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The Impact of Hepcidin in Diabetic Patients with Nephropathy

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Abstract

Chronic kidney disease (CKD) is one of the complications of diabetes. It is a dangerous disease the high mortality rate.This disease is accompanied with anemia, which is due to an imbalance in the secretion of the hormone erythropoietin. There is no biological factor evaluating the two cases linked to indicate the state of the disease. Hence the need for a vital indicator that helps assesses the deterioration of the disease. A total of 45 diabetic patients with nephropathy complication in different stage from out-patient clinic of the National Centre for Diabetes Treatment and Research, Mustansiriyah University were enrolled in the study. The patients were divided to three groups: (Group A) fifteen patients; normal-albumin-uria (albumin excretion in urine persistently lower than 30 mg/d), fifteen patients with micro-albuminuria (albumin 30-300 mg/d), and macro-albuminuria (albumin > 300 mg/d). Serum hepcidin, Fasting plasma glucose, hemoglobin, blood urea and creatinine were measured. There are a significant difference in serum hepcidin levels in control group (66.34±12.4 ng/ml) when compared to diabetic patients (92.41±27.33ng/m). Serum hepcidin also elevated in macro-albumin urea group (195.32±31.16 ng/ml) when compare to other groups. Hepcidin levels elevated in diabetic patients and more increase in macro and micro-albumin urea.

Keywords
Hepcidin, Diabetic nephropathy, chronic kidney disease (CKD)

Anemia is one of the diabetic nephropathycomplications.As a result of a defect in the secretion of the hormone erythropoietin, associated nephropathy. As it is associated with diabetes, macro and micro-vascular disorders which results in lack of oxygen in the tissues, which is one of the important causes of anemia, associated with diabetes nephropathy1. It has recorded that patients with diabetic patients had also anemia also in patientswith minor defect in renal function. The first cause of anemia is an inappropriate response of erythropoietin to anemia2.

Erythropoietin is an important hormone in the regulation of hemoglobin levels. Decreased erythropoietin levels lead to a significant decrease in hemoglobin levels, and this is common in chronic kidney disease. However, anemia is often discovered in the early stages of CKD3. It has been observed that impaired hemoglobin synthesis is accompanied by a reduced state of the early inflammatory process. We find a close association between chronic kidney disease accompanied by anemia and accompanied by a low grade of the inflammatory process4.

The defect of iron levels consider as important cause for anemia of chronic diseases (ACD); iron levels in the blood stream are reduced as result of decrease the a absorption of iron from intestine and the release of storage iron is reduce5.

A common complication of diabetic nephropathy is anemia. It has only lately been realized that anemia in diabetes patients frequently occurs not only in those who have preterminal renal failure but also in those who merely have mild renal function abnormalities. Anemia affects diabetic people more frequently and severely than non-diabetic patients at any level of glomerular filtration rate (GFR). An improper erythropoietin response to anemia is a significant contributor to anemia. Iron deficiency and iatrogenic factors, such as the use of ACE inhibitors, are additional risk factors. The erythropoietin concentration predicts a more rapid loss of glomerular function when serum creatinine is still normal. When serum creatinine levels rise, which is a reliable indicator of renal function, hemoglobin levels can be used to anticipate how quickly things will change.6. Because most of the late complications of diabetes involve ischemic tissue damage, it would be intuitively plausible that treatment with human recombinant erythropoietin should be beneficial, but definite evidence for this hypothesis is currently not available7.

Hepcidin is a hormone with active isoform hepcidin-25. It has an important role in iron metabolism and in controlling inflammatory processes8.

Hepcidin levels are found during the production of active red blood cells because erythropoietin regulates it along with iron. Hepcidin production is reduced during active erythropoiesis, increasing the amount of iron available for hemoglobin formation. Although the mechanism of inhibition is unclear, it might be a diffuse factor brought on by erythrocyte precursors in the bone marrow (erythrocyte factor)9.

The aim of the current study is that to evaluate the concentrations of hepcidin in circulation in diabetic nephropathy patients and compared with diabetic and healthy subjects.

Material and Methods

Theis study included 45 diabetic patients with various stages of nephropathy from the out-patient clinic of the National Centre for Diabetes Treatment and Research, Mustansiriyah University. The patients were split into three groups: group A, which included 15 patients with normal albuminuria (albumin excretion in urine consistently less than 30 mg/d), group B, which included 15 patients with micro-albuminuria (albumin 30-300 mg/d), and group C, which included 15 patients with macro-albuminuria (albumin 300 mg/d). Twenty healthy participants from the National Centre for Diabetes Treatment and Research in Baghdad, who were age and sex matched with the patients, were used as a control group. Each participant signed a written informed consent. The measurements included plasma fasting blood glucose (FPG), blood urea, serum creatinine. Serum hepcidin supplied by (Ray Bio tech, USA) were detected by enzyme-linked immunosorbent assay (ELISA).

Table-1: Patient's characteristics.

	Control n=20	Macro-albumin urea n=15	Micro-albumin urea n=15	DM n=15
Age	45.2±4.71	47.31±5.6	47.66±3.12	46.05±
Gander: Male Female	11(55%) 9 (45%)	9(60%) 6(40%)	7 (46.67%) 8 (53.33%)	8 (53.33%) 7 (46.67%)
BMI	26.65±3.1	27.21±2.4	27.38±3.1	28.6±3.05
Duration of Disease	-	8.43± 2.8 a	8.14±3.3 a	3.1±2.2 b
Treatment - Metformin - Glyburide - Combination (Metformin+Glyburide)	-	 3 (20%) 6 (40%) 6 (40%)	 4 (26.66%) 7 (46.6%) 4 (26.66%)	 9(60%) 5 (33.33%) 1 (6.67%)

a,b Different letters mean there were a significant difference($p<0.05$).

Statistical analysis

The sample size (n), mean, standard deviation (SD), and standard error of the mean were used to present the results (SEM). The student t-test and correlation test between different parameters were used to examine the statistical significance between the groups, with a P-value considered significant at a level < 0.05. All statistical significance was done using The Statistical Analysis System-SAS (2012).

Results and Discussion

Table-1 shows the characteristics of all volunteers in the current study.

The Mean of hepcidin levels show that there was a significant difference in patients groups when compare to control, as well as there was a significant difference among patients groups ($P<0.05$), as shown in table-2.

Table-2: The mean of serum hepcidin, Hb, urea, serum creatinine and FPG in all study groups.

Parameters	Control	Macro-albumin urea	Micro-albumin urea	DM
Hepcidin (ng/ml)	66.34±12.4 a	195.32±31.16 b	154.6±24.68 c	92.41±27.33 d
Hemoglobin (g/dl)	13.6±2.2a	8.4±2.8b	10.8±2.7c	13.4±3.1a
Urea (mg/dl)	27.6±7.8a	147.8±33.7b	83.2±24.8c	31.8±6.4a
serum creatinine (mg/dl)	0.82 ±0.14a	6.4±2.46b	3.32±1.93c	0.81±0.12a
FPG (mg/dl)	83.45±5.4a	187±33.5d	154.56±27.8c	127.4±12.4b

a,b,c.d Different letters mean there were a significant difference ($P<0.05$).

There was a significant difference in the mean of hemoglobin when compare between control and both macro and micro-albumin urea ($p<0.05$) but there was no significant difference between DM and control groups (table-2).

Both blood urea and serum creatinine were significantly higher in macro and micro-albumin urea groups when compare to control and diabetic patients groups, as well as there was a significant difference among the patients groups (macro and micro-albumin urea group), as shown in table-2.

Current study is designed to assess hepcidin levels in diabetic and healthy patients, as well as to study the effect of hepcidin levels in patients with diabetic nephropathy at different stages .

An imbalance in carbohydrate metabolism is a very common symptom in patients with chronic renal failure. Impaired glucose tolerance was reported with loss of renal function. Metabolism imbalances and insulin resistance appear when the GFR is less than 50 ml/minute10. The decrease in the rate of glucose metabolism as a result of impaired sensitivity of insulin receptors is the most common imbalance as it is associated with type 2 diabetes, impaired glucose oxidation, and an imbalance in insulin secretion, which leads to uremic glucose intolerance. Accumulation of uremic nitrogen toxins appears to be the main cause of a certain imbalance in the action of insulin11.

A complication associated with chronic kidney failure is metabolic acidosis, anemia, or secondary hyperparathyroidism. A recent study reported that the insulin/glucose-like regulation of blood iron concentrations, that is, hepcidin, was in response to glucose12. Moreover, cell culture experiments indicate that a pancreatic cell may be a source involved in the regulation of insulin and hepcidin after glucose is absorbed from the gut. These studies and evidence indicate that, by stimulating the release of hepcidin from pancreatic cells, glucose may have a role in regulating iron concentrations in the blood13.

Conclusion

From the results of this study, we can conclude that hepcidin in patients with CKD were reflects development of disease, while it was correlated to iron status in diabetic patients with CKD. However, hepcidin was considered as independent marker for assessment of iron statues and kidney functions. Moreover, hepcidin levels elevated in diabetic patients and more increase in macro and micro-albumin urea.

Conflict of Interest

There are no conflicts of interest to declare.

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