there was no statistically significant correlation between duration ,.of diabetes, serum iron and serum ferritin respectively. Thomas et al. studied the prevalence of anemia as defined by decreased Hb concentration and reported 14% in those with 20 years duration of diabetes (17) .

A study done by Ewa , reported that some significant inverse correlation in the MCH concentration in comparison with the children who have type 1 diabetes for more than 1 year. It has been shown that, when compared with those who had the disease for to 3 years (FMD), those who have it for 4 to 6 years (SMD), and 1 those who have it for more than 6 years (LD), more newly diagnosed type 1 diabetes (ND) children are characterized by the coexistence of at least 3 reduced values of the morphological blood parameters ,associated with iron-deficiency anemia (26%, 17%, 7% and 3%, respectively). At the same time, it has been found that the mean iron concentration in the blood serum of the ND group is significantly lower than that SMDand LD group (18).

Sinha., et al. reported low value of Hb A1c level in patients with severe irondeficiency anemia so it may indicate that iron deficiency

per se may elevate HbA1c level irrespective of the presence of anemia (19).

Conclusion

Iron-deficiency anemia is positively associated with increased HbA1c in type 1 diabetic children. So, the interpretation of HbA1c value should be interpreted with caution in newly diagnosed type 1 diabetic children with IDA and concomitant low diagnostic threshold of HbA1c. Furthermore, IDA should be treated first for proper use of HbA1c in monitoring glucose control in type 1 diabetic children.

references

1.Punthakee Z., et al. "Definition, classification and diagnosis of . diabetes, prediabetes and metabolic syndrome". Canadian Journal of Diabetes 42 (2018): S10-S15.

2.Thomas MC., et al. "Screening for chronic kidney disease in patients with diabetes: are we missing the point?" Nature Clinical Practice Nephrology 4.1 (2018): 2-3.

3.Brugnara C and Eckardt KU. "Hematologic aspects of kidney disease". In: Taal MW, ed. Brenner and Rector's The Kidney. 9th ed. Philadelphia: Saunders (2011): 2081-2120.

4.Thomas MC., et al. "Unrecognized anemia in patients with diabetes: a cross-sectional survey". Diabetes Care 26 (2003): 1164Y1169.

5.Liang R and Ghaffari S. "Advances in understanding the . mechanisms of erythropoiesis in homeostasis and disease". British Journal of Haematology (2016).

. Word Health OrganizationWorldwide prevalence of anemia 1993-620

7.Halliwell B and Gutteridge JM. Free radicals in biology and

medicine: Oxford University Press, USA (2015).

8.A. L. Christy, P. A. Manjrekar, R. P. Babu, A. Hegde, and M. S. Rukmini, "Influence of iron deficiency anemia on hemoglobin A1c levels in diabetic individuals with controlled plasma glucose levels," Iranian Biomedical Journal, vol. 18, no. 2, pp. 88–93, 2014.

9.M. E. Craig, C. Jefferies, D. Dabelea, N. Balde, A. Seth, and K. C. Donaghue, "ISPAD clinical practice consensus guidelines 2014. Definition, epidemiology, and classification of diabetes in children and adolescents," Pediatric Diabetes, vol. 15, no. S20, Supplement 20, pp. 4–17, 2014.

10.Clinical Diabetology, "2018 guidelines on the management of diabetic patients. A position of Diabetes Poland," Clinical Diabetology, vol. 7, no. 1, pp. 1–90, 2018.

11.Guo W., et al. "Increased levels of glycated hemoglobin a1c and. iron deficiency anemia: A review". Medical Science Monitor 25 8378-8371 :(2019)

12.El-Agouza I., et al. "The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: possible consequences for clinical diagnosis". Clinical and Laboratory Haematology 24.5 289-285 :(2002)

13.Madhu SV., et al. "Effect of iron deficiency anemia and iron supplementation on HbA1c levels - Implicationsfor diagnosis of prediabetes and diabetes mellitus in Asian Indians". Clinica Chimica Acta (2016)

14.Intra J., et al. "Glycosylated Hemoglobin in Subjects Affected . by Iron-Deficiency Anemia". Diabetes and Metabolism Journal 42 :(2018).

15.Solomon A., et al. "Effect of iron deficiency anemia on HbA1c ,in diabetic patients at Tikur Anbessa specialized teaching hospital Addis Ababa Ethiopia". BMC Hematology 19.1 (2019): 2.

16.Ewa M., et al. "The Occurrence of Iron-Deficiency Anemia in Children With Type 1 Diabetes". Journal of Investigative Medicine .(2014) 62.6

17.Sinha N., et al. "Effect of iron deficiency anemia on hemoglobin .A1c levels". Annals of Laboratory Medicine 32 (2012): 17-22.

18 .Dignass A., et al. "Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions". International .Journal of Chronic Diseases 2018 (2018): 1-11

19.Bell S., et al. "A genome-wide meta-analysis yields 46 new loci associating with biomarkers of iron homeostasis". Communications Biology 4 (2021): 156 (2021)