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Original Article

Influence of iron deficiency on Hb A1c levels in type 2 diabetic patients

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ABSTRACT

Aims: Hemoglobin A1c (HbA1c) is gold-standard for the assessment of glycemic control in diabetic patients. Previous studies have reported that iron deficiency may elevate A1c concentrations, independent of glycemia. This study aimed to analyze the effect of iron status on HbA1c levels in diabetic patients.
Methods: 661 patients 336 females (228 menopausal and 108 premenopausal) and 325 males (237 age> 50 years and 88 age < 50 years) were recruited.
HbA1c, ferritin, fasting plasma glucose, hemogram and medical history were recorded.
Analysis of variance ANOVA and Pearson's regression were applied.
Results: patients were divided according gender, age, glycemia and iron status (normal, latent iron deficiency LID, iron deficiency anemia IDA).All groups presented increasing HbA1c values in parallel with iron deficiency, subclinical and anemia, but the level of significance was not homogeneous in the different groups.
Controlled premenopausal women HbA1c in normal iron status and IDA groups P = 0.0048, between normal and LID, P = 0.033.
Not controlled premenopausal women Normal group and IDAP < 0.001, normal iron status and LID P = 0.019.
Controlled menopausal women normal group and IDAP < 0.0001, LID and IDA P = 0.01.
Not controlled menopausal women normal group and IDA P = 0.04.
Controlled men over 50 years normal and IDA groups P = 0.002, LID and IDA P = 0.02.
Controlled young men normal group and LID P = 0.03.
Conclusion: This study found a positive correlation between iron deficiency and increased HA1c levels. In diabetic patients with IDA should be interpreted with caution, due to the possibility of spurious increment in HbA1c.

1. Introduction

Hemoglobin A1c (HbA1c) is the gold-standard measure for the assessment of glycemic control in diabetic patients. According to the American Diabetes Association Guidelines published in 2007, HbA1c levels should be maintained below 7.0% (53 mmol/mol) in all patients in order to prevent the development of long term microvascular complications [1], and has recently been recommended for use in the diagnosis of diabetes [2].

Because of the long lifespan of erythrocytes, HbA1c levels reflect average plasma glucose concentration over a long-term period of time (2–3 months). However, HbA1c levels are not affected by blood glucose levels alone. They are also altered in hemolytic anemias [3], hemoglobinopathies [4], acute and chronic blood loss [5,6], pregnancy [7–9], and uremia [10–12]. Variation in the life span of erythrocytes [13], and iron deficiency anemia [14] have also been shown to affect HbA1c levels.

Iron deficiency (ID) is a reduced content of total body iron. Iron deficiency anemia (IDA) occurs when the iron content is insufficient to sustain erythropoiesis and therefore the hemoglobin level falls.

Normal hemoglobin (Hb) level does not exclude ID, because individuals must lose a large amount of body iron during a long period before the hemoglobin falls below the WHO definition of anemia, Hb< 120 g/L for females and Hb< 130 g/L for males [15].

The transition from the normal iron-replete state to the development of IDA entails two sequential processes: depletion of the storage iron compartment (stage I), followed by its exhaustion and the consequent depletion of the functional iron compartment (stage II) [16].

Non-anemic iron deficiency is sometimes termed 'latent iron deficiency' or subclinical iron deficiency. In this stage iron reserves

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Table 1
analytical data of 661 adult patients with type 2 Diabetes Mellitus: 336 females (228 menopausal and 108 premenopausal) and 325 males (237 age> 50 years and 88 age < 50 years). Data are recorded as mean (standard deviation, SD).

	Females >50 years mean (SD)	Females< 50 years	Males >50 years	Males <50 years
Glycemia mmol/L	7.22 (2.85)	6.05 (2.72)	7.6 (3.11)	8.2 (3.3)
HbA1c %	7.0 (1.5)	6.3 (1.3)	7.0 (1.6)	6.7 (1.6)
Hb g/L	134 (9)	130 (11)	145 (15)	148 (12)
MCV fL	91.0 (5.5)	90.0 (5.5)	92.1 (5.4)	93.5 (3.2)
MCH pg	29.9 (2.0)	29.7 (2.1)	30.5 (2.0)	31.8 (1.8)
RDW %	14.3 (1.8)	13.9 (1.5)	14.0 (1.4)	14.2 (1.2)
Ferritin μg/L)	81 (79)	46 (51)	149(116)	138 (96)

Hb, Hemoglobin; MCV, mean cell volume; MCH, mean cell hemoglobin; RDW, red cell distribution width.

are slowly used up and mean cell volume (MCV), mean cell hemoglobin (MCH) and red blood cell count (RBC) count start to decline, but in the initial phase the values can still remain higher than the lower limit of reference intervals. During this stage I, the main laboratory finding is low ferritin level [16].

The present study aimed to assess the effect of iron status (normal with sufficient iron stores, latent iron deficiency or subclinical, IDA) on HbA1c values in type 2 diabetic patients.

2. Methods

The study was conducted according to our Hospital Ethic Commission Guidelines.

Only adults (>18 years) patients with type 2 Diabetes Mellitus were included in the study.

During six months 767 individuals (410 females and 357 males) were referred by Endocrinologists, for routine analysis in our Laboratory.

Clinical data were retrieved from the Laboratory Information System (LIS) and Hospital Information System (HIS): none of the patients had blood transfusions nor were affected of bleeding episodes, nor received iron supplements nor erythropoiesis stimulating agents in the previous 6 months. Patients with macrocytic anemia, MCV > 98 fL were excluded ; acute phase response (APR), defined by CRP > 5.0 mg/L, was also an excluding criteria, because it causes spuriously high ferritin values.

HbA1c was analysed using a Menarini ARKRAY ADAMS™ A1C HA-8180 V analyser; ferritin, fasting plasma glucose (FBG), CRP were analysed in a Roche Hitachi Cobas c70; hemograms were performed on Beckman Coulter LH780 analyzers; CRP > 5.0 mg/L and /or ferritin > 450 μg/L were excluded.

Hb and ferritin defined iron status : females IDA Hb<120 g/L and ferritin < 30 μg/L latent iron deficiency (LID) Hb>120 g/L and ferritin < 30 μg/L ; males IDA Hb< 130 g/L and ferritin < 50 μg/L, LID Hb>130 g/L and ferritin< 50 μg/L.

2.1. Statistical analysis

Statistical software package SPSS (SPSS; Chicago, IL, USA) version 20.0 for windows was applied for statistical analysis of the results.

A contrast of normal distribution, Kolmogorov-Smirnofft test, in each studied parameter was calculated.

The data were presented as mean ± SD. Analysis of variance ANOVA test (Bonferroni method) was applied for multiple comparison of means in the diverse groups. Pearson's coefficient of correlation was calculated to determine the correlation between variables.

3. Results

We categorized the group separately according to gender and age, males, premenopausal women (18–50 years) and menopausal women (age>50 years) and controlled, fasting plasma glucose (FPG) < 7.0 mmol/L, or poorly controlled diabetics (FPG > 7.0 mmol/L).

One hundred and six patients were excluded, 37 of them (9 females and 28 males) because they had APR and other 9 had MVC > 98 fL; sixty females with gestational diabetes were excluded, because they received iron supplements.

The final number were 661 patients336 females (228 menopausal and 108 premenopausal) and325 males (237 age> 50 years and 88 age < 50 years). Table 1 summarizes their analytical data.

Patients are divided in groups, according to FPG (controlled < 7.0 mmol/L or not), iron status (normal, LID, IDA) gender (males, females) and age (18–50 years, >50 years).

Glycemic control was statistically different in those groups; 60% of post menopausal women had FPG < 7.0 mmol/L, and 75% of premenopausal women, while only 52% and 56% of old and young men respectively presented controlled glycemia.

Iron status in male over 50 years and menopausal women was similar, while in young females was significantly different

Table 2
Iron status of661 adult patients with type 2 Diabetes Mellitus : 336 females (228 menopausal and 108 premenopausal) and 325 males (237 age> 50 years and 88 age < 50 years).

	Female>50 years n (%)	Females <50 years n (%)	Males >50 years n (%)	Males <50 years n (%)
Normal Iron status	124(54.4)	45 (41.6)	138 (58.2)	61 (69.3)
LID	50(21.9)	41 (38.1)	39 (16.5)	27 (30.7)
IDA	54 (23.7)	22 (20.3)	60 (25.3)	0 (0)
TOTAL	228 (100)	108 (100)	237 (100)	88 (100)

LID, latent iron deficiency; IDA, Iron deficiency anemia.
Females IDA Hb<120 g/L and ferritin < 30 μg/L; LIDHb>120 g/L and ferritin < 30 μg/L; normal iron status Hb>120 g/L and ferritin >30 μg/L.
Males IDA Hb< 130 g/L and ferritin< 50 μg/L, LID Hb>130 g/L and ferritin< 50 μg/L;normal iron status Hb>130 g/L and ferritin >50 μg/L.