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Original Article

The effect of blood glucose regulation on iron metabolism and hepcidin in uncontrolled type 2 diabetic patients

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Abstract: Type 2 diabetes is a chronic progressive disease. In diabetes, where multiple systems are involved, iron metabolism is also affected. Nevertheless, it is unknown how blood glucose regulation and iron metabolism are effected and whether there are changes in hematologic parameters. The aim of our study was to investigate whether blood glucose regulation during diabetes has an effect on iron metabolism, hemoglobin, and hepcidin levels. Methods: Patients included in this study were aged between 30-70 years, who had previously been diagnosed as having diabetes and were under treatment with antidiabetics, with hemoglobin A1c (HbA1c) level ≥ 7%, hemoglobin level ≥ 13 gr/dL in men and ≥ 12 gr/dL in women. Patients with active infection, chronic kidney failure, liver disease, malignancy, and those using pioglitazone were excluded from the study. Seventy-six patients were enrolled in this study. Complete blood count, fasting blood glucose, HbA1c, C-peptide, C-reactive protein, hepcidin levels, iron, total iron binding capacity, and ferritin levels were measured. Albumin/creatinine ratio in spot urine was checked. Patients followed an appropriate diet program and received intensive medical treatment for 3 months. After 3 months, parameters were repeated and compared with previous values. Findings: Fifty-four patients (mean age 54.7 ± 8.3 years; women/men: 30/24) were enrolled in the study after 3 months of follow-up. A statistically significant decrease in HbA1c was observed (11.0% ± 1.8 vs 7.4 ± 1.2, P < 0.001). Although increased hepcidin levels showed no change (μg/L) (177.1 ± 146.5 vs 185 ± 172.9, p:NS), a significant decrease in ferritin and iron levels was seen (129.6 ± 121 vs 107.0 ± 94.8 ng/mL, P = 0.002, 83.3 ± 28.6 vs 75.3 ± 21.4 μg/L, P = 0.035, respectively). In patients whose body mass indexes were not changed, neutrophil/lymphocyte ratio and urinary albumin/creatinine excretion rate significantly decreased (2.33 ± 1.45 vs 1.93 ± 0.81, P = 0.035, 0.22 ± 0.2 vs 0.02 ± 0.02, P = 0.019, respectively). A significant decrease in hemoglobin levels was observed after 3 months (13.8 ± 1.4 vs 13.4 ± 1.4 g/dL, P < 0.001). This decrease was more prominent in those who progressed to insulin from oral antidiabetics (14.04 ± 1.2 vs 13.3 ± 1.21 g/dL, P < 0.001). It was seen that hepcidin levels increased as HbA1c levels increased. No association between hepcidin levels and development of anemia or hemoglobin values was found. Results: Serum hepcidin and ferritin levels increased in patients with poorly controlled diabetes. Whereas some of the inflammation markers and ferritin level decreased with blood glucose regulation, there was no change in hepcidin levels. No association between hepcidin levels, hemoglobin, and development of anemia was observed. There was a significant decrease in hemoglobin level, especially in those who were started on insulin after oral antidiabetics.

Keywords: Hepcidin, type2 diabetes, anemia, iron metabolism

Introduction

Type 2 diabetes (T2D) is a chronic and progressive disease characterized by disorders in carbohydrate, lipid, and protein metabolisms that result from defects in insulin secretion or insulin action, or both. Although it is accepted that T2D can be a trigger factor for vascular inflammation, it is also suggested that inflammation can lead to T2D.

Iron metabolism in diabetes has been drawing interest. It is known that increased iron load is present in T2D [1, 2]. Several opinions regarding

Table 1. Baseline Characteristics of the Study Group

Age (years)	54.7 ± 8.3
Duration of diabetes (years)	7.8 ± 4.1
Women, n (%)	30 (56.5)
Men, n (%)	24 (43.5)
Smoking ratio, n (%)	20 (37)
Body Mass Index (kg/m^2)	31.8 ± 4.8
Hemoglobin (g/dL)	13.8 ± 1.4
HbA1c (%)	11 ± 1.8

the cause of this increase have been proposed. However, there are no published studies explaining how iron metabolism affects blood sugar control and how it varies after blood sugar is regulated.

Iron metabolism is regulated by hepcidin, a 25-amino-acid synthesized in liver. Under normal circumstances, hepcidin controls the efflux of iron from duodenal enterocytes and macrophages [3]. Under chronic inflammatory conditions such as those observed in T2D, excessive cytokines such as IL-6 have a core function in hepcidin production. IL-6 acts directly on hepatocytes to stimulate hepcidin production [4]. Furthermore, clinical studies have shown higher hepcidin level in patients with diabetes, which correlated with IL-6 and ferritin levels [2, 5, 6]. Whether hepcidin has any influence on blood parameters of diabetes patients with poor blood sugar regulation is not fully known.

The aim of our study was to investigate whether blood sugar regulation has any effect on iron metabolism, hemoglobin, and hepcidin levels in diabetes.

Methods

Patients in our study were aged between 30-70 years, previously diagnosed as having T2D and under treatment with antidiabetics, hemoglobin A1c (HbA1c) level ≥ 7%, and with hemoglobin levels of ≥ 13 gr/dL in men and ≥ 12 gr/dL in women. Patients with active infections, chronic inflammatory disease, chronic kidney failure, liver disease, malignancy, and those using pioglitazone were excluded from the study. None of the patients were on any pharmacologic treatment containing iron and/or received a blood transfusion before the initiation of the study.

Study design

This prospective study was carried out in internal medicine outpatient clinics. Approval was obtained from the Medical Research Ethics Committee of Istanbul Okmeydani Training and Research Hospital. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

Study protocol and treatment

Initial visit: A total of 98 patients were screened. Due to non-accordance with the inclusion and exclusion criteria, only 76 patients were enrolled in this study. BMI was calculated (weight/height^2, kg/m^2). After 12 h of fasting, complete blood count, glucose, HbA1c, c-peptide, crp, hepcidin, iron, iron-binding capacity, and ferritin were analyzed in all patients. Neutrophil/lymphocyte ratio and albumin/creatinine ratio in spot urine was calculated.

The patients were recommended individualized medical nutrition therapy (MNT) and an exercise program. The MNT was prepared by a dietician who is experienced in diabetes nutrition. The patients were advised to receive 30% of their daily energy requirement from fats (< 7% from saturated fats) and 15% to 20% from proteins. Caloric intake regulation was planned to enable patients who were overweight to lose weight at a ratio of 5% in the first 3 months. Life styles, educational levels, and eating habits of the patients were considered in meal planning. Exercise programs were planned by evaluating possible adverse effects and contraindications. Moderate aerobic physical activity at least 3 days a week for 150 minutes in total for the whole week was prescribed. The patients were recommended to do mild resistance exercises for 3 days.

The medical treatments of the patients were determined individually. In general terms, the algorithm of the therapy was a follows: for patients with symptoms of hyperglycemia, random plasma glucose ≥ 300 mg/dL or HbA1c ≥ 10%, one of the insulin options was added to the therapy. If the target HbA1c level was not reached, a second or third oral antidiabetic (OAD; sulfonylurea, glinide, dipeptidylpeptidase 4 inhibitor) or one of the insulin options was added to the therapy.

Table 2. Baseline and Follow-up Treatment Patients

	Treatment at admission	Started treatment at first visit	Treatment at third month
Metformin, n (%)	54 (100)	54 (100)	54 (100)
Sulphonylurea, n (%)	11 (20.3)	5 (9.2)	5 (9.2)
Glinide, n (%)	1 (1.8)	2 (3.7)	2 (3.7)
DPP-4 inhibitors, n (%)	8 (14.8)	11 (20.3)	14 (25.9)
Acarbose, n (%)	2 (3.7)	1 (1.8)	1 (1.8)
Basal insulin, n (%)	9 (20.3)	27 (50)	26 (48.1)
Premix Insulin, n (%)	13 (24)	24 (40.7)	19 (35.1)
Ultra rapid Insulin (%)	6 (11.1)	22 (38.8)	20 (37)
Regular Insulin, n (%)	2 (3.7)	3 (5.5)	3 (55.5)

Abbreviations: DPP-4, dipeptidyl peptidase-4.

Table 3. Patients' results at the end of 3 months

	Baseline n = 54	Third Month n = 54	*P* value
Hepcidin (µg/L)	177.1 ± 146.5	185 ± 172.9	0.468
Iron (µg/L)	83.3 ± 28.6	75.3 ± 21.4	0.035
Ferritin (ng/mL)	129.6 ± 121	107.0 ± 94.8	0.002
TIBC	357 ± 49	359 ± 69	0.883
TS	0.24 ± 0.09	0.25 ± .03	0.771
HbA1c (%)	11.0 ± 1.8	7.4 ± 1.2	< 0.001
C-Peptide (ng/mL)	2.63 ± 1.3	2.47 ± 1.1	0.327
CRP (mg/L)	5.46 ± 3.4	5.04 ± 3.02	0.350
Hb (g/dL)	13.8 ± 1.4	13.4 ± 1.4	< 0.001
Neut/Lym	2.11 ± 1.1	1.83 ± 0.8	0.035
BMI (kg/m^2)	30.4 ± 4.8	30.2 ± 4.8	0.085
UACR (mg/gr)	220 ± 0.2	20 ± 0.02	0.019

Abbreviations: TIBC: total iron binding capacity; CRP: C-reactive protein; Hb: hemoglobin; BMI: body mass index; UACR: urine albumin/creatinine ratio; Neut/Lym: Neutrophil/Lymphocyte; TS: Transferrin saturation.

Serum hepcidin measurements: Two tubes of blood were centrifuged for 10 min at 4000 rpm and stored at -80° for the measurement of hepcidin. After collecting all blood samples, dissolved blood samples were analyzed using reagents, specifically the enzyme-linked immunosorbent assay (ELISA) using a hepcidin kit. The kit (Human Hepcidin ELISA kit, catalogue No: 201-12-1020) is produced by Sunred Scientific Research Laboratories (Shanghia/China).

Follow-up: Patients were followed up for 3 months. At the end of the third month, height, weight were measured, and laboratory analyses were repeated as in the first visit. The patients checked their blood glucose 5 times a day, and were called to weekly outpatient clinic checks until their blood glucose was regulated.

Statistical analysis

Statistical evaluation was made using IBM SPSS version 20.0 (SPSS Inc. Chicago Illinois). Parametric variables such as mean ± standard variation and categorical variables were presented in percentages (%). Paired simple test was used for the comparison of parametric data before and after blood glucose regulation between two dependent groups Wilcoxon test was used when there was no normal distribution. Independent sample t test was used to compare two independent parametric variables. Mann-Whitney test was used in situations with no normal distribution. Although the relation between hemoglobin and the parameters with normal distribution (Iron, BMI, HbA1c) was evaluated by Pearson correlation method, the relation between hemoglobin and ferritin, which has no normal distribution was evaluated by Spearman correlation method. Parameters that showed significant correlation between groups were evaluated with multivariate regression analysis.

Results

A total of 76 patients who were in accordance with the inclusion criteria were chosen for the study. Thirteen of these patients were excluded from the study due to incompatibility with treatment and 9 due to loss of follow-up. Fifty-four patients were followed up for 3 months and their data were analyzed. Baseline characteristics of the patients are given in **Table 1**.

Medications used by patients throughout the study are given in **Table 2**. Patients' baseline and third month results are given in **Table 3**. Although serum iron, ferritin and blood hemoglobin levels showed a significant decrease (P = 0.035; P = 0.002; and P < 0.001 respectively), there was no significant change in the levels of TIBC and Iron/TIBC. Moreover, the third month hepcidin and CRP levels did not manifest any significant change. There was a significant decrease in the neutrophil/lymphocyte ratio on third month (P = 0.035). In addition, UACR significantly decreased with blood sugar regulation (**Table 3**).

Table 4. Comparison of baseline values of patients with HbA1c ≥ 10% and < 10%

	HbA1c < 10% n = 24 (Baseline)	HbA1c ≥ 10% n = 30 (Baseline)	*P* value
Age (year)	54.9 ± 8.4	54.5 ± 8.3	0.569
Duration of diabetes (year)	8.1 ± 3.4	7.5 ± 4.7	0.269
Women/Men (n)	13/11	17/11	NS
Smoking n (%)	9 (37)	11 (36)	NS
Hepcidin (µg/l)	122.4 ± 47	220.9 ± 173	0.009
Iron (µg/l)	93.1 ± 28.3	76.8 ± 27.5	0.061
Ferritin (ng/ml)	109.1 ± 116	146.1 ± 123	0.324
TIBC	375.2 ± 41	356.1 ± 48	0.038
Hb (g/dL)	13.3 ± 1.5	14.2 ± 1.3	< 0.001
HbA1c (%)	9.4 ± 0.5	12.4 ± 1.4	< 0.001
C-Peptid (ng/ml)	2.43 ± 1.0	2.74 ± 1.6	0.250
CRP (mg/L)	5.03 ± 3.3	5.82 ± 3.5	0.295
UACR (mg/gr)	130 ± 40	300 ± 50	0.115
Neut/Lym	1.86 ± 0.8	2.31 ± 1.3	0.048
BMI (kg/m^2)	31.3 ± 3.9	29.8 ± 5.4	0.599

NS: non-significant.

Patients with a baseline HbA1c value ≥ 10% and < 10% were separated into two groups. While baseline hepcidin level was higher in patients with a Hb A1c value ≥ 10% compared with those with < 10% (P = 0.009), TIBC was lower (P = 0.038) (**Table 4**).

In addition, although both groups of HbA1c ≥ 10% and < 10% showed a significant decrease in HbA1c levels after 3 months (P < 0.001) there was no significant change in hepcidin levels. Ferritin levels significantly decreased in the group with HbA1c levels ≥ 10% (**Table 5**). Likewise, a significant decrease was observed in the UACR and neutrophil/lymphocyte ratio (**Table 5**).

We found that hemoglobin values significantly decreased compared with initial values in all groups (**Tables 4** and **5**). This decrease was most prominent in those who were given additional insulin (Hb: 14.0 ± 1.2 vs 13.3 ± 1.2, P < 0.001) (**Table 6**).

There was a significant correlation between the third month hemoglobin values and HbA1c, iron, ferritin and BMI (**Figure 1**).

A relation between hemoglobin and iron, ferritin and HbA1c was demonstrated with a multivariate regression analysis. Association with BMI was excluded. These 3 variables explain the independent variable hemoglobin to a rate of 44% (R^2 = 0.44). According to ANOVA, this model significantly justifies the dependent variable (P < 0.001). Impact factor of each variable on hemoglobin levels were B = 0.028 P = 0.001 for iron, B = 0.004 P = 0.025 for ferritin, B = 0.304 P = 0.032 for HbA1c.

Hemoglobin = 8.6 + (iron*0.028) + (ferritin*0.004) + (HbA1c*0.304).

Patients who initially used OAD and received additional insulin afterwards and those who used insulin + OAD from the start were separated into two groups. There were no differences in baseline values between the two groups (**Table 6**).

From these groups, only those on OAD and insulin were included at the end of third month. Baseline and third month values were compared within each group. Whereas no variation in hepcidin levels was observed after 3 months in patients who received insulin in addition to OAD, there was a significant decrease in ferritin levels (P = 0.002). This effect was not observed in those who had been on insulin from the beginning (**Table 6**).

Follow-up

During the follow-up process, 4 patients developed hypoglycemia. None of these hypoglycemic events required parenteral glucose infusion or glucagon injection. All of the patients recovered from hypoglycemia. Their insulin doses are titrated and none experienced further episodes of hypoglycemia.

All 3 patients who started with insulin treatment (2 premix, 1 intensive) at the initial visit had good glycemic regulation at the follow-up. Their insulin therapy was stopped and their glycemic regulation continued well with OAD treatment alone.

Discussion

Diabetes is accompanied by complications throughout its course due to its progressive,

Table 5. Comparison of patients with HbA1c ≥ 10% and HbA1c < 10% before and after treatment

	HbA1c < 10% (Baseline) n = 24			HbA1c ≥ 10% (Baseline) n = 30		
	Baseline	Third month	*P* value	Baseline	Third month	*P* value
Hepcidin (µg/l)	122.4 ± 47	141.6 ± 54	0.152	220.9 ± 173	220 ± 212	0.968
Iron (µg/l)	93.1 ± 28	79.8 ± 18	0.036	76.8 ± 27.5	71.7 ± 22	0.326
Ferritin (ng/ml)	109.1 ± 116	91.9 ± 78	0.097	146.1 ± 123	119 ± 104	0.013
TDBK	375.6 ± 41	371.1± 40	0.451	344.1 ± 50	362.1 ± 52	0.043
Hb (g/dL)	13.8 ± 1.4	13.3 ± 1.3	< 0.001	14.1 ± 1.3	13.6 ± 1.5	< 0.001
HbA1c (%)	9.4 ± 0.5	7.2 ± 0.7	< 0.001	12.4 ± 1.4	7.7 ± 1.4	< 0.001
C-peptide (ng/ml)	2.43 ± 1.0	2.52 ± 0.9	< 0.001	2.74 ± 1.6	2.43 ± 1.2	0.180
CRP (mg/L)	5.03 ± 3.3	4.91 ± 2.8	0.788	5.82 ± 3.5	5.17 ± 3.2	0.352
UACR (mg/gr)	130 ± 41	20 ± 10	0.657	300 ± 42	20 ± 11	0.010
Neut/Lym	1.86 ± 0.8	1.83 ± 0.7	0.791	2.31 ± 1.3	1.94 ± 0.7	0.048
BMI (kg/m²)	31.3 ± 3.9	30.6 ± 3.7	0.013	29.8 ± 5.4	29.2 ± 5.5	0.285

Table 6. The comparison of patients according to initial treatments

	Baseline: OAD 3. month: OAD + Insulin (n = 22)			Baseline: OAD + Insulin 3. month: OAD + Insulin (n = 23)		
	Baseline	3rd month	P	Baseline	3rd month	P
HbA1c (%)	11.3 ± 1.6	7.07 ± 1.0	< 0.001	11.0 ± 2.1	8.12 ± 1.2	< 0.001
C-peptide (ng/mL)	2.81 ± 0.8	2.69 ± 1.1	0.569	2.20 ± 1.1	2.30 ± 1.1	0.667
CRP (mg/L)	6.95 ± 4.1	4.74 ± 2.9	0.041	4.98 ± 2.9	5.42 ± 3.0	0.438
UACR (mg/gr)	190 ± 50	10 ± 2	0.167	260 ± 40	20 ± 2	0.059
Hb (g/L)	14.0 ± 1.2	13.3 ± 1.2	< 0.001	14.0 ± 1.6	13.6 ± 1.7	0.008
Neut/Lym	2.3 ± 1.2	2.01 ± 0.9	0.228	1.87 ± 0.6	1.83 ± 0.6	0.685
BMI (kg/m²)	30.6 ± 5.5	30.2 ± 5.3	0.224	31.0 ± 4.1	30.6 ± 4.2	0.240
Hepcidin (µg/L)	187 ± 149	186 ± 157	0.862	179 ± 146	194 ± 192	0.339
Iron (µg/L)	79.9 ± 26	75.7 ± 23	0.405	86.9 ± 31	74.2 ± 19	0.052
TIBC	360 ± 50	366 ± 43	0.551	353 ± 48	350 ± 89	0.858
Ferritin (ng/mL)	135 ± 123	101 ± 94	0.002	126 ± 120	114 ± 96	0.256

inflammatory nature. Along with its known vascular complications, it has negative effects on various mechanisms. Endothelium is the source of some of these effects, but harmful effects are also present from other sources.

Multiple tissues are negatively affected throughout the disease process where elevated blood glucose levels are prominent. These negative effects have been investigated and documented in multiple studies. It is possible for iron metabolism and Hb levels to be affected by this process. There are studies stating that there is serum iron overload especially in patients with diabetes [7-9]. A recent animal study reported that hepcidin was regulated by insulin and that increased iron load was the consequence of decreased hepcidin synthesis in the liver [5]. In our study, in addition to high levels of iron and ferritin, hepcidin levels increased as blood glucose regulation worsened. When the presence of a proinflammatory process is considered, increased hepcidin levels are not unexpected. In another study by Jiang F, serum ferritin and hepcidin levels were found to increase in patients with T2D [2]. As a result, it was reported that hepcidin levels in patients with insulin resistance decreased and iron overload increased. In contrast, in patients with a lack of insulin and high blood glucose, there is no reduction in hepcidin levels [10, 11]. It is known that some patients can develop anemia despite iron overload, especially in diabetes as a chronic disease [12]. A small scale study investigated this anemia and hepcidin was reported to have no role [12]. Increased hepcidin levels and neg-

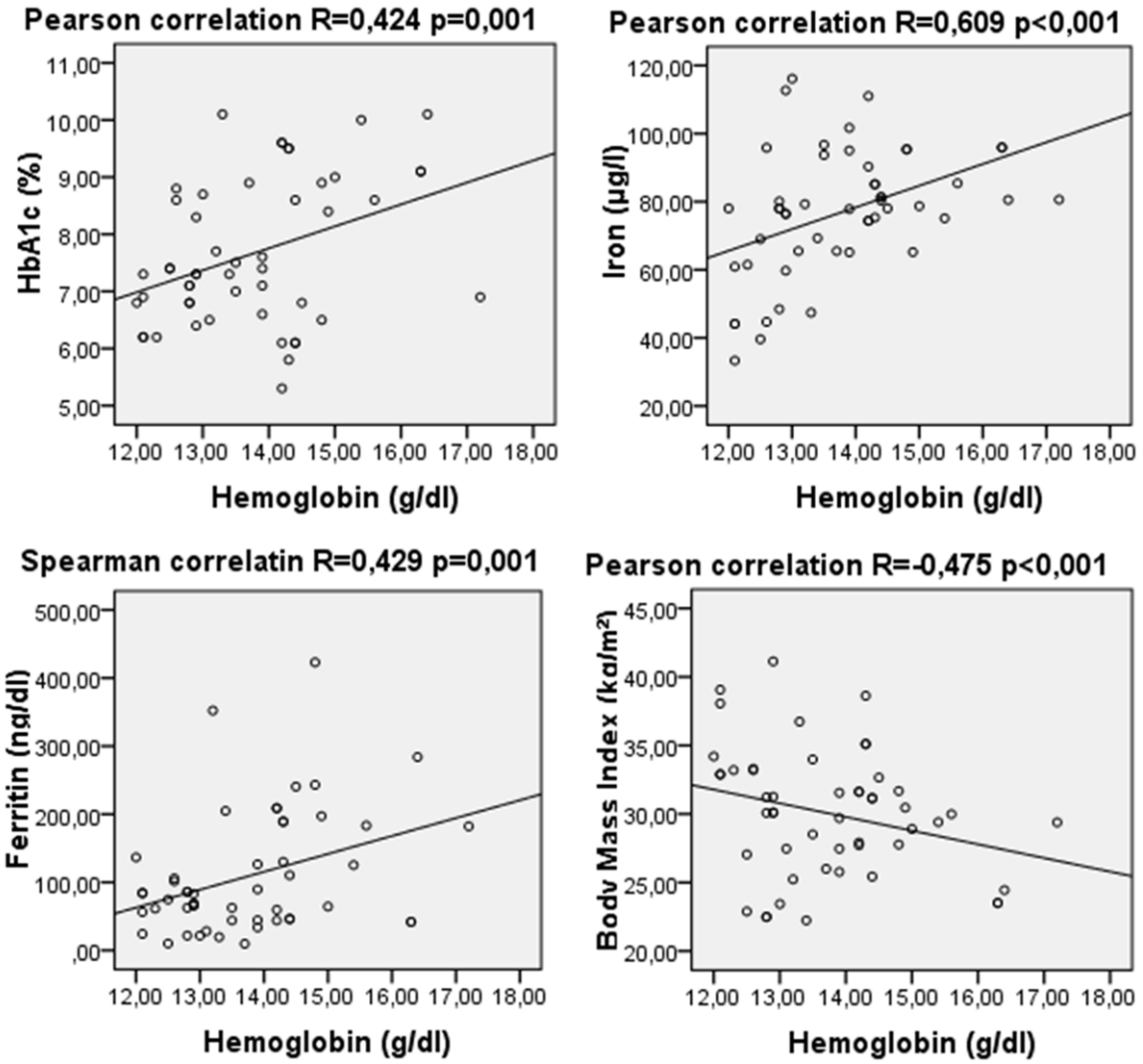

Figure 1. Relation between hemoglobin values and HbA1c, ferritin, iron, BMI.

atively affected iron metabolism is common in diabetes mellitus due to its chronicity. This process can be expected to cause chronic anemia in many patients. Likewise, in our study, hepcidin levels were higher in patients with very poor blood sugar control. After observing a decrease in hepcidin levels, it would be logical to expect blood glucose regulation with treatment would lead to a decrease in inflammation. However, our study results showed no change in blood hepcidin levels with blood glucose regulation in those without anemia and poorly controlled diabetes.

According to the current literature, it was reported that obese but not anemic diabetics had no variations in their iron status, but those who only had anemia had significant increases in hepcidin mRNA expression [8]. This led us to postulate a possible role of hepcidin in anemia observed in patients with diabetes. We found significantly increased hepcidin levels in non anemic patients with poor blood glucose regulation. We observed that after blood glucose regulation was restored, hepcidin levels did not alter in those with HbA1c level higher or lower than 10. This suggests that blood sugar regulation may not be the only cause of inflammation in diabetes, or that blood sugar regulation for three months may not suffice to have positive effects over inflammation. However, in a previous study, we demonstrated positive effects of three months of blood sugar regulation on endothelium. With blood sugar regulation, we observed a significant decrease in endocan levels that are normally secreted with endothelium

stimulation [13]. UACR levels also significantly decreased with blood sugar regulation, more prominently in those with very poor control. Although the neut/lymph ratio, which is one of the novel signs of inflammation, was observed to significantly decrease in our study, we found no changes in CRP levels. This led us to reflect on the complicated process of inflammation and how it is composed of various factors.

Another interesting finding was the significant drop in hemoglobin values. This decrease was observed in the whole group, both in very poorly controlled patients (HbA1c > 10) and those in better condition (HbA1c < 10). The decrease in the Hb level was greatest in patients who initially only used OAD and received additional insulin later in treatment. None of the patients were on glitazone. This unprecedented finding in the current literature could be due to increased Hb clearance resulting from the rapid drop in HbA1c levels, it might also be caused by high hepcidin levels and relative dysfunction in iron metabolism. It could also be due to an increase in plasma volume in patients who were started on insulin. From the iron metabolism standpoint, we discovered a decrease in both iron and ferritin levels without any change in transferrin saturation or total iron binding capacity. This decrease may also be due to the strict diet that patients received to achieve blood sugar regulation. However, taking into account their BMI and absence of weight loss after 3 months, we considered this effect to be limited.

To conclude; hepcidin levels were higher in patients with diabetes who had poor blood glucose control. When blood sugar regulation was restored at the end of three months, there was no decrease in the formerly high hepcidin levels. Despite the unchanged hepcidin levels, there was a significant drop in Hb values at the end of three months, especially in those who were recently started on insulin. Also, along with ameliorating endothelial function and decreasing neutrophil/lymphocyte ratio, iron and ferritin levels significantly decreased.

There is a need for more comprehensive studies to investigate whether the decrease in hemoglobin values observed in patients with diabetes with restored blood sugar regulation is clinically significant.

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Disclosure of conflict of interest

None.

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