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Original Research Article

Serum hepcidin, ferritin, MPO and M2-PK in inflammatory and tumor bowel diseases

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Abstract

Anemia is one of the most common symptoms not only in inflammatory bowel diseases, but in gastrointestinal cancer. New studies mark hepcidin as key iron metabolism regulator, blocking ferroportin, the only intracellular iron exporter. The main reason for hepcidin elevation is described as inflammation in ulcerative colitis and crohn's disease, and gastrointestinal tumor, which is connected to inflammatory cytokines, as interleukin-6. In latest years, ferritin is described as part of metabolomics of many neurodegenerative, tumor, and inflammatory diseases. We evaluated 30 patients with inflammatory bowel disease (IBD) and 19 Patient s with gastrointestinal tumor diseases in Clinic of Gastroenterology at University "Aleksandrovska" hospital; average age 51.9 ± 5.6. From 19 patients with gastrointestinal tumours, 52.6% were with stomach cancer, 47.4% with bowels intestinal cancer. Their results were compared to 49 age matched controls. Included both groups were measured for complete blood count (CBC) (on ADVIA 2120, by Siemens Healthcare), routine biochemical parameters, including Ferrozine iron and ferritin (on Dimension RxL MAX, by Siemens Healthcare), soluble transferrin receptors (by nephelometric method), hepcidin, myeloperoxidase (MPO), M2-pyruvatkinase (M2-PK) and interleukin-6 (IL-6) (by (ELISA methods). Correlations and significance were rated by Student's paired t-test and Pearson's correlation. Our study had showed elevated serum hepcidin levels in both IBD patients (61.1 ± 13.1µg/L), and in cases with gastrointestinal tumour (90.9 ± 12.1µg/L) compared to control group (21.5 ± 5.1 µg/L); *P*<0.001. Serum ferritin concentrations were elevated in IBD (261.1 ± 16.3 ng/mL) and gastrointestinal tumour cases (280.7 ± 20.0 ng/mL) compared to controls (198.7 ± 21.4 ng/mL); *P*<0.005. In both groups, we found increased MPO and M2-PK concentrations (MPO: 552.6 ± 99.7 ng/mL, and M2-PK: 88.9 ± 10.7 ng/mL) compared to healthy controls (194.7 ± 10.8 ng/mL, and 19.8 ± 1.7 ng/mL, resp.); *P*<0.001. MPO and M2-PK were correlated strongly and positively to serum hepcidin in patients with IBD and gastrointestinal tumour (r=0.670, and r=0.693; *P*<0.001). Ferritin was correlated positively to IL-6 concentrations in both groups as well (r=0.703, *P*<0.005). Increased iron is involved in production of free reactive radicals with pro-inflammatory effect in rectal, liver and prostate cancers. High hepcidin concentration is due to inadequate erythropoietin therapy in tumor diseases. Influence of hepcidin synthesis might be a new therapeutic tool for anemia diagnosis

and treatment in patients with IBD and gastrointestinal tumor diseases. Hepcidin quantification is important for individual approach in anemia treatment and therapy efficacy.

Key words: Chron's disease, ferritin, hepcidin, inflammation, interleukin-6, iron homeostasis, stomach tumour, ulcerative colitis

List of Abbreviations

ACD – anaemia of chronic disease; **CBC** – complete blood count; **CD** – Chron's disease; **ELISA** – enzyme-linked immunosorbent assay; **IBD** – inflammatory bowel disease; **IDA** – iron-deficiency anaemia; **IL-6** – interleukin-6; **M2-PK** – M2-pyruvatkinase; **MPO** – myeloperoxidase; **UC** – ulcerative colitis

INTRODUCTION

Inflammatory bowel diseases (IBD) usually include ulcerative colitis (UC) and Crohn's disease (CD). They have almost similar clinical symptoms, as diarrhea, rectal bleeding, stomach ache, weight loss (Frettland et al., 1990).

Anemia is one of the most common symptoms not only in IBD, but in gastrointestinal cancer. Its pathogenesis is usually complex, with disregulation in iron absorption, vitamin B_{12} and / or folic acid deficiency. New studies mark hepcidin as key iron metabolism regulator, blocking ferroportin, the only intracellular iron exporter (Ramey et al., 2010). Increased hepcidin in urine are found in patients with CD, especially in acute phase (Semrin et al., 2006). The main reason for hepcidin elevation is described as inflammation in both IBD and gastrointestinal tumor disease, which is connected to inflammatory cytokines, as interleukin-6 (IL-6).

In latest years, another marker for different diseases is described - ferritin. Metabolomics of neurodegenerative, tumor, inflammatory diseases are described (Kell and Pretorius, 2014). In 2015, Nakanishi K and col., describe hyperferritinemia and fever in adults with….. (Nakanishi and Kinjo, 2015).

Myeloperoxidase (MPO) is a key component from oxygen-dependent microbial activity, and tissue damage in acute or chronic inflammation. MPO is found localized in neutrophyls cytoplasm, and it might be use as inflammatory marker (Gonzales et al., 1999). This could be further elaborated in other studies which showed the elevated MPO concentration in UC and in CD (Palyu et al., 2011).

Pyruvatkinase is an important enzyme in glucose metabolism. In all tumors, including gastrointestinal, type M2 is mainly isolated. Various studies describe increased M2-PK in colon, rectal, stomach, esophageal, and pancreatic tumors (Turner et al., 2010).

We aimed to find a correlation between iron homeostasis regulator hepcidin and MPO and M2-PK in patients with IBD and gastrointestinal tumour diseases.

MATERIALS AND METHODS

We evaluated 30 patients with IBD and 19 patients with gastrointestinal tumor diseases in Clinic of Gastroenterology at University "Aleksandrovska" hospital; average age 51.9 ± 5.6. From 19 patients with gastrointestinal tumours, 52.6% were with stomach cancer, 47.4% with bowelsintestinal cancer. These two groups are considered as one in further presentation with results. Theirresults from patients with inflammatory and tumour bowel diseaseswere compared to 49 age matched controls. All includedBothgroups were measured for CBC (on ADVIA 2120, by Siemens Healthcare), routine biochemical parameters, including Ferrozine iron and ferritin (on Dimension RxL MAX, by Siemens Healthcare), soluble transferrin receptors (by nephelometric method), hepcidin, MPO, M2-PKand IL-6 (by ELISA methods).

Signed informed consent was obtained from all patients and controls according to the Declaration of Helsinki (Directive 2001/20/EO). This study is part of Grants 2016, sponsored by Medical University, Sofia, Bulgaria and was approved by its Ethics Committee.

For statistical evaluation of results we used SPSS 13.0 (IBM). Correlations and significance were rated by Student's paired t-test and Pearson's correlation.

RESULTS

Table 1 shows demographic parameters of patients with IBD and gastrointestinal tumor diseases and of control group.

Table 2 represents serum hepcidin concentration in patients with IBD and gastrointestinal tumor diseases and of control group.

Serum hepcidin concentrations are increased in IBD and gastrointestinal tumour patients compared to healthy

Table 1. Demographic parameters of patients with IBD and gastrointestinal tumor diseases and of control group

Groups	UC		CD		TUM	
	male	female	male	female	male	female
n	17		13		19	
n_1	8	9	7	6	11	8
average age (in years)	46.5	49.3	49.1	45.5	60.2	61.6

n – total number; n_1 – number by gender; UC – ulcerative colitis; CD – Chron's disease; TUM – tumor bowel diseases

Table 2. Serum hepcidin concentration in patients with IBD and gastrointestinal tumor diseases and of control group (presented as mean, minimal and maximal concentrations)

	Controls	UC	CD	TUM
n	49	17	13	19
$\bar{X}$	21.5 µg/L	65.5 µg/L	56.7 µg/L	90.9 µg/L
min	16.4 µg/L	48.9 µg/L	45.6 µg/L	78.8 µg/L
max	23.7 µg/L	82.1 µg/L	67.8 µg/L	103.0 µg/L

n – total number; UC – ulcerative colitis; CD – Chron's disease; TUM – tumor bowel diseases

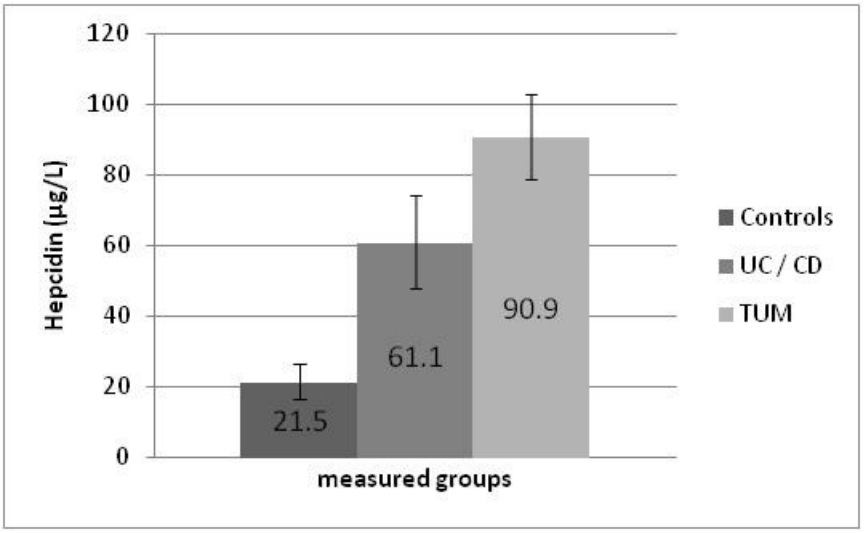

Figure 1. Quantified serum hepcidin levels in UC, CD, and gastrointestinal tumour diseases and in control group (presented as average level plus/minus error bar)

Table 3. Serum IL-6, MPO and M2-PK concentrations in patients with IBD and gastrointestinal tumor diseases and of control group (presented as mean and standard deviation)

	Controls	UC	CD	TUM
n	49	17	13	19
	mean ± SD	mean ± SD	mean ± SD	mean ± SD
IL-6 (pg/mL)	1.4 ± 0.3	10.5 ± 2.9	10.5 ± 3.5	10.8 ± 3.7
MPO (ng/mL)	194.7 ± 25.6	480.5 ± 103.4	488.4 ± 106.2	688.9 ± 107.7
M2-PK (ng/mL)	19.8 ± 4.1	85.4 ± 10.5	72.8 ± 11.6	108.1 ± 35.6

n – total number; UC – ulcerative colitis; CD – Chron's disease; TUM – tumor bowel diseases; IL-6 – interleukin-6; MPO – myeloperoxidase; M2-PK – M2-pyruvate kinase

controls; *P*<0.001. (Figure 1).

Table 3 represent serum IL-6, MPO and M2-PK concentrations in patients with inflammatory and tumor bowel diseases and of control group.

Table 4. Average levels and standard deviation of measured haematological and biochemical parameters in patients with IBD and gastrointestinal tumor diseases and in control group

Parameter	Controls mean ± SD	UC mean ± SD	CD mean ± SD	TUM mean ± SD
RBC (x10*12/l)	4.75 ± 0.5	4.0 ± 0.3	3.9 ± 0.2	3.1 ± 0.1
Hgb (g/l)	144.7 ± 10.4	116.4 ± 9.1	118.5 ± 11.1	101.7 ± 14.4
Hct (l/l)	0.432 ± 0.04	0.311 ± 0.006	0.313 ± 0.008	0.232 ± 0.035
Retic (%)	1.51 ± 0.3	1.2 ± 0.2	1.1 ± 0.1	1.3 ± 0.1
CHr (pg)	30.9 ± 2.1	23.2 ± 1.0	23.7 ± 1.2	20.7 ± 0.4
MCV (fl)	88.3 ± 7.1	75.2 ± 2.7	70.7 ± 2.2	69.8 ± 2.9
MCH (pg)	29.8 ± 2.3	25.3 ± 1.1	21.9 ± 0.5	20.8 ± 0.5
MCHC (g/l)	331.1 ± 10.8	316.4 ± 6.4	316.8 ± 8.0	311.4 ± 4.1
Fe (µmol/l)	19.7 ± 7.6	32.2 ± 2.8	35.7 ± 2.7	25.9± 2.3
TIBC (µmol/l)	61.8 ± 8.2	81.2 ± 1.7	80.1 ± 3.3	80.9 ± 1.5
TRSF (g/l)	2.96 ± 0.5	2.5 ± 0.3	3.0 ± 0.2	2.3 ± 0.2
solTRfR (mg/l)	2.13 ± 0.8	6.6 ± 0.9	9.0 ± 0.9	6.4 ± 1.0
Ferritin (ng/ml)	198.7 ± 21.4	262.3 ± 19.6	259.8 ± 12.9	280.7 ± 20.0
TSAT (%)	26.2 ± 4.9	18.5 ± 4.0	14.4 ± 2.6	16.7 ± 4.3
CRP (mg/l)	1.1 ± 0.2	7.2 ± 1.0	6.8 ± 1.2	10.1 ± 1.2

n – total number; UC – ulcerative colitis; CD – Chron's disease; TUM – tumor bowel diseases; IL-6 – interleukin-6; RBC – red blood cells; Hgb – hemoglobin; HCt – hematocrit; Retic – reticulocytes; CHr- concentration of hemoglobin in reticulocytes; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; Fe – iron; TIBC – total iron binding capacity; TRSF – transferrin; solTRfR – soluble transferrin receptors; TSAT – transferrin saturation; CRP – C-reactive protein

Serum IL-6, MPO and M2-PK concentrations were statistically increased in our patients compared to healthy controls; $P<0.001$.

Table 4 presented the haematological and biochemical parameters in patients with IBD and gastrointestinal tumor diseases and in control group.

DISCUSSION

Hepcidin plays a major role in iron homeostasis and iron absorption, blocking iron in macrophages, hepatocytes and duodenal enterocytes. Some studies mentioned that hepcidin levels are increased in CD, especially in acute phase (Semrin et al., 2006). In controversy, Arnold and col., described low hepcidin concentrations in IBD compared to healthy controls, irrespective of anemia (Arnold et al., 2009). This is probably due to the fact, that the liver secretion of hepcidin is regulated not only from inflammatory cytokines (such as interleukin-6), but from erythropoiesis activity and iron concentration. In our study we found increased serum hepcidin levels in patients with IBD and gastrointestinal tumor diseases (average level from 71.1 ± 6.8 µg/l) compared to healthy controls (21.5 ± 5.1 µg/l), $P<0.001$.

In a larger study by Bergamaschi and col., the hepcidin levels were found increased significantly, that correlates to the disease activity and inflammation (Bergamaschi et al., 2013). They also found positive correlation between hepcidin and CRP and ferritin, and negative connection between hepcidin and hemoglobin concentrations. In our study we found a positive correlation between serum ferritin concentrations and IL-6 levels in IBD and tumor diseases patients (r=0.793, $P<0.001$). Ferritin is increased due to the inflammation in the intestines. However, few other studies marked that the hepcidin concentration is decreased in case of iron-deficiency anemia (Mecklenburg et al., 2014; Di Sabatino et al., 2013). The difference between serum hepcidin levels is important for differentiation between iron-deficiency anemia (IDA) and anemia of chronic disease (ACD). Quantification of serum hepcidin in IBD patients is a key element in the diagnosis and treatment of anemia. Inflammatory cytokines, released in acute or chronic infection stimulates hepcidin secretion (Sun et al., 2012). In patients with ACD serum hepcidin levels, transferrin saturation and reticulocytes are low (Stephens et al., 2013). In our study we found increased hepcidin and iron concentrations, compared to healthy controls; $P<0.05$. Serum iron correlates positively to hepcidin in IBD patients; r=0.791, $P<0.005$. Similar results were found in our other unpublished study – in patients with neurodegenerative diseases, as Alzheimer's (61.1 ± 20.7 µg/L) and Parkinson's diseases (54.9 ± 5.7 µg/L), Huntington's disease (51.6 ± 10.2 µg/L) and amyotrophic lateral sclerosis (52.4 ± 8.8 µg/L). In these cases we found correlation between serum hepcidin and quantified trace elements – selenium, zinc and copper [Manolov and col., unpublished data from Medical University-Sofia, Grant 2017, Project № 8082/2016].

Myeloperoxidase (MPO) is a key component from oxygen-dependent microbial activity, and tissue damage in acute or chronic inflammation (Palyu et al., 2011). In our study we found increased MPO concentration in IBD

and intestinal tumor diseases patients (average level 552.6 ± 99.7 ng/mL) compared to healthy controls (194.7 ± 10.8 ng/mL); *P*<0.001. MPO correlates strongly and positively to serum hepcidin in included patients (r=0.670; *P*<0.001).

Pyruvatkinase as an important enzyme in glucose metabolism is mainly isolated as typ M2. In different studies increased M2-PK is connected to colon, rectal, stomach, esophageal, and pancreatic tumors (Annaházi et al., 2013). Our study found increased M2-PK levels in patients with inflammatory and tumor bowel diseases (mean level 88.9 ± 10.7 ng/mL) compared to healthy controls (19.8 ± 1.7 ng/mL); *P*<0.001. M2-PK show strongand positive correlation to serum hepcidin in included patients (r=0.693; *P*<0.001).

Chronic bowel inflammation, especially ulcerative colitis is characterized by increased risk of colorectal cancer. Iron deposition in colonocytes play pro-oncogenic role (Sasu et al., 2010). Increased tissue iron is connected to elevation in hepcidin secretion, in combination with production of IL-6, transferrin receptors 2, and other (Wang et al., 2012). Increased iron is involved in production of free reactive radicals with pro-inflammatory effect in rectal, liver and prostate cancers. High hepcidin concentration can be explained by inadequate erythropoietin therapy in tumor diseases. Influence of hepcidin synthesis might be a new therapeutic tool for anemia diagnosis and treatment in patients with with IBD and gastrointestinal tumor diseases.

Hepcidin quantification is important for individual approach in anemia treatment and therapy efficacy.

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Ethics

Signed informed consent was obtained from all subjects and controls according to the Declaration of Helsinki (Directive 2001/20/EO). This study was a part of Grants 2016, sponsored by Medical University, Sofia, Bulgaria and was approved by its Ethics Committee.

Declaration of Interest

The participants: *Manolov Victor, Petrova Julia, HadjidekovaSavina, GeorgievOgnyan, Stefanova-Petrova Diana, TzrynchevaRadoslava, Vasilev Vasil, Petrova Maria, KunchevTodor, JelevYavor, JeliazkovPetar, MarinovBorislav, GramatikovaZlatina, TzatchevKamen, TraykovLatchezar, MitevVanio,* Declare that we have no-conflicts with any organization or institute during preparation of materials in short communication called “Serum hepcidin, ferritin, MPO and M2-PK in inflammatory and tumor bowel diseases” that is given to *Merit Research Journal of Medicine and Medical Sciences (MRJMMS)*. 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 withinflammatory and tumour bowel diseasesfrom theClinic of Gastroenterology at"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 statesthat no potential conflicts exist.

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