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Serum hepcidin concentrations correlate with ferritin in patients with inflammatory bowel disease☆

Ingo Mecklenburg[a,1], Diana Reznik[a,1], Elizaveta Fasler-Kan[a,b], Jürgen Drewe[a], Christoph Beglinger[a], Petr Hruz[a,*], On behalf of the Swiss IBD Cohort Study Group

[a] *Department of Gastroenterology and Hepatology, University Hospital Basel, Basel, Switzerland*
[b] *University of Applied Sciences Northwestern Switzerland (FHNW), Institute of Chemistry and Bioanalytics, Muttenz, Switzerland*

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Abstract

Background and aims: Anemia is a frequent complication of inflammatory bowel disease (IBD). Hepcidin, a key mediator in this anemia, is up-regulated by high iron levels and inflammation, and serum levels are elevated in IBD. However, the extent of inflammatory activity and iron deficiency for the regulation of hepcidin is not known. This study aimed to evaluate serum hepcidin levels in anemic and non-anemic IBD patients, with iron or non-iron deficiency, and active or inactive disease.

Methods: This retrospective, observational study analyzed serum hepcidin levels from 247 patients with IBD (130 Crohn's patients and 117 with ulcerative colitis) recruited at Swiss Inflammatory Bowel Disease Cohort Study centers. Patients were divided into 5 different groups using criteria of active and inactive diseases (C-reactive protein, and CDAI/MTWAI = disease activity-index), anemia (hemoglobin) and iron deficiency (ferritin) and compared to healthy controls with no signs of anemia and normal ferritin levels. Hepcidin was measured using enzyme-linked immunosorbent assay.

Results: Independent of inflammatory activity, all patients with decreased ferritin (<30 μg/L) had significantly lower hepcidin levels when compared to patients and healthy controls having

Abbreviations: UC, Ulcerative colitis; CD, Crohn's disease; IBD, Inflammatory bowel disease; SIBDCS, Swiss Inflammatory Bowel Disease Cohort Study; ACD, Anemia of chronic disease; CRP, C-reactive protein; CDAI, Crohn's disease activity index; MTWAI, Modified Truelove and Witts activity Index; ELISA, Enzyme-linked immunosorbent assay.

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* Corresponding author at: Department of Gastroenterology and Hepatology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. Tel.: +41 61 328 66 09; fax: +41 61 265 53 52.
E-mail address: petr.hruz@usb.ch (P. Hruz).

[1] Both authors contributed equally to this work.

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normal ferritin (>30 μg/L). A significant correlation between serum ferritin levels and serum hepcidin was found (Spearman's Rho = 0.491; $p < 0.001$). A backward multi-linear stepwise regression analysis showed that only ferritin, and none of the inflammatory markers or age and sex correlated significantly ($p = 0.005$) with hepcidin.
Conclusion: This retrospective analysis suggests that iron deficiency is the key trigger for hepcidin regulation in IBD patients with anemia.

1. Introduction

Inflammatory bowel disease (IBD) defined as chronic inflammatory and frequently relapsing disease of the gastrointestinal tract, implies two major disorders, Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by a discontinuous, transmural inflammation that can occur anywhere in the gastrointestinal tract, whereas UC shows a more superficial, continuous colonic inflammation that affects only the mucosal and submucosal layers.[1] Both diseases are idiopathic, but the chronic inflammatory condition of the gut is related to a combination of genetic and environmental factors that impact on normal host–microbe interactions.[2] The prevalence of CD in Europe varies from 1.52 to 213 cases per 100,000 persons, whereas the prevalence of UC is slightly higher and varies from 2.42 to 294 cases per 100,000 persons.[3]

Recent studies have demonstrated that anemia represents the most common systemic complication of IBD patients.[4,5] In an analysis of the Swiss IBD Cohort Study, anemia was found in 21.2% of all IBD patients, with a higher rate in patients from tertiary referral centers (28.8%) when compared to general practice patients (12.9%).[6] The cause of anemia in chronic inflammatory diseases is multifactorial. Most often anemia in IBD results in iron deficiency anemia (IDA), caused by reduced iron uptake from enterocytes and obvious chronic blood loss due to mucosal inflammation. Other causes that can aggravate anemia in IBD patients include vitamin B12 deficiency, folate deficiency and drug-induced anemia. On the other hand, in IBD patients, anemia of chronic diseases (ACD) can also occur, which is mediated via inflammatory mechanisms with the consequence of decreased iron levels in the circulation and limited iron availability for erythroid cells. In this latter cause of anemia, pro-inflammatory cytokines induce the formation of hepcidin, a key regulator of iron homeostasis. Hepcidin is a small antimicrobial peptide produced in the liver and transcriptionally up-regulated by high iron levels as well as inflammation.[7] Hepcidin reduces the amount of circulating iron by binding to ferroportin, a divalent iron transporter, located on the cell surfaces of hepatocytes, macrophages and the basolateral membranes of enterocytes.[8,9] Ferroportin blocks cellular iron (Fe^{2+}) export from macrophages and inhibits the transfer of absorbed iron from the basolateral membranes of enterocytes into the circulation. The reduced circulating iron results in a limited availability for erythroid progenitors and impaired erythropoiesis.

Various studies in patients having IBD and anemia exposed a relationship between hepcidin and Crohn's disease and ulcerative colitis.[10–13] Hepcidin is upregulated by inflammation through IL6-mediated STAT3 signaling.[14,15] It triggers an anti-inflammatory response in macrophages and, through its antimicrobial activity, hepcidin may be involved in the control of microbial growth. These characteristics make hepcidin an interesting target of IBD research as these suggest a dual role in host defense and iron homeostasis.[10] Hepcidin is significantly elevated in patients with CD and UC.[13] However, the exact contribution of inflammatory activity (hepcidin's function as an acute phase protein) and iron deficiency (hepcidin's function as gatekeeper of iron homeostasis) in the regulation of hepcidin in patients with IBD is not known.

With this observational study, we aimed to assess serum hepcidin levels in IBD patients with active and inactive IBDs and to correlate these levels with C-reactive protein (CRP), ferritin and hemoglobin.

2. Methods

2.1. Study patients

In this observational study, we evaluated serum hepcidin levels from 247 patients with IBD (130 patients with CD and 117 with UC), recruited at the centers participating in the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS)—a national prospective clinical cohort that started in 2006. A full description of the cohort profile has been published previously.[16] Patients were recruited through their gastroenterologists in private practices, regional hospitals and tertiary centers. Inclusion criteria were diagnoses of CD or UC established at least 4 months before inclusion and confirmed by radiological, endoscopic or surgical assessment, or after at least one recurrence of the disease. CD case ascertainment was made based on Lennard-Jones criteria.[17] Patients were excluded if they suffered from another form of colitis, were not regularly followed up for CD or UC, had no permanent residency in Switzerland, or if they did not sign the informed consent form. Patients with UC and CD included in this analysis were divided into 5 different groups, based on criteria for active and inactive diseases, presence or absence of anemia, and iron deficiency. Allocation into groups with active or inactive disease was based on measurement of C-reactive protein (CRP > 5 mg/L) and the clinical disease activity indices, CDAI (Crohn's disease activity index) for CD and MTWAI (Modified Truelove and Witts activity index) for UC. In addition, anemia (serum hemoglobin level: men Hb < 140 g/L; for women Hb < 120 g/L) and iron deficiency (serum ferritin < 30 μg/L) were used for further group stratification. A group of 21 healthy subjects with no laboratory or clinical signs of acute or chronic inflammation was used as the control group. These subjects had no laboratory signs of anemia and had normal iron status parameters. The study was approved by the local ethical committee.

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