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Elevated hepcidin, ferroportin associated with glucose metabolism disorder in midpregnancy

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Abstract

[Objective]: Hepcidin and ferroportin are major regulators of iron metabolism. Although many previous studies have shown that iron metabolism disorder may contribute to the pathogenesis of Type 2 diabetes mellitus (DM), few studies have investigated hepcidin and other iron metabolism parameters in women with gestational diabetes mellitus (GDM). The purpose of this study was to determine the relationship between hepcidin, ferroportin and GDM. [Methods]: A case-control study was conducted in 85 women with GDM and 85 women without GDM (controls) who received regular prenatal care at the Obstetrics and Gynecology Hospital of Fudan University from October 2015 to May 2016. Serum ferritin (SF), hepcidin (Hepc), ferroportin (FPN), and soluble transferrin receptor (sTfR), as well as other clinical parameters, were detected and analyzed in all groups. [Results]: The levels of fasting plasma glucose (FPG), oral glucose tolerance test OGTT 1-h and 2-h plasma glucose, glycated hemoglobin (HbA1c), SF, Hepc, FPN and sTfR as well as homeostasis model assessment for insulin resistance (HOMA-IR) were significantly higher in the GDM group ($P<0.05$ for all). In the GDM group, FPN was positively correlated with plasma glucose 1 h and 2 h. In the control group, only sTfR was positively correlated with plasma glucose 1 h. There was no correlation between the iron metabolism indicators in both GDM and control group. [Conclusion]: Hepc, FPN, sTfR and SF levels were higher in the GDM group. Elevated Hepc and FPN are associated with glucose metabolism disorder and may play an important role in GDM.

Key Words: hepcidin, ferroportin, gestational diabetes mellitus, glucose metabolism

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1. Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy that can adversely affect both maternal and fetal health. Feig et al.[1], for instance, investigated 659,164 women from 1995 to 2001 who did not have prepregnancy diabetes and found a postpregnancy incidence of Type 2 diabetes in pregnant women with GDM of 18.9%, while the corresponding incidence among pregnant women who had normal plasma glucose was only 1.95%. After controlling for mixed factors such as age, parity, and income status, GDM was the most significant risk factor for developing postpartum diabetes mellitus. Kim et al.[2] reviewed studies that examined women 6 weeks to 28 years postpartum and noted that the incidence of type 2 diabetes in women with prior GDM ranged from 2.6% to more than 70%. Moreover, children of mothers who had GDM are also more prone to develop type 2 diabetes. In recent years, the incidence of GDM has increased; in China, incidence estimates range from approximately 13% to 20.9% [3, 4].

Iron plays an essential role in human health and survival. The World Health Organization (WHO) recommends that pregnant women receive 30-60 mg of iron daily to improve pregnancy outcomes, especially for pregnant women with iron deficiency anemia (IDA) [5]. In recent years, however, studies have shown that iron, as a strong oxidant and transitional metal, may affect glucose metabolism and can be harmful to maternal and fetal health through the Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{HO}^-$) [6,7, 8].

Hepcidin (Hepc) is a 25-amino-acid peptide secreted by the liver that is metabolized by the kidney and is considered a “core factor” in regulating iron metabolism[9]. Ferroportin (FPN)—the only iron exporter protein known to exist in mammals, is a 62.5-kDa protein consisting of 12 transmembrane domains[10]. Studies [9] [11, 12] have shown that mice lacking the hepcidin gene as well as humans with hepcidin gene mutations suffer severe iron overload or other related diseases. Ganz T et al.[13] found that inactivation of the FPN gene was associated with severe iron overload in the liver and the pancreas. The ferroportin-hepcidin axis plays an important role in iron homeostasis.

Soluble transferrin receptor (sTfR) is a single-polypeptide chain of 85 kDa produced by the proteolytic cleavage of the 190 kDa transmembrane transferrin receptor, a glycoprotein primarily expressed in cells requiring iron. sTfR is commonly used for the clinical determination of iron status, which is less affected by inflammation. Although recent data showed that serum ferritin levels were positively and independently associated with insulin resistance (IR)[13], Ambroszkiewicz J et al[15] found that soluble transferrin receptor, which was less affected by inflammation, was a better marker of iron status than other parameters. Many previous studies have shown that iron metabolism disorder may contribute to the pathogenesis of GDM. However, the correlation between iron metabolism and GDM is not well known. For this reason, the purpose of this study was to determine the relationship between hepcidin, ferroportin, ferritin, soluble transferrin receptor and gestational diabetes mellitus.

2. Patients and Methods

2.1. Written informed consent was obtained from subjects after discussion in the Chinese language, aided by written information. Ethical approval was granted by the medical ethics committee of the Obstetrics and Gynecology Hospital of Fudan University. For GDM diagnostic criteria, we utilized the standards studied and recommended by the International Association of Diabetes and Pregnancy Study Group (IADPSG) in 2010[16]. Women who had other complications during follow-up were excluded.

Oral glucose tolerance test (OGTT): The presence of at least one of the following abnormal values was sufficient to diagnose GDM: plasma glucose ≥ 5.1 mmol/L after an overnight fast; plasma glucose level ≥ 10.0 mmol/L 1 h after consuming 75 g of glucose; or plasma glucose level ≥ 8.5 mmol/L 2 h after consuming 75 g of glucose.

2.2. Patients

This case-control study was conducted at the Obstetrics and Gynecology Hospital of Fudan University from October 2015 to May 2016. Eighty-five women with GDM (GDM group) and 85 women without GDM (control group) were selected. The inclusion criteria were the following: 1) singleton pregnancy; 2) absence of any other health complications; 3) 25-35 years of age; 4) 24-28 gestational weeks; and 5) Han nationality.

2.3. Research Methods

2.3.1. Clinical characteristics: We collected information including participant age, height, weight, body mass index (BMI), OGTT results and glycated hemoglobin (HbA1c).

2.3.2. Collection of plasma samples: We collected plasma samples from participants in both groups during the late second trimester (24-28 weeks). Whole blood was collected in EDTA tubes. To obtain plasma, the blood was centrifuged at $1000\times g$ for 10 min at 4°C . Plasma specimens were stored at -80°C until further analysis.

2.3.3. Test methods: Ferroportin, hepcidin, soluble transferrin receptor and insulin (INS) levels were determined using ELISA kits (CUSABIO, Wuhan, China). The intra- and interassay CVs were all less than 10%. Serum ferritin was determined by chemiluminescent microparticle immunoassay (ARCHITECT-I2000, Hitachi, Tokyo, Japan). The intra- and interassay CVs were less than 5%.

2.4. Insulin resistance (IR) evaluation indices:

The homeostasis model assessment for insulin resistance (HOMA-IR) was used to evaluate IR.

$$\text{HOMA-IR} = [\text{Ins} \times \text{fasting plasma glucose (FPG)}] / 22.5.$$

2.5. Statistical Analysis

Statistical analyses were performed using SPSS 22.0. The Shapiro-Wilk test was used to evaluate distributions for normality. For quantitative variables with normal distribution, ANOVA were used for between-group comparisons, and the results are expressed as the means±standard deviation (SD). Serum ferritin values failed the normality test; therefore, those data were described using median and interquartile range (25th–75th percentiles). The nonparametric chi-square test was used to compare differences between two groups. Correlation analysis was conducted for the GDM group and the control group separately. Serum ferritin did not have a normal distribution, and Spearman correlation analysis was used. Pearson correlations were used to analyze Hepc, FPN, sTfR and glucose metabolism parameters. Statistical significance was defined as P<0.05.

3. Results

3.1. At 24-28 weeks, the values for Hepc, sTfR, SF, FPN, HOMA-IR, FPG, OGTT-1 h and 2 h plasma glucose and HbA1c were all significantly higher for participants in the GDM group than those in the normal group (P<0.05 for all). However, as shown in Table 1, the serum insulin levels in the two groups were similar (P=0.077).

Table 1. Clinical and biochemical characteristics of women with and without GDM

Parameter	GDM (n=85)	Control (n=85)	p-value
Age (years)	31.36±4.66	30.89±4.28	0.291
Weight (kg)	61.16±9.59	54.99±7.65	0.059
BMI (kg/m ²)	22.86±3.17	20.39±3.66	0.724
Height (m)	1.63±0.52	1.63±0.45	0.102
FPG (mmol/L)	5.00±0.06	4.34±0.03	0.000*
OGTT-1 h (mmol/L)	10.05±1.51	6.96±1.36	0.000*
OGTT-2 h (mmol/L)	8.42±1.43	6.11±0.96	0.010*
HbA1c (%)	4.94±0.43	4.62±0.29	0.016*
Ins (ug/L)	4.18±0.31	3.50±0.24	0.077
HOMA-IR	0.95±0.07	0.69±0.05	0.006*
SF (ng/mL)	24.90(14.15 – 41.55)	19.60(10.45 – 30.55)	0.025*
Hepc (ug/ml)	158.96±22.49	135.13±18.24	0.023*

FPN (ng/L)	564.61±80.96	467.09±62.41	0.007*
sTfR (ug/mL)	21.36±3.11	17.44±2.30	0.003*

The results are presented as means±standard deviations for normally distributed data or medians and interquartile ranges (25th-75th) for nonnormally distributed variables.

* Compared with the normal group, P<0.05. BMI—body mass index, FPG—fasting plasma glucose, OGTT-1 h—glucose level 1 h after 75 g glucose intake, OGTT-2 h—glucose level 2 h after 75 g glucose intake, HbA1c – glycated hemoglobin, Ins—insulin, HOMA-IR—homeostasis model assessment for insulin resistance, SF—serum ferritin, FPN—ferroportin, Hepc—hepcidin, and sTfR—soluble transferrin receptor.

3.2. A correlation analysis of the relationship between iron and glucose metabolism was conducted. In the women with GDM, FPN was positively correlated with OGTT-1 h and OGTT-2 h. SF, Hepc and sTfR were not correlated with any glucose metabolism parameter. In the control group, only sTfR was positively correlated with OGTT-1 h. SF, Hepc and FPN were not correlated with any glucose metabolism parameter. Besides, there was no correlation between the iron metabolism indicators in both GDM and control group. (see Table 2 and Table 3).

Table 2. Correlation analyses of iron metabolism and glucose metabolism in women with GDM

Parameter	SF		Hepc		FPN		sTfR	
	r	p	r	p	r	p	r	p
FPG	0.136	0.268	-0.179	0.145	0.172	0.160	0.170	0.165
OGTT-1 h	0.032	0.795	-0.009	0.954	0.249	0.040*	-0.135	0.273
OGTT-2 h	-0.066	0.593	-0.102	0.409	0.400	0.001*	0.177	0.124
HbA1c	0.178	0.145	-0.030	0.808	0.198	0.108	-0.067	0.587
HOMA-IR	0.083	0.500	0.043	0.730	-0.044	0.720	0.072	0.558
Ins	-0.141	0.253	0.081	0.509	-0.043	0.729	-0.043	0.727
SF	1	/	-0.026	0.812	-0.091	0.407	0.042	0.700
Hepc	-0.026	0.812	1	/	-0.020	0.858	-0.176	0.108
FPN	-0.091	0.407	-0.020	0.858	1	/	0.153	0.163
sTfR	0.042	0.700	-0.176	0.108	0.153	0.163	1	/

Table 3. Correlation analyses of iron metabolism and glucose metabolism in women without GDM

Parameter	SF		Hepc		FPN		sTfR	
	r	p	r	p	r	p	r	p
FPG	-0.104	0.390	-0.031	0.796	0.223	0.061	0.029	0.808
OGTT-1 h	0.037	0.757	0.103	0.391	0.171	0.153	0.235	0.048*

OGTT-2 h	-0.021	0.221	0.156	0.193	-0.029	0.813	0.072	0.551
HbA1c	0.041	0.736	0.021	0.861	-0.090	0.457	-0.028	0.815
HOMA-IR	0.081	0.504	0.112	0.350	0.091	0.451	-0.076	0.531
Ins	-0.141	0.253	0.032	0.793	0.076	0.530	-0.007	0.956
SF	1	/	-0.196	0.123	0.050	0.647	0.013	0.909
Hepc	-0.196	0.123	1	/	0.353	0.001*	0.039	0.722
FPN	0.050	0.647	0.353	0.001*	1	/	0.100	0.364
sTfR	0.013	0.909	0.039	0.722	0.100	0.364	1	/

4. Discussion

There was no significant difference in clinical characteristics between the two groups. At present, the pathogenesis of gestational diabetes mellitus is not completely clear, but the most widely accepted views involve insulin resistance and relative insulin deficiency [17, 18]. Consistent with this view, our findings showed that FPG, OGTT-1-hour and 2-hour plasma glucose and HOMA-IR in pregnant women with GDM were significantly higher than those values for women in the normal group.

Ferritin, a key protein regulating iron metabolism, is an important clinical determinant of iron status [19-22]. Multiple experimental studies[7, 8, 23-26] have shown that serum ferritin levels are significantly higher in women with GDM than in women without GDM. Moreover, serum ferritin levels have been found to strongly correlate with levels of plasma glucose, insulin and HbA1c, and elevated ferritin is an independent risk factor for the development of GDM. In the present study, we also found that ferritin levels were significantly higher in the GDM group relative to the normal group. However, there was no correlation between SF and any glucose metabolism parameters in the two groups. Pharm et al[27]reported that serum ferritin levels were positively associated with HOMA-IR in men but not in women, even postmenopausal women. In a recent trial in Finland, no significant difference was observed in the combined incidence of GDM between women who were advised to take routine iron supplementation (100 mg elemental Fe) and women who were not advised to take iron supplements unless they were anemic[28].

It should be noted that SF is an acute-phase reactant that may increase as a result in the subclinical inflammation associated with GDM. sTfR, a soluble form of the membrane receptor derived from its proteolysis, is negatively correlated with intracellular iron levels and less affected by inflammation. However, in this study, the sTfR level was higher in the GDM group. We also found that sTfR level was not correlated with any glucose metabolism parameters except OGTT-1 hour plasma glucose in the normal group. Abou-Shousha S et al.[29] and Anqiang Yang[30] found that elevated sTfR levels were associated with increased diabetes risk. Rajpathak SN et al [31]observed a significant positive association between sTfR levels and diabetes mellitus (DM) risk; after adjusting SF and CRP, the association was still present. They thought the possible reason was that sTfR levels may be associated with increased DM risk through a mechanism unrelated to iron overload. Other studies also

indicated that hyperinsulinemia in states of insulin resistance may contribute to high circulating sTfR levels[32]. Katherine A. Bowers found that after adjustment for prepregnancy BMI, sTfR was not associated with GDM risk[33]. We thought that the sTfR and GDM relationship is complex, elevated sTfR level is the characteristic feature of functional iron deficiency, a situation defined by tissue iron deficiency despite adequate iron stores. Whether sTfR meaningfully captures the association between higher iron concentrations and GDM is currently unclear but worthy of further investigation. Maybe when SF present in excessive amounts, the concentration of various iron regulators changes, catalyzing several cellular reactions that result in the production of reactive oxygen species, and then insulin resistance.

Hepcidin plays an important role in iron homeostasis, and FPN is the only known cellular iron exporter. The present study showed that serum Hep and FPN reflected functional iron status. Multiple studies have shown that in patients with diabetes, the concentration of hepcidin is significantly increased [24, 34, 35]. Martinelli et al. [36] found that the hepcidin level in patients with metabolic syndrome was higher than those in patients without metabolic syndrome, and these results were maintained after correcting for age and gender. An animal experiment constructed by Jingwen Wang et al.[37] found that serum ferritin, hepcidin and ferroportin levels all increased with increases in iron load in mice. Aydemir F et al. [38] found that when iron was overloaded, the levels of FPN, mRNA and xenogeneic nuclear RNA also increased, as did the level of transcription. In the present study, we also found that Hepc and FPN levels were significantly higher in the GDM group relative to the normal group. However, in the women with GDM, only FPN was positively correlated with OGTT-2 h plasma glucose, and there was no correlation between Hepc and FPN and any glucose metabolism parameters in the control group. Guo X et al.[39] also found that hepcidin was not associated with insulin resistance. Interestingly, studies have shown both positive[40] and negative [41, 42] associations between hepcidin and insulin resistance.

Interestingly, there was no correlation between iron metabolism parameters in both GDM and control group. We know Hepc is considered a "negative regulator" of ferritin. Aeberli et al. [43] and Nazif et al. [44] found higher concentrations of sTfR associated with higher values of hepcidin. Some studies have even shown that iron plays an independent role in the transcription of FPN, but the results have varied in different cell types[45]. In the present study, although Hepc was negatively correlated with ferritin, there was no significant difference. The probable cause is that women with abnormal glucose metabolism may have iron metabolism disorder caused by iron overload. Rametta R et al [45]also found that dysmetabolic iron overload syndrome may be associated with a hepcidin resistance state. Besides, Hepc, FPN, SF, and sTfR levels are affected by various factors, such as obesity, inflammation, erythropoiesis, and hypoxia. Due to experimental limitations, we did not test these parameters. Further studies are required to better characterize the molecular mechanism underpinning this new iron metabolism alteration.

It should be noted that there was no correlation between insulin, HOMA-IR and any iron metabolism parameters in two groups. However, several studies have shown

that markers of insulin resistance are strongly related to markers of iron metabolism. Marleen M. J. et al.[47] found over a 7-year follow-up period that iron metabolism and related factors may contribute to IR in muscle, liver, and adipocytes, eventually leading to impaired glucose metabolism. Mi-Ra Cho et al.[14] reported that serum ferritin levels were positively and independently associated with IR. However, Bonfils L et al.[48] observed an association between ferritin and decreased insulin sensitivity among men and older women, but not among younger women. Arija et al.[49] also did not find a significant correlation between sTfR and HOMA-IR. Therefore, we think that the association between iron metabolism and glucose metabolism is affected by multiple factors.

Our study has several limitations. First, the findings were obtained from a relatively small sample of subjects. In addition, ferritin, ferroportin and hepcidin levels are affected by multiple factors, such as C-reactive protein, hypoxia and other inflammatory media, and we were unable to measure the inflammatory media. Additionally, in this study, the use of multivitamins or nutritional supplements was not assessed. Another limitation is the lack of assay standardization for sTfR.

5. Conclusion

In summary, our study suggests that ferritin, sTfR, hepcidin and ferroportin were higher in the GDM group than in the control group. Elevated hepcidin and ferroportin are associated with glucose metabolism disorder in midpregnancy. Women with abnormal glucose metabolism may have iron metabolism disorder caused by iron overload, which play an important role in GDM.

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Ethical approval

Ethical approval was granted by the medical ethics committee of the Obstetrics and Gynecology Hospital of Fudan University. Eighty-five pregnant women participated in this study. Each participant signed an independent, three-page informed consent form.

All authors declare no conflicts of interest.

References:

- [1] Feig DS, Zinman B, Wang X et al (2008) Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CAN MED ASSOC J 179(3):229-234
- [2] Kim C, Newton KM , Knopp RH(2002) Gestational Diabetes and the Incidence of Type 2 Diabetes. DIABETES CARE 25:1862-1869.
- [3] Sun X, Su SP, Yang HX et al (2014) Evaluation of diabetic pregnancy outcome and one-day care for gestational diabetes mellitus after application of new diagnostic criteria. Chin J Perinat Med,17(3):186-190
- [4] Zhu WW, Yang HX, Wei YM et al (2013) Evaluation of the Value of Fasting Plasma Glucose in the First Prenatal Visit to Diagnose Gestational Diabetes Mellitus in China. DIABETES CARE 36(3):586-590
- [5] Kataria Y, Wu Y, Horskjær P et al (2018) Iron Status and Gestational Diabetes—A Meta-Analysis. NUTRIENTS 10(5):621
- [6] Liu JX, Cheng Y, Cheng HD et al (2017) Advances in research on relationship between iron supplementation and gestational diabetes. Chin J Perinat 20(5):393-396.
- [7] Zein S, Rachidi S, Awada S et al (2015) High iron level in early pregnancy increased glucose intolerance. J TRACE ELEM MED BIO 30:220-225
- [8] Zein S, Rachidi S, Hininger-Favier I (2014) Is oxidative stress induced by iron status associated with gestational diabetes mellitus? J TRACE ELEM MED BIO 28(1):65-69
- [9] Gajewska J, Ambroszkiewicz J, Klemarczyk W et al (2018) Ferroportin-Hepcidin Axis in Prepubertal Obese Children with Sufficient Daily Iron Intake. INT J ENV RES PUB HE 15(10):2156
- [10] Pietrangelo A (2017) Ferroportin disease: pathogenesis, diagnosis and treatment. HAEMATOLOGICA 102(12):1972-1984
- [11] Casu C, Oikonomidou PR, Chen H et al (2016) Minihepcidin peptides as disease modifiers in mice affected by β -thalassemia and polycythemia vera. BLOOD 128(2):265-276
- [12] Xu Z, Sun WJ, Li YH, et al(2016)The regulation of iron metabolism by hepcidin contributes to unloading-induced bone loss. Bone 94:152-161.
- [13] Ganz T, Nemeth E (2011) The hepcidin-ferroportin system as a therapeutic target in anemias and iron overload disorders. Hematology. American Society of Hematology. Education Program 2011(1):538-542
- [14] Cho M, Park J, Choi W et al (2017) Serum ferritin level is positively associated with insulin resistance and metabolic syndrome in postmenopausal women: A nationwide population-based study. MATURITAS 103:3-7
- [15] Ambroszkiewicz J, Klemarczyk W, Mazur J et al (2017) Serum Hepcidin and Soluble Transferrin Receptor in the Assessment of Iron Metabolism in Children on a Vegetarian Diet. BIOL TRACE ELEM RES 180(2):182-190
- [16] International Association of Diabetes and Pregnancy Study Groups (2010) International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. DIABETES CARE 33(3):676-682
- [17] Kusunoki Y, Katsuno T, Nakae R et al (2015) Insulin resistance and β -cell function influence postprandial blood glucose levels in Japanese patients with gestational diabetes mellitus. GYNECOL ENDOCRINOL 31(12):929-933
- [18] Simcox JA, McClain DA(2013)Iron and Diabetes Risk. CELL METAB 5: 329-341.
- [19] Braga F, Infusino I, Dolci A et al (2014) Soluble transferrin receptor in complicated anemia. CLIN

CHIM ACTA 431143-147

- [20] Beguin Y (2003) Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. CLIN CHIM ACTA 329(1-2):9-22
- [21] Nemeth E, Tuttle MS, Powelson J, et al (2004) Hepcidin regulates cellular iron efflux by binding to ferroportin and including its internalization. SCIENCE 306: 2090 -2093.
- [22] Schmidt P J, Toran PT, Giannetti AM, et al (2008) The Transferrin Receptor Modulates Hfe-Dependent Regulation of Hepcidin Expression. CELLMETAB 7:205-214.
- [23] Kataria Y, Wu Y, Horskjær P, et al (2018) Iron Status and Gestational Diabetes—A Meta-Analysis. NUTRIENTS 10(5):621
- [24] Rawal S, Hinkle SN, Bao W, et al (2017) A longitudinal study of iron status during pregnancy and the risk of gestational diabetes: findings from a prospective, multiracial cohort. DIABETOLOGIA 60(2):249-257
- [25] Zhang C, Rawal S (2017) Dietary iron intake, iron status, and gestational diabetes. The American Journal of Clinical Nutrition 106(Supplement 6):1672S-1680S
- [26] Fu S, Li F, Zhou J, et al (2016) The Relationship Between Body Iron Status, Iron Intake And Gestational Diabetes. MEDICINE 95(2):e2383
- [27] Pham NM, Nanri A, Yi S, et al (2013) Serum ferritin is associated with markers of insulin resistance in Japanese men but not in women. METABOLISM 62(4):561-567
- [28] Khambalia AZ, Aimone A, Nagubandi P, et al (2016) High maternal iron status, dietary iron intake and iron supplement use in pregnancy and risk of gestational diabetes mellitus: a prospective study and systematic review. DIABETIC MED 33(9):1211-1221
- [29] Abou-Shousha S, Abd EI-Megeed MH, Sultan HK (2006) Interleukin-8, Ferritin and Soluble Transferrin Receptors in Type II Diabetes Mellitus. Egypt J Immunol 13(1):19-25.
- [30] Yang A, Zhao J, Lu M, et al (2016) Expression of Hepcidin and Ferroportin in the Placenta, and Ferritin and Transferrin Receptor 1 Levels in Maternal and Umbilical Cord Blood in Pregnant Women with and without Gestational Diabetes. INT J ENV RES PUB HE 13(8):766
- [31] Rajpathak SN, Wylie-Rosett J, Gunter MJ, et al (2009) Biomarkers of body iron stores and risk of developing type 2 diabetes. Diabetes, Obesity and Metabolism 11(5):472-479
- [32] Fernandez-Real JM, Moreno JM, Lopez-Bermejo A, et al (2007) Circulating Soluble Transferrin Receptor According to Glucose Tolerance Status and Insulin Sensitivity. DIABETES CARE 30(3):604-608
- [33] Bowers KA, Olsen SF, Bao W, et al (2016) Plasma Concentrations of Ferritin in Early Pregnancy Are Associated with Risk of Gestational Diabetes Mellitus in Women in the Danish National Birth Cohort. The Journal of Nutrition 146(9):1756-1761
- [34] Aydin S, Celik O, Gurates B, et al (2013) Concentrations of preptin, salusins and hepcidins in plasma and milk of lactating women with or without gestational diabetes mellitus. PEPTIDES 49:123-130
- [35] Derbent AU, Simavli SA, Kaygusuz I, et al (2013) Serum hepcidin is associated with parameters of glucose metabolism in women with gestational diabetes mellitus. The Journal of Maternal-Fetal & Neonatal Medicine 26(11):1112-1115
- [36] Martinelli N, Traglia M, Campostrini N, et al (2012) Increased Serum Hepcidin Levels in Subjects with the Metabolic Syndrome: A Population Study. PLoS One 7(10):e48250.
- [37] Wang JW, Xu LH, Yao X, et al (2017) Expression Changes of Hepcidin and Ferroportin 1 in Murine Model of Iron Overload. J EXP HEMATOL 25(03):936-940.
- [38] Aydemir F, Jenkitkasemwong S, Gulec S, et al (2009) Iron Loading Increases Ferroportin

Heterogeneous Nuclear RNA and mRNA Levels in Murine J774 Macrophages. The Journal of Nutrition 139(3):434-438

- [39] Guo X, Zhou D, An P et al (2013) Associations between serum hepcidin, ferritin and Hb concentrations and type 2 diabetes risks in a Han Chinese population. BRIT J NUTR 110(12):2180-2185
- [40] Jiang F, Sun Z, Tang Y et al (2011) Hepcidin expression and iron parameters change in Type 2 diabetic patients. DIABETES RES CLIN PR 93(1):43-48
- [41] Sam AH, Busbridge M, Amin A et al (2013) Hepcidin levels in diabetes mellitus and polycystic ovary syndrome. DIABETIC MED 30(12):1495-1499
- [42] Le Guenno G, Chanséaume E, Ruivard M et al (2007) Study of iron metabolism disturbances in an animal model of insulin resistance. DIABETES RES CLIN PR 77(3):363-370
- [43] Aeberli I, Hurrell RF, Zimmermann MB(2009)Overweight children have higher circulating hepcidin concentrations and lower iron status but have dietary iron intakes and bioavailability comparable with normal weight children. Int J Obes(Lond) 33(10):1111-7.
- [44] Nazif HK, El-Shaheed AA, El-Shamy KA et al (2015) Study of Serum Hepcidin as a Potential Mediator of the Disrupted Iron Metabolism in Obese Adolescents. Int J Health Sci (Qassim) 9(2):172-178
- [45] Marro S, Chiabrandov, Messana E,et al(2010)Heme controls ferroportin1 (FPN1) transcription involving Bach1, Nrf2 and a MARE/ARE sequence motif at position -7007 of the FPN1 promoter. HAEMATOLOGICA,95(8):1261-1268.
- [46] Rametta R, Dongiovanni P, Pelusi S,et al(2016)Hepcidin resistance in dysmetabolic iron overload.Hepcidin resistance in dysmetabolic iron overload. Liver Int 36(10):1540-8.
- [47] Wlazlo N, van Greevenbroek MMJ, Ferreira I et al (2015) Iron metabolism is prospectively associated with insulin resistance and glucose intolerance over a 7-year follow-up period: the CODAM study. ACTA DIABETOL 52(2):337-348
- [48] Bonfils L, Ellervik C, Friedrich N et al (2015) Fasting serum levels of ferritin are associated with impaired pancreatic beta cell function and decreased insulin sensitivity: a population-based study. DIABETOLOGIA 58(3):523-533
- [49] Arija V, Fernández-Cao JC, Basora J et al (2014) Excess body iron and the risk of type 2 diabetes mellitus: a nested case-control in the PREDIMED (PREvention with MEDiterranean Diet) study. BRIT J NUTR 112(11):1896-1904