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The determinants of hepcidin level in chronic kidney disease and hemodialysis Saudi patients

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ARTICLE INFO

Article history:
Received 17 October 2013
Accepted 9 April 2014
Available online 20 May 2014

Keywords:
Anemia
Chronic kidney disease
Glucose
Insulin resistance
Hepcidin
Iron

ABSTRACT

Background: Chronic kidney failure is associated with many kinds of metabolic changes caused by the kidney disease itself and by dialysis treatment. Chronic kidney disease (CKD) and hemodialysis patients (HD) are associated with increased serum hepcidin levels, the main regulator of iron metabolism and modulated in response to anemia, hypoxia, or inflammation.

Objectives: To investigate the determinants of hepcidin levels in patients with CKD on conservative treatment and in hemodialysed patients.

Subjects and methods: Thirty healthy controls, 40 patients with CKD and 54 consecutive patients on hemodialysis were included in the study. Serum hepcidin and markers of iron status and inflammation, glycemic status including fasting blood sugar (FBS), fasting serum insulin (FSI), the lipid profile and renal function, all were assessed using standard laboratory methods. The homeostasis model assessment-insulin resistance index (HOMA-IR) was calculated. GFR was estimated using MDRD formula.

Results: In CKD and HD patients, hepcidin was correlated to FBS, FSI, HOMA-IR and, total protein, creatinine and ferritin. eGFR was associated with hepcidin only in HD patients. In HD patients, the best predictors of hepcidin levels were serum ferritin, FBS and creatinine while in CKD patients the best predictors for hepcidin levels were serum albumin, cholesterol and HOMA-IR.

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Peer review under the responsibility of Beni-Suef University

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.bjbas.2014.05.007

Conclusions: Hepcidin levels are correlated to the glycemic status in CKD and HD patients and hepcidin levels in hemodialysed patients were significantly correlated with eGFR but it is not considered as an independent predictor for hepcidin level in these patients.

1. Introduction

Chronic kidney disease is a very real and growing problem. The total number of treated patients has markedly increased during the last 30 years (Snyder and Pendergraph, 2005). The cause of this may be explained by the growing percentage of elderly people in the population as well as by technical progress and broader availability of dialysis therapy also the increasing number of diabetic patients may be a further important factor (Van Biesen et al., 2006).

Many kinds of metabolic changes may accompany chronic kidney failure either caused by the kidney disease itself or due to dialysis treatment. The accumulation or deficit of various substances and dysregulation of metabolic pathways may participate and combine in the pathogenesis of these changes. Chronic kidney failure may cause deficit of some important substances that may be caused by increased losses during dialysis sessions, deficient intake in the diet, impaired intestinal absorption, or disturbed synthesis of some essential metabolic regulators such as erythropoietin or active vitamin D in kidneys (Cibulka and Racek, 2007).

Metabolic complications of chronic kidney failure and hemodialysis include changes in acid-base balance and changes in metabolism of proteins, carbohydrates and lipids. Additionally, chronic kidney disease is complicated by renal anemia, bone mineral disease, atherosclerosis and cardiovascular disease and oxidative stress (Cibulka and Racek, 2011). Hepcidin is a small defensin-like peptide produced primarily by hepatocytes, also by other cells like macrophages. Hepcidin has antimicrobial properties and it is the main regulator of iron metabolism that controls both the amount of dietary iron absorbed in the duodenum and the iron release by reticuloendothelial cells (Tsuchiya and Nitta, 2013). The expression of hepcidin is upregulated by a variety of stimuli such as inflammation and iron overload, and downregulated by hypoxia, anemia, and iron deficiency. CKD is associated with increased serum hepcidin levels that may contribute to the development and severity of anemia and to resistance to erythropoiesis-stimulating agents. Elevated serum hepcidin levels contribute to the dysregulation of iron homeostasis in CKD patients (Tsuchiya and Nitta, 2013). Treatment with agents that lower serum hepcidin levels or inhibit its actions may be an effective approach for restoring normal iron homeostasis and improving anemia in CKD patients. The aim of this article was to investigate first, the correlation of hepcidin levels with the glycemic status, lipid profile, inflammatory status, and iron status in patients with CKD on conservative treatment and in hemodialysed patients. Second, the predictors of hepcidin level in these patients.

2. Subjects and methods

2.1. Subjects

The study included thirty healthy controls, 40 consecutive patients with CKD who visited the outpatient Nephrology clinic of different hospitals in Taif, KSA, to ensure coverage of the full GFR range and 54 consecutive patients on hemodialysis, using a biocompatible Fresenius Polysulfone R dialysis membrane. These patients did not receive intravenous iron or erythropoietin (EPO) during dialysis. Relevant clinical and biochemical data were retrieved from the patients' records.

Inclusion criteria for the maintenance hemodialysis patients were the initiation of maintenance hemodialysis ≥ 6 months (three times per week for 4–5 h per session) prior the study and a baseline hemoglobin (Hb) level > 10 g/dl.

Exclusion criteria were the previous treatment with immunosuppressive drugs, active inflammatory disease, clinical signs of acute infection, liver disease, any malignancy, evidence of blood loss gastrointestinal bleeding, trauma, etc. Healthy controls had to have no clinical or laboratory evidence of any chronic disease. The study was approved by all participants gave informed consent and the study followed the rules of the National Medical Committee for Medical and Bioethics. Thorough clinical examination including waist circumference height, weight, BMI is also calculated as weight in kg/(height in meters)^2. Blood pressure measurement was done using manual sphygmomanometer. Mean arterial blood pressure (MAP) was also calculated. MAP = [(2 × diastolic) + systolic]/3.

2.2. Sampling

In hemodialysis patients, blood samples were collected at the start of hemodialysis. Peripheral blood samples were collected midweek from maintenance hemodialysis patients, after an overnight fast, immediately before and after a single session of hemodialysis. The samples were put into pyrogen-free tubes containing clot activator (without anticoagulant). After coagulation, samples were centrifuged (at 1500 × g for 15 min) and serum was harvested, aliquoted and stored at −70 °C until analysis. For healthy control subjects, and chronic kidney disease, blood was also drawn from a peripheral vein after an overnight fast.

2.3. Methods

Serum hepcidin levels were measured using the commercially available human hepcidin C-ELISA kit (Cusabio Biotech, Wuhan, China) according to the manufacturer's instructions. Fasting blood sugar (FBS), Total cholesterol (TC), triglycerides (TG), hemoglobin (Hb), hematocrit (Ht), total protein, albumin,