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A Study of Changes in Prohepcidin and Iron Levels in Patients with Liver Transplant and Chronic Viral Hepatitis

Karaciğer Naklinde ve Kronik Viral Hepatitli Hastalarda Prohepsidin ve Demir Parametrelerinin Değişiminin Araştırılması

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ABSTRACT

Aim: To study changes in hepcidin, a key protein synthesized in the liver, following chronic viral hepatitis, cirrhosis and/or liver transplant, as well as the effect of hepcidin level variation on liver function tests and iron levels.

Materials and Methods: The patient population was distributed as follows: Group 1: inactive chronic hepatitis B (n=31); Group 2: chronic hepatitis C (n=30); Group 3: decompensated cirrhosis linked to hepatitis C virus (HCV) or hepatitis B virus (HBV) (n=29); Group 4: decompensated HCV- or HBV-related cirrhosis treated by liver transplantation (n=31).

Results: The following characteristics were unequally distributed among the groups: age, Hb, AST, ALP, LDH, T. bil, albumin, total cholesterol, HDL, serum total iron binding capacity, and transferrin saturation (TS). In the two-group comparison of Groups 1 and 2, significant differences in Hb, AST, AP, albumin, and prohepcidin were observed; the latter was more elevated in HCV patients (Group 2) ($p<0.05$). Comparison between Groups 3 and 4 yielded significant differences in Hb, AST, LDH, T. bil, albumin, total cholesterol, serum iron, and TS. Prohepcidin was most elevated in Group 2. Prohepcidin level was positively correlated with ferritin and negatively with albumin and Hb in all study groups. The highest concentration of ferritin was encountered in Group 4 patients, who had undergone liver transplant, followed in decreasing order by Group 3, Group 2 and Group 1; however, no statistically significant difference could be established ($p=0.052$).

Conclusion: In our study, a significantly positive correlation between AST/ALT and prohepcidin levels in patients who had liver transplantation caused by HBV or HCV was established. This finding may be an indicator of inflammation after transplantation.

Keywords: Liver transplant, chronic viral hepatitis, prohepcidin

ÖZ

Amaç: Çalışmamızda, karaciğerde sentezlenen ve demir regülasyonunda anahtar role sahip olan hepsidinin kronik viral hepatit, siroz ve nakil sonrası hepsidin düzeyindeki değişimin karaciğer fonksiyon testleri ve demir parametreleri ile ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Hasta popülasyonu, Grup 1: inaktif kronik hepatit B (n=31); Grup 2: kronik hepatit C (n=30); Grup 3: Hepatit C virüs (HCV) veya hepatit B virüse (HBV) bağlı dekompanse siroz (n=29); Grup 4: HCV ya da HBV nedeniyle dekompanse siroz gelişip karaciğer nakli yapılan hastalar (n=31) olarak dağıtıldı.

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Bulgular: Tüm guruplar ele alındığında yaş, cinsiyet, Hb, AST, ALP, GGT, LDH, T. bil; albumin, toplam kolesterol, yüksek yoğunluklu lipoprotein, SDBK ve transferrin satürasyonunda (TS) fark saptandı. Kronik inaktif HBV ile kronik HCV hastaları arasında Hb, AST, ALP, albumin ve prohepsidin düzeyleri arasında anlamlı fark saptanmış olup prohepsidin düzeyi HCV olgularında daha fazla bulundu (p<0,05). Dekompanse siroz hastaları (Grup 3) ile karaciğer Tx (Grup 4) hastaları karşılaştırıldığında Hb, AST, LDH, T. bil, albumin, toplam kolesterol, Fe ve TS arasında anlamlı fark bulundu. Prohepsidin düzeyinin özellikle Kronik HCV olgularında daha yüksek olduğu, prohepsidinin tüm gruplarda ferritin ile pozitif korelasyon içerisinde olduğu, hemoglobin ile negatif korelasyon içerisinde olduğu saptandı. Ferritinin gruplar arası dağılımına bakıldığında en fazla karaciğer nakli yapılan grupta yüksek olduğu, bunu da sırasıyla karaciğer sirozu, HCV grubu ve kronik inaktif HBV hastalarının izlediği görüldü, ancak aralarında istatistiksel olarak anlamlı bir fark saptanmadı (p=0,052).

Sonuç: Çalışmamızda HBV veya HCV'ye bağlı karaciğer nakli yapılan hastalarda AST/ALT ve prohepsidin düzeyleri arasında anlamlı pozitif korelasyon saptandı. Bu bulgu nakil sonrası enflamasyonun göstergesi olabilir.

Anahtar Kelimeler: Karaciğer nakli, kronik viral hepatit, prohepsidin

INTRODUCTION

Studies in recent years have increased our understanding of iron metabolism by identifying new molecules that play a role in iron homeostasis. Hepcidin, a small-molecule peptide hormone, was discovered to take part in the regulation of immunity and inflammation in addition to iron metabolism. This discovery led to an elucidation of the pathogenesis of different types of hereditary hemochromatosis (HH) and changed our pathophysiologic understanding of anemia in inflammation[1,2].

The observation of increased hepcidin synthesis, parallel to increased dietary iron intake, has prompted the thought that hepcidin participates in iron metabolism. Its specific role was investigated in transgenic mouse models by looking for the effects of hepcidin deficiency or excess. Results have indicated that mouse hepcidin is a negative regulator of intestinal iron absorption, placental iron transport and iron secretion by macrophages[3,4]. Hepcidin synthesis is triggered by increases in plasma levels and tissue stores of iron; hepcidin then increases iron release from macrophages and duodenal enterocytes into the plasma. While this homeostasis ensures the maintenance of plasma iron within a stable range, it prevents excessive resorption of iron and its accumulation in the tissue[5]. Hepcidin is a short-living hormone (serum half-life of several minutes) and is subjected to a complex regulation with hypoxia, anemia and iron deficiency, being the major suppressors while inflammation and iron overload are the major inducers[6,7].

Hepcidin expression increases in the case of iron deficiency and decreases with iron overload[5]. Its negative regulation of intestinal iron absorption and iron release by macrophages makes it a direct-acting mediator in the pathogenesis of anemia in chronic diseases[1]. It also has intrinsic antimicrobial activity and inflammation stimulates hepcidin expression. The liver regulates hepcidin secretion according to the presence of excessive iron stores, hypoxia, anemia, and numerous other physiologic situations. In response to such stimuli, a certain number of signals that are not yet well explained, such as transferrin receptor 2, IL-6 receptor, the *HFE* gene and hemojuvelin, intervene in receptor mechanisms that affect hepcidin secretion by the hepatocytes[8,9]. Excess iron induces free radical formation through Fenton's reaction, especially that of highly reactive hydroxyl radicals, leading to lipid, protein and DNA damage. Mitochondrial membranes are sensitive to oxidative stress; mitochondrial dysfunction leads in turn to hepatocyte injury. Hepatic stellate cells are also affected by oxidative stress. Hepatocyte injury may contribute to the transformation of stellate cells into collagen-producing cells, resulting in the development of fibrosis. Reactive oxygen radicals arising from iron excess may also create an inflammatory environment that impairs liver function[10].

The hepatotropic viruses hepatitis B (HBV) and hepatitis C (HCV) are among the main causes of chronic liver disease, progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Even though the mechanisms of liver damage by chronic hepatitis is not entirely understood, excessive iron stores are known to have a role. Different authors have shown the frequent increase of serum ferritin and iron levels and transferrin saturation (TS) in cases of chronic hepatitis B (CHB) and hepatitis C (CHC)[11,12].

MATERIALS AND METHODS

Patients who were followed up at the Gastroenterology and Liver Transplantation Outpatient Clinics of the Department of Gastroenterology and Hepatology, Dokuz Eylül University Faculty of Medicine, from November 2010 to June 2011, were included in the study. The study was approved by Dokuz Eylül University Faculty of Medicine Clinical Research Ethics Committee (date: 29.09.2010, no: 2010/13-21). The patients recruited into the study had CHB or CHC, decompensated cirrhosis of the liver, or had received a liver transplant as a result of either HBV or HCV.

The study population was divided as follows: patients with inactive CHB (n=31); those with CHC (n=30); patients with decompensated cirrhosis developing in the presence of HBV or HCV (n=29); and those with decompensated HCV- or HBV-related cirrhosis treated by liver transplantation (n=31).

Diagnostic criteria were, for HCV infection: Anti-HCV antibody and HCV RNA positive (+), negative (-) Hb surface antigen (HBsAg); for chronic inactive HBV infection: HBsAg (+), anti-HBe (+), HBV DNA (-) and normal liver function test (LFT). Patients receiving antiviral treatment, those diagnosed with iron deficiency anemia, and patients receiving iron replacement therapy were deemed ineligible for the study. Also, those who had other causes of chronic hepatitis, such as Wilson's disease or HH, those with autoimmune, alcoholic or toxic hepatitis and patients with HCC or chronic renal failure were found to be ineligible for the study.

Proprietary ELISA assay kits (Prohepcidin EIA-4644 DRG Diagnostics, DRG Instruments GmbH, Marburg, Germany) were used to determine prohepcidin serum levels.

Determinations of Hb, aspartate aminotransferase (AST), alanine aminotransferase (ALT), AP, GGT, LDH, T. bil, albumin, T. chol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), Fe, serum TIBC, TS and ferritin levels were performed in the institutional biochemistry laboratory; the patients' medical charts were reviewed retrospectively with regard to hepatic disease.

Statistical Analysis

The Statistical Package for the Social Sciences 15.0 statistical package was used for data evaluation. The statistical significance threshold was set at a p value of <0.05. The Kolmogorov-Smirnov test was used for fitness of sample values to normal distribution. In the absence of normal distribution and in cases when one of the groups had less than 30 patients, it was decided to apply non-parametric tests. Descriptive statistics were expressed as the mean and standard deviation for age, Hb, albumin, T. chol, HDL, LDL, Fe, serum TIBC, ferritin and prohepcidin; median and range were reported for the other measurements. Differences among the groups for continuous variables were tested for significance with the Kruskal-Wallis test; whenever such significance was identified, two-group comparisons were performed using the Mann-Whitney U test.

RESULTS

The 83 men and 38 women in the study were aged 18-70 years. The distribution of all recorded characteristics and parameters are shown in Table 1. Significant differences among the groups were found for age, gender, Hb, AST, AP, GGT, LDH, T. bil, albumin, T. chol, HDL, TIBC, and TS.

In the two-group comparison of Groups 1 and 2, a significant difference in Hb, AST, AP, albumin and prohepcidin was observed; prohepcidin was more elevated in Group 2 (HCV patients; p=0.009). Groups 1 (chronic inactive HBV patients) and 3 (decompensated cirrhosis patients) were significantly different in AST, AP, GGT, LDH, T. bil, albumin, T. chol, HDL, TIBC, TS and ferritin levels (p<0.05).

Comparison of Group 1 to Group 4 (liver transplant patients) revealed significant differences in Hb, AP, GGT, T. bil, HDL, Fe, and ferritin (p<0.05). Ferritin was highest in liver transplant patients.

Groups 2 and 4 significantly differed in AST, AP, GGT, T. bil, albumin, T. chol, HDL, TIBC, and TS (p<0.05). Groups 1 and 4 showed differences in Hb, AP, LDH, T. bil, and albumin (p<0.05). Significant differences between Groups 3 and 4 (untransplanted vs. transplanted decompensated cirrhosis) were found in Hb, AST, LDH, T. bil, albumin, T. chol, Fe, and TS (p<0.05).

The distribution of prohepcidin levels among the four groups showed no significant differences, as shown in Table 2, although higher values were seen in Group 2 (cases of CHC). Prohepcidin level was positively correlated with ferritin and negatively with Hb across the four groups. A significant positive correlation was found between AST and ALT values and prohepsidin levels in patients who underwent liver transplantation due to HBV or HCV (p=0.046).

Ferritin levels were positively correlated with those of prohepcidin, Fe, TIBC and T but negatively correlated with albumin. The highest concentrations of ferritin were found in Group 4 patients, who had undergone liver transplant, followed in decreasing order by Group 3 (untransplanted cirrhosis), then Group 2 (HCV) and Group 1 (inactive HBV); however, no statistically significant difference could be established (p=0.052).

DISCUSSION

Numerous studies on excessive iron storage and its relationship with liver damage in chronic hepatic disease have been published; the discovery of prohepcidin has helped elucidate previously unclear aspects of iron metabolism. A study by Aoki et al.[13] on the potential role of prohepcidin in the natural history of chronic hepatitis showed a significant correlation between liver hepcidin mRNA expression and hepatic iron levels and serum ferritin, but not the intensity of liver inflammation and the stage of fibrosis, in CHC patients. These authors also pointed to a cell-mediated immune response in CHC infection, in which the secreted amounts of interferons IL-2, IL-4, IL-10, tumor necrosis factor-alpha, and γ-interferon affect hepcidin mRNA expression, while mRNA levels are not related to hepatic inflammation and correlate with hepatic iron stores and serum ferritin. These observations suggest that liver hepcidin secretion increases in response to iron stores, leading to reduced iron absorption[13]. Iron and related parameters were measured in 14,462 persons by Shan et al.[14]. They indicated that serum ferritin and Fe levels were significantly higher in

Table 1. Distribution of recorded characteristics for patients in four groups

	1. Chronic inactive HBV (n=31)	2. Chronic HCV (n=30)	3. Liver cirrhosis (n=29)	4. Liver transplant (n=31)	p
Gender					
M	61.3%	43.3%	82.8%	87.1%	
F	38.7%	56.7%	17.2%	12.9%	
Age	51.7±2.56	58.8±1.8	58.6±1.4	51.6±1.9	0.009
Hb (mg/dL)	14.6±0.2	12.5±0.3	11.9±0.3	13.3±0.3	0.001
AST	21 (15-37)	27 (13-140)	44 (13-133)	25 (13-107)	0.001
ALT	21 (12-56)	23 (9-166)	25 (3-154)	23 (8-125)	0.79
AP	70 (31-99)	93 (31-510)	107 (59-315)	134 (63-497)	0.001
GGT	22 (14-64)	23 (8-474)	47 (12-294)	50 (10-305)	0.001
LDH	171 (26-305)	205 (63-399)	202 (112-370)	176 (132-327)	0.018
T. bil	0.6 (0.2-1.5)	0.68 (0.3-2.3)	1.7 (0.8-5.9)	0.9 (0.2-5.7)	0.001
Albumin	4.5±0.05	4.2±0.6	2.7±0.1	4.3±0.07	0.001
T. chol	180±5.6	181±9.4	156±5.9	178±8.7	0.041
HDL	46.6±2.1	48.7±3.2	40.6±3.6	39.6±1.8	0.014
LDL	117±4.3	116±6.4	102±5.3	114±6.5	0.455
Fe	79±3.7	80.7±7.4	88.9±8.9	65±5.5	0.082
TIBG	328±6	348±16	279±15	315±13	0.004
TS (%)	23.7±1.1	24.5±2.3	36.2±4.3	21.7±2.2	0.022
Ferritin	59.8±10.7	128.5±34.8	131.7±25.5	138.6±26.9	0.052
Prohepcidin	91±7.2	116.9±7.4	108.4±7.9	109.9±8.8	0.087

The data are described as mean±SD or median (minimum-maximum).

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AP: Alkaline phosphatase, GGT: γ-glutamyl transferase, LDH: Lactate dehydrogenase, T. bil: Total bilirubin, T. chol: Total cholesterol, TS: Transferrin saturation (%), HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation, Fe: Iron, M: Male, F: Female, HBV: Hepatitis B virus, HCV: Hepatitis C virus

Table 2. Distribution in study groups by patient gender

Group	Male	Female
Group 1. Chronic inactive HBV (n=31)	19	12
Group 2. Chronic HCV (n=30)	13	17
Group 3. Cirrhosis (n=29)	24	5
Group 4. Liver transplant (n=31)	27	4

HCV: Hepatitis C virus, HBV: Hepatitis B virus

HCV patients compared to subjects without any liver disease and ferritin level was correlated with ALT, AST and GGT.

Lee et al.[15] compared serum prohepcidin and IL-6 levels in HCV, alcoholic liver disease and non-alcoholic steatohepatitis (NASH) patients. Both prohepcidin and IL-6 levels were significantly higher in cases of CHC compared to healthy subjects, whereas patients with alcoholic liver disease and NASH did not differ from healthy subjects in these parameters.

In another study, Olmez et al.[16] examined the correlations of plasma prohepcidin with iron and related parameters, histologic activity index (HAI) and liver fibrosis score. Prohepcidin level was reported to be higher in CHC patients compared to HB. A similar result was found for the prohepcidin/ferritin ratio, while an inverse correlation existed between prohepcidin level in CHC and the HAI and fibrosis stage; no such correlation was established for HBV subjects. No significant correlation could be established between the two groups for iron and prohepcidin levels.

Consistent with the literature, the current study also showed significantly higher prohepcidin levels in HCV than in HBV patients. No correlation between prohepcidin and AST, ALT, AP, GGT, LDH, T. bil or the lipid panel tests could be evidenced in either group. Fe, TS and ferritin levels were also higher in HCV. Despite an appearance of coordination between LFT and Fe-related parameters, no statistically significant difference was detected. As seen in Figure 1, prohepcidin was highest in Group 2 (cases of CHC). The prohepcidin level was positively correlated with ferritin and liver hepcidin was shown to increase in response to an elevation of ferritin, representing the iron stores. Also, there was an inverse relationship between prohepcidin and albumin levels, which supports their opposing functions as positive and negative acute-phase reactants, respectively.

The relationship between the ferritin elevation observed in cirrhosis patients and the developing disease complications is not yet entirely understood. The relationship between elevated

iron load and hepatocyte damage has been shown by several reports. It is also hypothesized that increased hepatic iron negatively affects the post-transplantation outcome. Stuart et al.[17] studied the post-transplantation outcomes of 282 patients who received a transplant for cirrhosis and they found iron accumulation in 37% of the patients and iron storage was found to be significantly correlated with diffuse liver disease. HFE gene mutation was not found to be widespread among patients with increased iron stores. Ferritin levels were elevated in our study, especially in CHC, cirrhosis and liver transplant patients. Published studies generally include patients with CHB instead of chronic inactive HBV as in our study, in which the ferritin levels in chronic inactive HBV were lower than in the HCV and cirrhosis patients. Compared to the latter two groups, ferritin levels were higher in cases of cirrhosis than in the HCV group, supporting a correlation between ferritin level and degree of fibrosis.

Détivaud et al.[18] found the level of fibrosis in the non-tumoral liver tissues of 36 patients operated for liver cancer (primary or secondary) or liver transplantation to be negatively correlated with hepcidin mRNA expression and urinary hepcidin levels. However, the study results were affected by patient heterogeneity and the variability in the extent of fibrosis. When patients with mild fibrosis were excluded from the analysis, only a weak correlation could be observed. There was also a positive correlation between Hb concentration and hepatic iron stores. No statistically significant differences could be identified in our study in the prohepcidin level of patients having undergone liver transplant as a result of HB or HC, those with chronic inactive HBV, those with HCV and the cases with cirrhosis (p=0.087).

Anemia following liver transplantation is attributed to many different factors, including intra-operative blood loss, medication, immune suppressive treatment, hemolysis, renal failure, aplastic anemia, Graft-versus-host disease (GvHD), and others. The incidence of such anemia varies from 4.3% to 28%. The etiology of post-transplantation anemia varies according to the time interval. On postoperative days 0-14, the most frequent causes are bleeding, sepsis, medication and hemolysis, while postoperative weeks 2-6, aplastic anemia, medication, GvHD, cytomegalovirus, and parvovirus B19 are seen. After the first 6 weeks, medications remain significant, along with iron deficiency, kidney failure and post-transplant lymphoproliferative syndrome[19]. Hemoglobin changes begin stabilizing only following the first 6 post-transplant months. Therefore, only transplant patients who had completed their first post-operative year were included in our study.

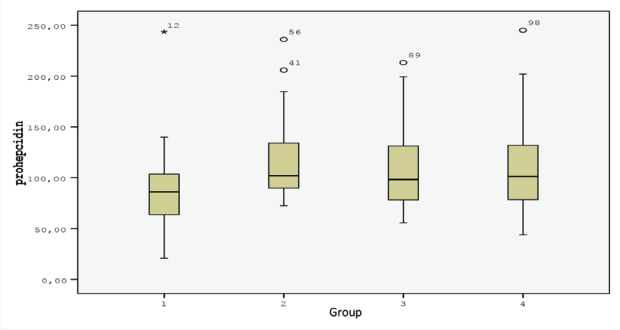

Figure 1. Distribution of prohepcidin levels among the different disease groups (Group 1=Chronic inactive HBV; Group 2=Chronic HCV; Group 3=Cirrhosis; Group 4=Liver transplant)

HCV: Hepatitis C virus, HBV: Hepatitis B virus

Studies have shown that decreased serum hepcidin levels are associated with poor survival in patients with alcoholic liver cirrhosis[20]. Since decreased hepcidin has been reported in patients with hepatic dysfunction, hepcidin levels are expected to decrease in acute liver injury[21,22]. In a study by Spivak et al.[23], hepcidin was reported to have a much shorter half-life, especially when compared to established liver function parameters such as albumin or INR. Thus, hepcidin may better reflect the dynamic changes that occur in acute liver failure. In contrast, transferrin may be a better predictor in disorders associated with a more pronounced inflammation. To summarize, ferritin levels were higher in patients with liver transplant compared to all three other groups; however, the difference was not statistically significant. On the other hand, our study revealed a positive correlation between prohepcidin levels and the patients' AST and ALT values (p=0.046).

Study Limitations

The present study has some limitations. Firstly, only the correlation with albumin and ferritin was examined, but the relationship with other acute phase reactants such as CRP, sedimentation, and fibrinogen could not be examined. In addition, we could not share the survival data as it was a prospective study.

CONCLUSION

Prohepcidin levels in our study were higher in patients with liver transplant compared to those with chronic inactive HBV and cirrhosis, while prohepcidin was even higher in patients with HCV. Our study revealed a significant correlation between prohepcidin levels in patients transplanted for HBV or HCV and patients' AST and ALT values. This correlation suggests that prohepcidin might be useful as a parameter for the post-transplant follow-up of liver reserve functionality. Additionally, this finding may be an indicator of inflammation after transplantation. Hepatic iron stores may be a prognostic factor in patients who have undergone liver transplantation.

This was a pioneering study on the role of prohepcidin, an important factor in Fe metabolism following liver transplant. Prospective, long-term studies on iron-related parameters and prohepcidin levels are needed to further elucidate the role of prohepcidin following liver transplantation.

Ethics

Ethics Committee Approval: The study was approved by Dokuz Eylül University Faculty of Medicine Clinical Research Ethics Committee (date: 29.09.2010, no: 2010/13-21).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ö, T.Ü., F.D., S.K., Concept: Ö.Ö, M.A., P.T.T., A.B., T.Ü., F.D., S.K., Design: Ö.Ö, M.A., P.T.T., A.B., T.Ü., F.D., S.K., Data Collection or Processing: Ö.Ö, P.T.T., F.Y., A.B., Analysis or Interpretation: Ö.Ö, P.T.T., F.Y., A.B., Literature Search: Ö.Ö, M.A., T.Ü., F.D., S.K., Writing: Ö.Ö, M.A., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Murali AR, Gupta A, Brown K. Systematic review and meta-analysis to determine the impact of iron depletion in dysmetabolic iron overload syndrome and non-alcoholic fatty liver disease. Hepatol Res. 2018;48:30-41.
2. Ramos E, Ruchala P, Goodnough JB, Kautz L, Preza GC, Nemeth E, et al. Minihepcidins prevent iron overload in a hepcidin-deficient mouse model of severe hemochromatosis. Blood. 2012;120:3829-36.
3. Babitt JL, Huang FW, Xia Y, Sidis Y, Andrews NC, Lin HY. Modulation of bone morphogenetic protein signaling in vivo regulates systemic iron balance. J Clin Invest. 2007l;117:1933-9.
4. Agarwal AK, Yee J. Hepcidin. Adv Chronic Kidney Dis. 2019;26:298-305.
5. Billesbølle CB, Azumaya CM, Kretsch RC, Powers AS, Gonen S, Schneider S, et al. Structure of hepcidin-bound ferroportin reveals iron homeostatic mechanisms. Nature. 2020;586:807-11.
6. Ruchala P, Nemeth E. The Pathophysiology and Pharmacology of Hepcidin. Trends Pharmacol Sci. 2014;35:155-61.
7. Sangkhae V, Nemeth E. Regulation of the Iron Homeostatic Hormone Hepcidin. Adv Nutr. 2017;8:126-36.
8. Wrighting DM, Andrews NC. Interleukin-6 induces hepcidin expression through STAT3. Blood. 2006;108:3204-9.
9. Hugman A. Hepcidin: an important new regulator of iron homeostasis. Clin Lab Haematol. 2006;28:75-83.
10. Galli A, Svegliati-Baroni G, Ceni E, Milani S, Ridolfi F, Salzano R, et al. Oxidative stress stimulates proliferation and invasiveness of hepatic stellate cells via a MMP2-mediated mechanism. Hepatology. 2005;41:1074-84.
11. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008;6:541-52.
12. Piperno A, D'Alba R, Fargion S, Roffi L, Sampietro M, Parma S, et al. Liver iron concentration in chronic viral hepatitis: a study of 98 patients. Eur J Gastroenterol Hepatol. 1995;7:1203-8.
13. Aoki CA, Rossaro L, Ramsamooj R, Brandhagen D, Burritt MF, Bowlus CL. Liver hepcidin mRNA correlates with iron stores, but not inflammation, in patients with chronic hepatitis C. J Clin Gastroenterol. 2005;39:71-4.
14. Shan Y, Lambrecht RW, Bonkovsky HL. Association of hepatitis C virus infection with serum iron status: analysis of data from the third National Health and Nutrition Examination Survey. Clin Infect Dis. 2005;40:834-41.
15. Lee SH, Jeong SH, Park YS, Hwang JH, Kim JW, Kim N, et al. Serum prohepcidin levels in chronic hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease. Korean J Hepatol. 2010;16:288-94.
16. Olmez OF, Gurel S, Yilmaz Y. Plasma prohepcidin levels in patients with chronic viral hepatitis: relationship with liver fibrosis. Eur J Gastroenterol Hepatol. 2010;22:461-5.
17. Stuart KA, Fletcher LM, Clouston AD, Lynch SV, Purdie DM, Kerlin P, et al. Increased hepatic iron and cirrhosis: no evidence for an adverse effect on patient outcome following liver transplantation. Hepatology. 2000;32:1200-7.
18. Détivaud L, Nemeth E, Boudjema K, Turlin B, Troadec MB, Leroyer P, et al. Hepcidin levels in humans are correlated with hepatic iron stores, hemoglobin levels, and hepatic function. Blood. 2005;106:746-8.
19. Maheshwari A, Mishra R, Thuluvath PJ. Post-liver-transplant anemia: etiology and management. Liver Transpl. 2004;10:165-73.
20. Nahon P, Nuraldeen R, Rufat P, Sutton A, Trautwein C, Strnad P. In alcoholic cirrhosis, low-serum hepcidin levels associate with poor long-term survival. Liver Int. 2016;36:185-8.
21. Tan TC, Crawford DH, Franklin ME, Jaskowski LA, Macdonald GA, Jonsson JR, et al. The Serum Hepcidin:Ferritin Ratio Is a Potential Biomarker for Cirrhosis. Liver Int. 2012;32:1391-9.
22. Girelli D, Nemeth E, Swinkels DW. Hepcidin in the Diagnosis of Iron Disorders. Blood. 2016;127:2809-13.
23. Spivak I, Arora J, Meinzer C, Durkalski-Mauldin V, Lee WM, Trautwein C, et al. Low Serum Hepcidin Is Associated With Reduced Short-Term Survival in Adults With Acute Liver Failure. Hepatology. 2019;69:2136-49.