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The Role of Insulin Therapy in Correcting Hepcidin Levels in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objectives: Iron overload can cause or contribute to the pathogenesis of type 2 diabetes mellitus (T2DM), but how the major parameters of iron metabolism change in different settings of diabetes are still unclear. The aim of this study was to determine the relationship between iron, ferritin, and hepcidin levels in diabetic patients and the effect of insulin treatment. ***Methods***: The study included 80 subjects, 60 with T2DM and 20 without (control group). Serum hepcidin, insulin, ferritin, and iron levels were determined as well as other clinical parameters. The associations between these parameters were analyzed between both groups. ***Results:*** Hepcidin levels expressed as mean± standard deviation between groups showed no significant changes (14.4±6.7 ng/mL for the control group, and 18.4±7.9 ng/mL for patients with diabetes, $p = 0.069$). Parameters of iron metabolism showed modest correlation with the parameters of glucose metabolism. However, the correlation between ferritin and insulin in both groups was statistically significant ($p = 0.032$; $\rho = 0.480$ vs. $p = 0.011$; $\rho = 0.328$). ***Conclusions:*** Our study showed that hepcidin levels in patients with T2DM on insulin therapy do not change, which might be a result of treatment with insulin. In this context, insulin treatment can be used as a novel method for correction of hepcidin levels. By correcting hepcidin levels, we can prevent cellular iron overload and reduce the risk of diabetes.

Type 2 diabetes mellitus (T2DM) is a condition reaching epidemic proportions worldwide.[1] While physical activity and other healthy habits are recommended as effective means to curb this epidemic,[2] there are other ways through which we can improve the burden of diabetes. One of them would be by controlling known and suspected pathophysiological processes that can deteriorate glucose metabolism. In this context, controlling iron metabolism through its main regulatory protein, hepcidin, could prove beneficial. The reason for this approach is based on links found between glucose and iron metabolism.[3] Some studies have linked iron excess with risk for T2DM. One of the most studied pathologies characterized with organ iron load is hemochromatosis (HH), which increases the risks of developing T2DM.[4] However, the pathophysiological series of events that lead to glucose dysregulation in these patients have still not been fully clarified. The pancreas is one of the most affected organs in HH, and its main endocrine cells (beta cells) are very sensitive to iron load.[5] Liver dysfunction through the mechanism of insulin resistance can be another pathophysiological factor in this setting.[6] Liver injury caused by chronic infection with hepatitis C virus (HCV) is linked with an increased risk for T2DM, especially when HCV infection is accompanied by high ferritin levels.[7]

There seems to be little doubts on iron load (reflected by ferritin levels) and its role in the pathophysiology of T2DM.[8,9] Studies have shown that ferritin levels are positively correlated with levels of glucose in serum.[10] High levels of ferritin have also been observed in prediabetes.[11] Reducing iron load through treatment with phlebotomy does decrease glucose and glycated hemoglobin (HBA_{1c}) levels in diabetic patients and may increase insulin sensitivity,[12] though other positive effects of phlebotomy should not be excluded.[13]

If iron load is clearly linked with risk of developing diabetes then what are the mechanisms behind these

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links? We have already mentioned that beta cells of the pancreas are vulnerable to high iron levels, which is why beta cell dysfunction has been observed in HH. Beta cell dysfunction impairs insulin production, which can cause glucose dysmetabolism.[14] Iron overload also affects the metabolism of nutrients in skeletal muscle by decreasing glucose oxidation and increasing lipid oxidation.[15] In dysmetabolic iron-overload syndrome (DIOS), iron overload is accompanied by insulin resistance, obesity, and chronic hepatitis. Furthermore, iron status affects insulin receptor expression in hepatocytes and intracellular insulin signaling.[16] Iron load can affect beta cell capacity to produce insulin, but also can cause insulin resistance in hepatocytes and decreased glucose oxidation in skeletal muscle. By affecting the most important organs responsible for glucose homeostasis, iron load can be responsible for glucose dysmetabolism and resultant diabetes.

The main regulator of iron metabolism, hepcidin, was discovered in the early 21st century and is increasingly studied in relation to T2DM.[17,18,19] This small protein is known to affect iron efflux by inducing ferroportin (FPN) degradation in target cells (enterocytes, macrophages).[20] FPN is the major protein channel that exports iron from cells into plasma.[20]

Systemic hepcidin is produced by hepatocytes, and is mainly regulated by iron load in cells.[21] It is believed that iron load through yet unknown mechanisms stimulates production of bone morphogenetic protein-6 (BMP6), which binds to its receptor on hepatocytes.[21] This binding activates the SMAD pathway in hepatocytes, which as a result increases the expression of hepcidin.[21] Hepcidin, through its effects on FPN, lowers the levels of plasma iron. Though hepatocytes produce most hepcidin, local production of this protein has been observed in many organs (e.g., heart, kidney, beta cells of the pancreas),[22] but the physiologic importance of local hepcidin is still unclear.[21] Another important factor that controls hepcidin production is increased erythropoietic activity. During increased erythropoiesis (i.e., anemia), iron is needed for hemoglobin production, and hepcidin is suppressed in this setting.[21]

Studies have shown that there are two types of diabetic patients when it comes to hepcidin levels: those with elevated hepcidin serum levels and those with low hepcidin serum levels. More is understood about why hepcidin levels are elevated in patients with T2DM. Many of the factors that increase the expression of hepcidin are present in patients with elevated hepcidin levels. These factors include inflammation, chronic renal impairment, and morbid obesity.[23] The cause of T2DM accompanied with low levels of hepcidin is unclear, but insulin resistance is thought to play a role.[24] This suggests

Table 1: Clinical and laboratory data in healthy control subjects and patients with T2DM.

Laboratory	Control	T2DM
Number (male/female)	20 (12/8)	60 (37/23)
Age, years	58.1 ± 9.3	55.6 ± 6.1
BMI, kg/m^2	27.2 ± 3.4	28.4 ± 3.7
CRP, mg/L	0.3 ± 0.1	0.4 ± 0.1
AST, IU/L	23.3 ± 7.1	23.4 ± 8.5
ALT, IU/L	26.5 ± 13.5	29.4 ± 16.3
LDH, IU/L	256.1 ± 66.5	291.9 ± 78.0
Iron, µmol/L	21.0 ± 3.8	17.5 ± 5.4
TIBC, µmol/L	58.9 ± 9.5	50.1 ± 15.1
UIBC, µmol/L	32.9 ± 8.9	32.6 ± 13.2
TS, %	39.7 ± 8.6	36.4 ± 12.1
GLU, mmol/L	5.0 ± 0.5	9.7 ± 3.3
HBA_{1c}, %	4.0 ± 0.8	6.2 ± 1.6
TC, mmol/L	4.8 ± 0.9	5.4 ± 1.4
TG, mmol/L	1.6 ± 0.9	2.8 ± 2.0
HDL, mmol/L	1.1 ± 0.5	1.6 ± 0.6
LDL, mmol/L	3.1 ± 0.6	3.1 ± 0.8
RBC, ×10^6/µL	5.0 ± 0.7	4.8 ± 0.6
WBC, ×10^3/µL	6.6 ± 1.8	7.9 ± 3.2
Hb, g/dL	14.5 ± 1.5	14.1 ± 1.9
HCT, %	43.8 ± 4.3	43.4 ± 5.2
Urea, mmol/L	4.4 ± 1.0	5.9 ± 3.2
Uric acid, mmol/L	220.8 ± 42.7	308.5 ± 98.0
CRE, mmol/L	65.6 ± 5.0	76.3 ± 20.3
Insulin, ng/mL	1.9 ± 1.5	2.3 ± 1.9
Ferritin, ng/mL	280.1 ± 112.9	254.7 ± 111.4
Hepcidin, ng/mL	14.4 ± 6.7	18.4 ± 7.9
Hepcidin/ferritin ratio	0.06 (0.03–0.07)	0.07 (0.05–0.09)

Data are presented as mean ± standard deviation or median (interquartile range). BMI: body mass index; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; TIBC: total iron binding capacity; UIBC: unsaturated iron binding capacity; TS: transferrin saturation; GLU: glucose; HBA_{1c}: glycated hemoglobin; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; RBC: red blood cells; WBC: white blood cells; Hb: hemoglobin; HCT: hematocrit; CRE: creatinine; T2DM: type 2 diabetes mellitus.

Table 2: Correlation between serum ferritin, hepcidin, and insulin levels in patients with T2DM.

Laboratory	Ferritin		Hepcidin		Insulin	
	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value
AST	0.057	0.660	0.039	0.766	0.194	0.138
ALT	0.055	0.670	0.015	0.910	0.120	0.362
LDH	0.204	0.110	0.205	0.116	0.072	0.583
Iron	0.370	0.004**	0.088	0.506	0.154	0.239
TIBC	0.135	0.303	0.111	0.400	0.043	0.745
UIBC	0.009	0.940	0.094	0.475	0.087	0.511
TS	0.233	0.073	0.060	0.651	0.165	0.207
GLU	0.030	0.822	0.084	0.526	0.013	0.924
HBA_{1c}	0.038	0.776	0.150	0.907	0.079	0.549
TC	0.035	0.791	0.105	0.427	0.022	0.866
TG	0.001	0.992	0.105	0.425	0.062	0.637
HDL	0.012	0.930	0.041	0.757	0.036	0.784
LDL	0.025	0.848	0.145	0.269	0.094	0.475
RBC	0.185	0.157	0.011	0.931	0.084	0.523
WBC	0.141	0.283	0.208	0.110	0.220	0.092
Hb	0.170	0.195	0.040	0.760	0.108	0.410
HCT	0.212	0.104	0.037	0.781	0.132	0.314
Urea	0.104	0.427	0.228	0.080	0.099	0.449
UA	0.127	0.332	0.109	0.408	0.091	0.489
CRE	0.026	0.844	0.058	0.660	0.025	0.851
Insulin	0.328	0.011*	0.130	0.320	-	-
Ferritin	-	-	0.412	0.001**	0.328	0.011*
Hepcidin	0.412	0.001**	-	-	0.130	0.320

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; TIBC: total iron binding capacity; UIBC: unsaturated iron binding capacity; TS: transferrin saturation; GLU: glucose; HBA_{1c}: glycated hemoglobin; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; RBC: red blood cells; WBC: white blood cells; Hb: hemoglobin; HCT: hematocrit; UA: uric acid; CRE: creatinine; T2DM: type 2 diabetes mellitus.
**Correlation significant at the 0.05 level (2-tailed). **Correlation significant at the 0.01 level (2-tailed).*

that regulation of insulin production could correct hepcidin levels.

We sought to determine the effects of insulin treatment in patients with T2DM without known factors that increase hepcidin expression and study the relationship between hepcidin levels and insulin production. We hypothesized that if insulin resistance does cause low hepcidin levels, then correction of insulin signaling with insulin therapy could reverse these levels back to normal.

METHODS

Our study included 80 subjects, 60 with T2DM on insulin therapy (case group), and 20 without T2DM (control group). Incident cases of diabetes were not subjects of investigation and were not recorded. All patients and control individuals gave written informed consent for the collection, analysis, and the use of data for publication. The study was approved by the institutional ethics committee.

Patients with hepatic malignancy, HH, or receiving therapy with a known influence on iron metabolism were excluded from the study. Patients with high C-reactive protein (CRP) levels and significant differences in body mass index (BMI) levels were excluded from the study. None of our patients were under any treatment with iron or immune-suppressive drugs and/or had undergone blood transfusion before the start of our study.

Blood samples were obtained for hematological and biochemical tests at 8 am after overnight fasting in two containers, one containing EDTA and another without anticoagulant. Complete blood count and hemoglobin (Hb) were determined using the ERMA 750 Hematology Analyzer (Erma Inc, Japan). Serum

Table 3: Correlations between serum ferritin, hepcidin, and insulin levels in control subjects.

Laboratory	Ferritin		Hepcidin		Insulin	
	ρ	*p*	ρ	*p*	ρ	*p*
AST	0.253	0.281	0.293	0.209	0.123	0.605
ALT	0.024	0.919	0.040	0.867	0.038	0.874
LDH	0.043	0.857	0.376	0.103	0.030	0.900
Iron	0.159	0.502	0.260	0.268	0.010	0.967
TIBC	0.056	0.814	0.043	0.858	0.229	0.331
UIBC	0.084	0.723	0.154	0.517	0.092	0.700
TS	0.043	0.857	0.164	0.491	0.092	0.700
GLU	0.331	0.154	0.005	0.984	0.034	0.887
HBA_{1c}	0.249	0.290	0.375	0.103	0.108	0.651
TC	0.044	0.852	0.413	0.071	0.203	0.390
TG	0.133	0.576	0.140	0.556	0.004	0.987
HDL	0.257	0.274	0.607	0.005**	0.300	0.199
LDL	0.044	0.855	0.264	0.261	0.023	0.922
RBC	0.100	0.674	0.261	0.266	0.229	0.331
WBC	0.119	0.617	0.333	0.151	0.470	0.037*
HGB	0.232	0.324	0.096	0.689	0.272	0.246
HCT	0.229	0.332	0.208	0.379	0.354	0.126
Urea	0.387	0.091	0.248	0.291	0.051	0.830
UA	0.064	0.789	0.058	0.807	0.119	0.617
CRE	0.280	0.232	0.159	0.504	0.151	0.524
Insulin	0.480	0.032*	0.112	0.639	-	-
Ferritin	-	-	0.241	0.307	0.480	0.032*
Hepcidin	0.241	0.307	-	-	0.112	0.639

AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; TIBC: total iron binding capacity; UIBC: unsaturated iron binding capacity; TS: transferrin saturation; GLU: glucose; HBA_{1c}: glycated hemoglobin; TC: total cholesterol; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; RBC: red blood cells; WBC: white blood cells; Hb: hemoglobin; HCT: hematocrit; UA: uric acid; CRE: creatinine.
**Correlation significant at the 0.050 level (2-tailed). **Correlation significant at the 0.001 level (2-tailed).*

samples were analyzed for aspartate aminotransferase (AST), alanine aminotransferase(ALT), gamma-glutamyltransferase (GGT), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol using the Miura Biochemical Analyzer (I.S.E. SRL, Italy). Serum ferritin, insulin, and hepcidin were measured by ELISA (Cloud-Clone Corp., Houston, USA) according to manufacturers' instructions.

To improve and strengthen the statistical analysis results logarithm with base 10 were analyzed. Statistical analyses between two groups were carried out by Mann-Whitney U test. The associations of serum hepcidin with ferritin, insulin, iron, and other parameters were tested with Spearman rank correlation. Multiple linear regression models were used to evaluate the effective hematological variables, group of iron variables, lipid, glucose, enzyme metabolism variables and degradation products with serum hepcidin, insulin, and ferritin production.

In all cases $p < 0.050$ was considered statistically significant. Statistical analysis was done using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA).

RESULTS

The patient characteristics are presented in Table 1. The results of correlation tests for both groups of patients are shown in Tables 2 and 3.

Both study groups were matched and had no major differences in BMI, CRP, urea, and creatinine (CRE) levels. We observed a negative but statistically insignificant correlation between insulin and glucose in the T2DM group ($p = 0.924$; $\rho = 0.013$). In the control group, analysis showed a

weak positive insignificant correlation (p = 0.887; ρ = 0.034). Results for insulin, ferritin, hepcidin and their correlation with HbA_{1c} and glucose showed no statistical significance. A negative to moderate insignificant correlation was found between insulin and almost all of the measured parameters.

A statistically significant positive correlation was found between ferritin and serum iron in the T2DM group (p = 0.004; ρ = 0.370).This was also found between ferritin and insulin in both groups (p = 0.011; ρ = 0.328 in the T2DM group and p = 0.032; ρ = 0.480 in the control group).

We found a significant difference in glucose levels between the case and control groups (z = -5.745 and p < 0.001). The results for hepcidin and the hepcidin/ferritin ratio between the groups were not statistically significant (for hepcidin z = -1.817, p = 0.069 and hepcidin/ferritin ratio z = -1.883, p = 0.060).

Multiple linear regression analysis was used to test the relationship between variables of interest (insulin, ferritin, and hepcidin) and parameters that have the same metabolic path or are directly connected.

Applied linear regression model on insulin and glucose metabolism parameters like glucose and HbA_{1c} showed that adjusted R^2 was -0.032 and p = 0.920 for the T2DM group, and R^2 = 0.011 and p = 0.353 in the control group. Applied linear regression model on ferritin and its association with other parameters of iron metabolism (serum iron, total iron binding capacity (TIBC), and unsaturated iron binding capacity (UIBC)) in the control group was R^2 = -0.79 and p = 0.665. For the T2DM group only 1.9% association can be explained by the model (R^2 = 0.019 and p = 0.256). When we analyzed the hematological parameters as a group, their connection with the ferritin results were: R^2 = 0.016 and p = 0.306 for the group with T2DM, and R^2 = 0.101 and p = 0.243 for the control group. Taking the iron metabolism parameters of the control group, their interaction with the hepcidin results were serum iron, TIBC, and UIBC shown adjusted R^2 = -0.133 and p = 0.856, while adjusted R^2 for hematological parameters was -0.117 and p = 0.735. The results, for the same previously described parameters in the T2DM group were R^2 = -0.018 and p = 0.582 for the analysis of iron metabolism parameters, and R^2 = -0.027 and p = 0.653 for the hematological parameters.

DISCUSSION

Our study showed that when on insulin therapy, patients with T2DM do not have lowered values of hepcidin in serum. We found no statistically significant differences in hepcidin values between the control group and the group of patients with T2DM on insulin therapy.

Studies in rats have shown that insulin resistance can cause low hepcidin levels and that insulin therapy reverses these levels.[25] These levels rise when insulin signaling is improved. What is more interesting is that the study identified the biochemical pathway (STAT3 pathway) through which insulin signaling corrects hepcidin values.[25]

Our patients were good models to study because they were matched by the usual factors that increase the levels of hepcidin (urea, CRE , CRP, and BMI). Diabetic patients matched by these factors usually have low levels of hepcidin, but our diabetic patients had similar levels to the control group. Studies on rats with models of insulin resistance have not been equaled by similar studies on human patients with T2DM.

Insulin resistance is linked with low levels of hepcidin not only in patients with T2DM. In hyperprolactinemia, hepcidin levels are low and reduced expression of the prolactin receptor is linked with insulin resistance.[26] The prolactin receptor affects insulin sensitivity through the STAT5 pathway.[27] Loss of STAT5 can cause insulin resistance. STAT5 is known to compete with STAT3 in regulating the expression of different genes.[28]

Other mechanisms can affect hepcidin levels in T2DM patients. Pancreatic beta cells are known to have the highest expression of hepcidin in pancreas tissue.[29] Also, beta cells can co-secrete hepcidin and insulin,[29] which further strengthens the links between glucose and iron metabolism.

These mechanisms should be studied further to establish a better explanation of how insulin resistance affects hepcidin levels. In future studies, we intend to investigate the effect of insulin therapy on hepcidin levels by comparing these levels in different groups of patients with T2DM.

CONCLUSION

Our study intended to investigate how can insulin therapy affects hepcidin production, which is important because iron load precipitates or

deteriorates T2DM. We have found that insulin therapy might be the reason why our patients with diabetes have no changes in hepcidin levels. This means that one of the benefits of insulin therapy (maybe even in prediabetes) could be lowering of the iron load in cells.

Disclosure
The authors declared no conflicts of interest. No funding was received for this study.

REFERENCES

1. Dwyer-Lindgren L, Mackenbach JP, van Lenthe FJ, Flaxman AD, Mokdad AH, Vos T, et al. Diagnosed and Undiagnosed Diabetes Prevalence by County in the U.S.,1999-2012. Diabetes Care 2016 Sep;39(9):1556-1562.
2. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends.Oman Med J 2012 Jul;27(4):269-273.
3. Bowers KA, Olsen SF, Bao W, Halldorsson TI, Strøm M, Zhang C. Plasma Concentrations of Ferritin in Early Pregnancy Are Associated with Risk of Gestational Diabetes Mellitus in Women in the Danish National Birth Cohort. J Nutr 2016 Sep;146(9):1756-1761.
4. Muckenthaler MU, Wu X, Wang Y, Wu Q, Feder J, Gnirke A, et al. How mutant HFE causes hereditary hemochromatosis. Blood 2014 Aug;124(8):1212-1213.
5. Fernández-Real JM, McClain D, Manco M, Finch C, Jehn M, Clark J, et al. Mechanisms Linking Glucose Homeostasis and Iron Metabolism Toward the Onset and Progression of Type 2 Diabetes. Diabetes Care 2015 Nov;38(11):2169-2176.
6. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes Care 2007 Mar;30(3):734-743.
7. Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, García L, et al. Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection. Diabetes Care 2004 Nov;27(11):2669-2675.
8. Simcox JA, McClain DA. Iron and diabetes risk. Cell Metab 2013 Mar;17(3):329-341.
9. Swaminathan S, Fonseca VA, Alam MG, Shah SV. The role of iron in diabetes and its complications. Diabetes Care 2007 Jul;30(7):1926-1933.
10. Fernández-Real JM, Ricart-Engel W, Arroyo E, Balançá R, Casamitjana-Abella R, Cabrero D, et al. Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 1998 Jan;21(1):62-68.
11. Sharifi F, Nasab NM, Zadeh HJ. Elevated serum ferritin concentrations in prediabetic subjects. Diab Vasc Dis Res 2008 Mar;5(1):15-18.
12. Equitani F, Fernandez-Real JM, Menichella G, Koch M, Calvani M, Nobili V, et al. Bloodletting ameliorates insulin sensitivity and secretion in parallel to reducing liver iron in carriers of HFE gene mutations. Diabetes Care 2008 Jan;31(1):3-8.
13. Houschyar KS, Lüdtke R, Dobos GJ, Kalus U, Broecker-Preuss M, Rampp T, et al. Effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome: results from a randomized clinical trial. BMC Med 2012 May;10:54.
14. Cooksey RC, Jouihan HA, Ajioka RS, Hazel MW, Jones DL, Kushner JP, et al. Oxidative stress, β-cell apoptosis, and decreased insulin secretory capacity in mouse models of hemochromatosis. Endocrinology 2004 Nov;145(11):5305-5312.
15. Huang J, Jones D, Luo B, Sanderson M, Soto J, Abel ED, et al. Iron overload and diabetes risk: a shift from glucose to Fatty Acid oxidation and increased hepatic glucose production in a mouse model of hereditary hemochromatosis. Diabetes 2011 Jan;60(1):80-87.
16. Fargion S, Dongiovanni P, Guzzo A, Colombo S, Valenti L, Fracanzani AL. Iron and insulin resistance. Aliment Pharmacol Ther 2005 Nov;22(Suppl 2):61-63.
17. Pechlaner R, Weiss G, Bansal S, Mayr M, Santer P, Pallhuber B, et al. Inadequate hepcidin serum concentrations predict incident type 2 diabetes mellitus. Diabetes Metab Res Rev 2016 Feb;32(2):187-192.
18. Sam AH, Busbridge M, Amin A, Webber L, White D, Franks S, et al. Hepcidin levels in diabetes mellitus and polycystic ovary syndrome. Diabet Med 2013 Dec;30(12):1495-1499.
19. Suárez-Ortegón MF, Moreno M, Arbeláez A, Xifra G, Mosquera M, Moreno-Navarrete JM, et al. Circulating hepcidin in type 2 diabetes: A multivariate analysis and double blind evaluation of metformin effects. Mol Nutr Food Res 2015 Dec;59(12):2460-2470.
20. Ward DM, Kaplan J. Ferroportin-mediated iron transport: expression and regulation. Biochim Biophys Acta 2012 Sep;1823(9):1426-1433.
21. Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochim Biophys Acta 2012 Sep;1823(9):1434-1443.
22. Krause A, Neitz S, Mägert HJ, Schulz A, Forssmann WG, Schulz-Knappe P, et al. LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity. FEBS Lett 2000 Sep;480(2-3):147-150.
23. Young B, Zaritsky J. Hepcidin for clinicians. Clin J Am Soc Nephrol 2009 Aug;4(8):1384-1387.
24. Le Guenno G, Chanséaume E, Ruivard M, Morio B, Mazur A. Study of iron metabolism disturbances in an animal model of insulin resistance. Diabetes Res Clin Pract 2007 Sep;77(3):363-370.
25. Wang H, Li H, Jiang X, Shi W, Shen Z, Li M. Hepcidin is directly regulated by insulin and plays an important role in iron overload in streptozotocin-induced diabetic rats. Diabetes 2014 May;63(5):1506-1518.
26. Wang J, Liu G, Xu Z, Dai J, Song P, Shi J, et al. Hepcidin levels in hyperprolactinemic women monitored by nanopore thin film based assay: correlation with pregnancy-associated hormone prolactin. Nanomedicine 2015 May;11(4):871-878.
27. Yu J, Xiao F, Zhang Q, Liu B, Guo Y, Lv Z, et al. PRLR regulates hepatic insulin sensitivity in mice via STAT5. Diabetes 2013 Sep;62(9):3103-3113.
28. Walker SR, Nelson EA, Yeh JE, Pinello L, Yuan GC, Frank DA. STAT5 outcompetes STAT3 to regulate the expression of the oncogenic transcriptional modulator BCL6. Mol Cell Biol 2013 Aug;33(15):2879-2890.
29. Kulaksiz H, Fein E, Redecker P, Stremmel W, Adler G, Cetin Y. Pancreatic beta-cells express hepcidin, an iron-uptake regulatory peptide. J Endocrinol 2008 May;197(2):241-249.