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Short Communication

Iron homeostasis in inflammatory bowel diseases

Manolov Victor[1*], Georgiev Ogniyan[2], Petrova Julia[3], Vasilev Vasil[4], Stefanova-Petrova Dyana[2], Tzrancheva Radoslava[2], Tzatchev Kamen[1] and Mitev Vanio[5]

[1]Department of Clinical laboratory and clinical immunology, Medical University Sofia

[2]Department of Propaedeutics of Internal diseases, Medical University Sofia

[3]Department of Neurology, Medical University Sofia

[4]Clinical laboratory and clinical pharmacology, University "Aleksandrovska" hospital, Sofia

[5]Department of Medical chemistry and biochemistry, Medical University Sofia

***Corresponding Author's E-mail: victhedoc2@yahoo.com**
Tel.: +359 2 9230 928

Abstract

Inflammatory Bowel Disease (IBD) includes various intestinal pathologies, the most common of which are Ulcerative Colitis (UC) and Crohn's disease (CD). Anemia is one of the most common symptoms of inflammatory bowel disease. Hepcidin is a major mediator of anemia and plays a central role in the homeostasis of the iron metabolism. It regulates the absorption of iron and release of the element from the cells by blocking the action of ferroportin, which is the only known iron exporter from macrophages, hepatocytes and duodenal enterocytes. Nineteen UC patients and 26 CD were included. They were evaluated for serum iron and hepcidin levels. Interleukin-6 (IL-6) and C-reactive protein (CRP) were measured as inflammation markers. Hepcidin and IL-6 were measured by ELISA methods. Atomic absorption spectroscopy (AAS) was used for quantification of serum Fe. CRP was quantified by nephelometric method. The results form IBD patients were compared to age and gender matched healthy controls. Statistical analysis of established results was performed using Pearson's correlation and Student's paired t-test. We found statistically significant elevated serum iron results in CD and UC patients (41.1µmol/Land 42.3µmol/L) compared to healthy controls (21.7 µmol/L); *P*<0.001. Hepcidin concentrations were increased in CD and UC cases (51.9 µg/L and 58.9 µg/L) compared to controls (24.8 µg/L); *P*<0.001. IL-6 and CRP levels were elevated in both CD and UC (IL-6: 12.4pg/mL and 13.7pg/mL; CRP: 12.9mg/L and 13.1mg/L) in comparison to normal values in healthy controls (IL-6: 4.4pg/mL; CRP: 1.0mg/L); *P*<0.005.Evaluation of serum hepcidin in IBD patients may become a key element in the diagnosis and treatment of anemia in the near future. The study of hepcidin has potential role in diagnostic algorithms for differentiation between iron deficiency anemia (IDA) and anemia of chronic diseases (ACD) and the combination of IDA/ACD.

Keywords: Crohn's Disease, Hepcidin, Inflammatory Bowel Disease, Iron Homeostasis, Ulcerative Colitis

List of abbreviations

AAS– Atomic Absorption Spectroscopy; **ACD** – Anemia of Chronic Disease
ADMA – Asymmetric Dimethylarginine; **ALT** – Alanine Amino-Transferase
AST – Aspartate Amino-Transferase; **ATP** – Adenosine Triphosphate
CBC – Complete Blood Count; **CHr** – Hemoglobin Concentration in Reticulocytes
CRP – C-reactive Protein; **DAS** – Disease Activity Score;
IDA – Iron Deficiency Anemia; **RA** – Rheumatoid Arthritis
Se – selenium; **TIBC** – Total Iron-Binding Capacity
VEGF – Vascular Endothelial Growth Factor

INTRODUCTION

IBD includes various intestinal pathologies, the most common of which are UC and CD. As UC and CD are manifested clinically with similar symptoms which may include diarrhea, rectal bleeding, abdominal pain and weight loss (Frettland et al., 1990). Although the pathogenesis of IBD remains still not well understood, IBD is defined as a multifactorial disease that involves both genetic and autoimmune components, as well as environmental factors (Kim et al., 2012). It is believed that the inflammatory changes in the intestinal mucosa associated with an increased risk of bacterial invasion and endotoxemia.

Recent data suggests that hepcidin is a major mediator of anemia and plays a central role in the homeostasis of the iron metabolism. It regulates the absorption of iron and release of the element from the cells by blocking the action of ferroportin which is iron exporter from macrophages, hepatocytes and duodenal enterocytes. Literature on the role of hepcidin in the pathogenesis of anemia in IBD patients are quite limited and the results - contradictory. We have established high levels of urinary hepcidin in patients with CD mainly in the active phase of the disease (Semrin et al., 2006).

Contrary to this, Arnold and co-authors establish significantly reduced serum concentrations of hepcidin compared with healthy controls, regardless of the presence or absence of anemia (Arnold et al., 2009). Probably, the reason for these divergent results is due to the fact that serum concentrations of hepcidin are regulated not only by inflammatory cytokines (such as IL-6), but also by other factors such as serum iron and activity of erythropoiesis.

MATERIALS AND METHODS

Nineteen UC patients and 26 CD were included. They were evaluated for serum iron and hepcidin levels. IL-6 and CRP were measured as inflammation markers. Hepcidin and IL-6 were measured by ELISA methods. AAS was used for quantification of serum Fe. CRP was quantified by nephelometric method. The results from IBD patients were compared to age and gender matched healthy controls. Statistical analysis of established results was performed using Pearson's correlation and Student's paired t-test.

All patients included in the trial have signed Informed Consent according to respective requirements from The Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

We found statistically significant elevated serum iron results in CD and UC patients (41.1 µmol/Land 42.3 µmol/L) compared to healthy controls (21.7 µmol/L); $P<0.001$. Hepcidin concentrations were increased in CD and UC cases (51.9 µg/L and 58.9 µg/L) compared to controls (24.8 µg/L); $P<0.001$. IL-6 and CRP levels were elevated in both CD and UC (IL-6: 12.4pg/mL and 13.7 pg/mL; CRP: 12.9 mg/L and 13.1 mg/L) in comparison to normal values in healthy controls (IL-6: 4.4pg/mL; CRP: 1.0 mg/L); $P<0.005$.

DISCUSSION

Evaluation of serum hepcidin in IBD patients may become a key element in the diagnosis and treatment of anemia in the near future. The study of hepcidin has potential usefulness in diagnostic algorithms for differentiating between IDA, ACD and the combined state IDA/ACD. Until recently, the molecular mechanisms and pathogenesis in disturbed distribution of iron in ACD was unknown. It is now clear that inflammatory cytokines are released during acute infection or chronic disease may alter the systemic metabolism of iron by stimulating the synthesis of hepcidin, iron regulatory hormone Sun CC et al., 2012). Patients with ACD have low serum iron concentration, low or normal total iron-binding capacity and low transferrin saturation, and low number of reticulocytes (Stephens BJ et al., 2013). Researches over the past 10 years have shown that functional iron deficiency in ACD may be due to increased levels of regulatory hormone hepcidin.

The assessment of the severity of inflammation in the intestinal mucosa comprises determining the activity of certain biomarkers (C-reactive protein, myeloperoxidase, pyruvate kinase, etc.), Inflammatory cytokines (IL-6, TNF-α and IL-1β) and hematological parameters (HB, leukocyte and platelet count, MPV, RDW, ESR).

CRP is one of the most commonly studied in serum inflammatory marker to assess the degree of inflammation. It was found that serum levels were different in the UK and CD. In approximately 80% of patients CD register highly overestimation of the CRP, until such dependence in UK was not found Saverymuttu SH et al., 1986). These differences still no definite explanation, more so in both forms of IBD are elevated levels of inflammatory cytokines IL-6, TNF-α and IL-1β (Vermeire S et al., 2006; Gross V et al., 1992). The role of CRP levels in IBD is associated primarily with monitoring the course of disease and change the inflammatory status of inactive inflammation (remission) in active (relapse) (Consigny Y et al., 2001). The accumulation of iron in the colon is most likely due to increased serum levels of hepcidin, combined with increased production of interleukin-6, STAT-3, TFR2, BMP4 (Wang L et al., 2012). Several studies show

featuring hepcidin in carcinogenesis and metastasis processes. It is directly involved prooncogen or indirectly by altering the homeostasis of the iron. Iron leads to formation of reactive free radicals to proinflammatory effects in carcinogenesis of the rectum, small intestine, liver and prostate. Hepcidin high levels are the cause of an inadequate therapeutic response to erythropoietin stimulating agents in the treatment of anemia in a number of tumor diseases. The response of the synthesis of hepcidin could be a novel therapeutic approach in patients with anemia and tumor diseases.

CONCLUSION

Hepcidin concentrations were increased in CD and UC cases (51.9 µg/L and 58.9 µg/L) compared to controls (24.8 µg/L). Evaluation of serum hepcidin in IBD patients may become a key element in the diagnosis and treatment of anemia in the near future. The study of hepcidin has potential role in diagnostic algorithms for differentiation between iron deficiency anemia (IDA) and anemia of chronic diseases (ACD) and the combination of IDA/ACD.

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Conflict of Interest

The participants declare that we have no-conflicts with any organization or institute during preparation of materials in short communication called “Iron homeostasis in inflammatory bowel diseases” that is given to *Merit Research Journals of Medicine and Medical Sciences*. All patients included in the trial have signed Informed Consent according to respective requirements from The Code of Ethics of the World Medical Association (Declaration of Helsinki).

This article has been prepared after collection of samples from patients diagnosed with inflammatory bowel diseases from the Clinic of Gastroenterology at University "Aleksandrovska" hospital. During this period no pharmaceutical or other company was involved in the trial.

All authors disclose that have no any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

There is no any potential Conflicts of Interest Related to Individual Authors' Commitments. All authors are responsible for disclosing all financial and personal relationships that might bias their work. All authors states that no potential conflicts exists.

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