World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i8.302

World J Hepatol 2010 August 27; 2(8): 302-310
ISSN 1948-5182 (online)

REVIEW

Gender-related variations in iron metabolism and liver diseases

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Author contributions: Harrison-Findik DD wrote solely the paper.
Supported by the NIH Grant (R01AA017738) to Duygu Dee Harrison-Findik
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Received: May 17, 2010 Revised: June 30, 2010
Accepted: July 7, 2010
Published online: August 27, 2010

Abstract

The regulation of iron metabolism involves multiple organs including the duodenum, liver and bone marrow. The recent discoveries of novel iron-regulatory proteins have brought the liver to the forefront of iron homeostasis. The iron overload disorder, genetic hemochromatosis, is one of the most prevalent genetic diseases in individuals of Caucasian origin. Furthermore, patients with non-hemochromatotic liver diseases, such as alcoholic liver disease, chronic hepatitis C or nonalcoholic steatohepatitis, often exhibit elevated serum iron indices (ferritin, transferrin saturation) and mild to moderate hepatic iron overload. Clinical data indicate significant differences between men and women regarding liver injury in patients with alcoholic liver disease, chronic hepatitis C or nonalcoholic steatohepatitis. The penetrance of genetic hemochromatosis also varies between men and women. Hepcidin has been suggested to act as a modifier gene in genetic hemochromatosis. Hepcidin is a circulatory antimicrobial peptide synthesized by the liver. It plays a pivotal role in the regulation of iron homeostasis. Hepcidin has been shown to be regulated by iron, inflammation, oxidative stress, hypoxia, alcohol, hepatitis C and obesity. Sex and genetic background have also been shown to modulate hepcidin expression in mice. The role of gender in the regulation of human hepcidin gene expression in the liver is unknown. However, hepcidin may play a role in gender-based differences in iron metabolism and liver diseases. Better understanding of the mechanisms associated with gender-related differences in iron metabolism and chronic liver diseases may enable the development of new treatment strategies.

Key words: Alcohol; Hepcidin; Hepatitis C; Hemochromatosis; Non-alcoholic steatohepatitis

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Harrison-Findik DD. Gender-related variations in iron metabolism and liver diseases. *World J Hepatol* 2010; 2(8): 302-310 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i8/302.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i8.302

INTRODUCTION

Clinical data suggest that men and women exhibit differences regarding the progression of certain liver diseases such as alcoholic liver disease, chronic hepatitis C and non-alcoholic steatohepatitis. Sex hormones and their effect on metabolic processes and oxidative stress have been suggested to play a role in this process. Interestingly, patients with alcoholic liver disease, chronic hepatitis C or non-alcoholic steatohepatitis often display elevated serum iron and mild to moderate hepatic iron overload. Recently, alcohol, hepatitis C viral proteins and obesity have all been shown to affect the expression of the key

iron regulatory protein, hepcidin. Oxidative stress and sex-specific differences have also been postulated to be involved in the regulation of hepcidin expression by alcohol in the liver. However, it is unclear whether the pathophysiological differences observed between men and women with chronic liver disease are associated with gender-based variances in iron metabolism. This review will highlight gender-related differences in liver diseases and iron metabolism including the role of the key iron-regulatory hormone, hepcidin.

IRON

Iron is essential for an array of key biological processes including erythrocyte production, DNA synthesis and cellular respiration[1-3]. The normal iron content of the body in an adult male is 35 to 45 mg of iron per kilogram of body weight. The majority of the iron is bound to hemoglobin in erythrocytes. Macrophages of the reti culoendothelial system supply the iron to the plasma transferrin pool to be delivered to bone marrow (~24 mg/d) for hemoglobin synthesis in red blood cell precursors[4-6]. About 20% of women, 50% of pregnant women and 3% of men do not have adequate iron stores. Based on the differences between the amount of iron available for absorption and the increased requirement for iron, most females of reproductive age, especially in the developing world, exhibit iron deficiency anemia[7]. Pregnant women require more iron due to the increasing iron demands of the growing fetus, the placenta and the elevated red cell mass of the mother[8]. However, it must also be noted that there is no regulated pathway for the excretion of iron in the body except by blood loss or desquamated intestinal cells. Parenchymal cells of the liver and reticuloendothelial macrophages serve as depots for excess iron storage. Liver not only carries the main burden of iron overload but also acts as the central organ in the regulation of body iron stores[9].

PRIMARY AND SECONDARY IRON OVERLOAD, GENDER-DIFFERENCES AND LIVER DISEASES

Hepatic iron overload is common in many liver diseases where iron is a risk factor in disease progression[10-16]. Genetic hemochromatosis (GH) is a prevalent iron overload disorder among the Caucasian population. Mutations in the Hfe gene are the main cause of primary iron overload observed in GH[14]. Patients with genetic hemochromatosis absorb more than the normal amount of iron through the intestine. Iron accumulation subsequently results in organ damage including liver injury[17,18]. GH is not a gender-specific disease. However, more males than females present with symptoms of hemochromatosis. Men accumulate more iron and have a higher incidence of liver injury. Iron overload also affects the hypothalamic-pituitary axis eventually leading to hypogonadism, exposure of sperm to oxidative injury and infertility[19]. The clinical symptoms of GH usually start later with women, possibly due to blood loss experienced with menstruation and childbirth. The majority of patients exhibiting the clinical symptoms of GH are homozygous for a Cys282-Tyr (C282Y) mutation in GH gene, Hfe[20]. Of note, a male-specific association of C282Y mutation with childhood acute lymphoblastic leukemia has also been reported[21]. The C282Y mutation inhibits the heterodimer formation of Hfe with the beta2-microglobulin (β_2M) light chain and its delivery to the plasma membrane[22]. Interestingly, female mice deficient in β_2M expression have been shown to exhibit more hepatic iron loading than male β_2M-deficient mice which is in contrast to that observed with genetic hemochromatosis patients[23]. However, it should be noted that unlike humans, female laboratory mice do not experience menstrual bleeding and live in a controlled environment. The observed sex differences in β_2M-deficient mice may be due to a possible protective effect of the Y chromosome or to hormonal differences[23].

β-thalassemia is a genetic hematological disorder whereby repeated blood transfusions and dysregulated iron homeostasis lead to secondary iron overload[24,25]. Distinct from GH, patients with β-thalassemia also exhibit iron deposition in the pituitary gland and hypothalamus[26,27]. Thalassemic males develop hypogonadotropic hypogonadism whereas females have amenorrhea due to pituitary and gonadal damage caused by iron overload[26,28]. However, paternity has been shown to be less common in males including those with normal sperm counts[27-29].

Patients with non-hemochromatotic liver diseases such as chronic hepatitis C, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) frequently display an increase in serum iron values and mild to moderate elevation of hepatic iron concentrat ion[11-13,15,30-37]. Studies with HCV-infected chimpanzees also demonstrate that the viral infection leads to an increase in body iron levels[38]. Furthermore, as shown by *in vitro* studies, iron alters HCV replication[39,40]. In male patients with chronic hepatitis C over 50 years of age, iron has been implicated to be a fibrinogenetic factor in comparison to female patients of the same age[41]. Menstruating or iron deficient women with chronic hepatitis C have been reported to have a slower rate of disease compared to men of comparable age and women with normal iron status[42]. Population-based studies indicate differences in HCV clearance rates and the severity of disease between men and women[43-45]. IL-10 promoter polymorphisms have also been postulated to be associated with gender susceptibility to HCV infection[46].

In vivo whole-body retention studies have demonstrated a two-fold increase in intestinal iron absorption in chronic alcoholics[13]. Recently, even mild to moderate alcohol consumption has been shown to elevate the indices of iron stores[12]. Experimental animal models of ALD have also been reported to exhibit increased iron content in Kupffer cells which leads to the activation of the

transcription factor, nuclear factor-kappa (NF-κB), and increased expression of the proinflammatory cytokine, tumor necrosis factor-alpha (TNF-α)[47,48]. These effects are abolished by iron chelation, thereby indicating a role for iron-mediated cell signaling in the pathogenesis of experimental alcoholic liver disease[49]. There are sex-specific differences in the metabolism and elimination of ethanol both in humans and rodents[50,51]. The rates of ethanol elimination are higher in women[50]. The activity of the alcohol metabolizing enzyme, alcohol dehydrogenase (ADH) in rodent livers is elevated in females and castration of males increases ADH activity[52]. Moreover, men with prostatic metastatic carcinoma who have undergone therapeutic orchiectomy have been shown to exhibit an increase in ethanol elimination[53]. Clinical studies demonstrate that females exhibit a greater susceptibility to alcohol-induced liver injury than men[54]. Estrogens, endotoxin and inflammatory processes have been suspected to play a role. However, it is unknown whether there is any association between iron and the gender-related differences observed in alcohol-induced liver injury. Alcohol suppresses the expression of the key iron regulatory molecule, hepcidin in the liver, which leads to an increase in duodenal iron transport[55-58]. Interestingly, male mice have been reported to display significantly lower hepcidin expression compared to female mice following acute alcohol exposure[55].

NAFLD is the hepatic manifestation of metabolic syndrome[59-61]. NAFLD ranges from benign steatosis to nonalcoholic steatohepatitis (NASH) which is differentiated by histopathologic evaluation[62]. NASH is the severe manifestation of disease which can lead to liver fibrosis and hepatocellular carcinoma[63,64]. Increased iron stores have been reported in NAFLD/NASH[15,36,37,65,66]. However, the relevance of iron accumulation in disease progression is unclear[15,36,37,65,66]. Excess hepatic iron is postulated to cause insulin resistance[16,67]. Interestingly, iron depletion *via* phlebotomy in patients with NAFLD has been shown to have a positive effect on insulin resistance and to reduce serum TNF-α levels[68,69]. Serum ferritin levels are also positively associated with BMI and serum glucose levels[70-73]. However, it should be noted that ferritin is an acute phase protein and may not accurately reflect the extent of iron overload in NAFLD. There is a relationship between gender and NAFLD. However, the data from several studies are conflicting regarding the prevalence of NAFLD among men and women[74-79]. Population-based studies suggest a protective role for endogenous estrogens in non-alcoholic hepatic steatosis[80]. The prevalence of NAFLD increases in women over 50 years of age[81]. Interestingly, the deletion of histone variant macroH2A1 which is enriched on the inactive X-chromosome in females has been postulated to cause female-specific steatosis in mice[82].

IRON REGULATORY PROTEINS

Since there is no physiological pathway of excretion for excess iron in the body, the uptake, transport and storage of iron must be tightly regulated. Divalent metal transporter 1 (DMT1), a multi-transmembrane protein, is responsible for importing dietary non-heme iron through the apical site of absorptive enterocytes in the duodenum[83,84]. Conversely, the iron transporter ferroportin is responsible for exporting iron into the circulation[85]. The ferroportin Q248H polymorphism is associated with increased serum ferritin levels in Sub-Saharan Africans and African Americans[86]. The frequency of ferroportin Q248H polymorphism has been reported to be higher in African American males with elevated serum ferritin levels compared to those with normal serum ferritin. However, these differences were not observed among African American women. Furthermore, men with elevated serum ferritin were three times more likely to have Q248H polymorphism than women with elevated serum ferritin[86].

In the duodenum, the basolateral transport of iron from the enterocytes into the bloodstream also requires hephaestin, a transmembrane-bound multicopper ferroxidase[87,88]. Like its homolog ceruloplasmin in the liver, hephaestin also links copper and iron metabolism[89]. Sex-linked anemia is an X-linked inherited iron deficiency anemia, first observed in the male descendants of an irradiated mouse[90]. Sex linked anemia (*sla*) mice are impaired in intestinal iron transport and contain a deletion in *Heph* gene yielding a truncated hephaestin protein[87].

In the plasma, iron circulates by binding to the glycoprotein, transferrin[91]. There are different glycosylated forms of transferrin which are different in the number of N-linked oligosaccharide chains[92,93]. Heavy alcohol drinkers display abnormal serum transferrin profile[94,95]. Males with high alcohol intake have been shown to display higher amounts of disialotransferrin in the serum when compared to females. There are no gender-related differences in serum disialotransferrin levels between nondrinker males and females[96]. Iron-bound transferrin is taken up into the cell by transferrin receptors 1 and 2 (TrfR1, TrfR2)[97,98]. TrfR1 is ubiquitously expressed whereas TrfR2 is mainly expressed in the liver[98]. The regulation of iron metabolism involves multiple organs including the duodenum, liver and bone marrow. Hepcidin is the iron-regulatory hormone which mediates iron homeostasis between these distant organs[2,99].

Hepcidin is a circulatory antimicrobial peptide, synthesized in the hepatocytes of the liver as an 84 amino acid precursor protein[100,101]. It is subsequently cleaved into the 25 amino acid cysteine-rich mature (biologically active) peptide form[102,103]. Hepcidin achieves the regulation of iron homeostasis by binding to the iron exporter ferroportin and thereby inhibiting the iron trans port in the duodenum and the release of iron from reticuloendothelial macrophages (Figure 1)[104]. During pregnancy, iron is transferred from the mother to the fetus and hepcidin regulates maternofetal iron transport across the placenta[105]. Transgenic mice studies have confirmed the role of hepcidin in the regulation of iron metabolism[106,107]. Hepcidin synthesis in the liver is

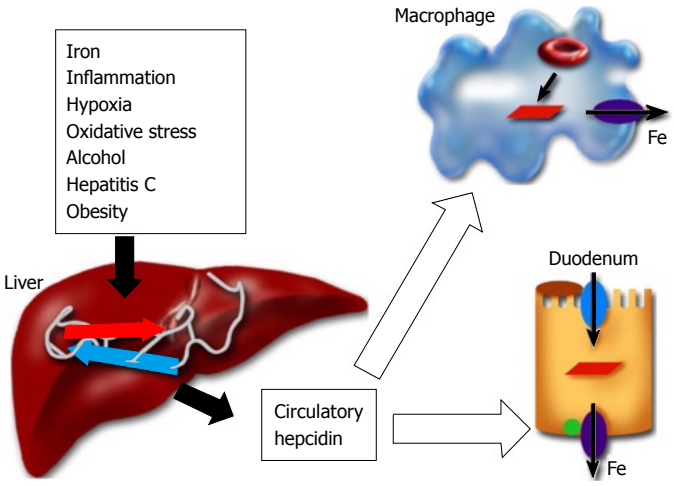

Figure 1 Regulation of hepcidin and iron metabolism. The key iron-regulatory hormone hepcidin is primarily synthesized in the parenchymal cells of the liver and is subsequently released into the circulation. The transcriptional regulation of hepcidin in the liver is regulated by various factors. Hepcidin released into the circulation in turn regulates iron metabolism by controlling the iron transport in the duodenum and iron export in the macrophages. Hepcidin achieves this by binding to the iron exporter protein ferroportin and inducing its internalization and degradation.

sensitive to body iron levels; increasing with iron overload and decreasing in the case of iron deficiency[2]. Hepcidin levels in humans have been reported to correlate with the liver iron concentration and the parameters of hepatic function (e.g. serum albumin)[108]. Furthermore, inflammatory signals and the inflammatory cytokines IL-1 and IL-6 elevate hepcidin expression in the liver[109,110]. Conversely, hypoxia and anemia down-regulate hepcidin expression[111]. The decrease in hepcidin expression in the liver leads to increased iron absorption through the duodenum and the mobilization of iron from reticuloendothelial stores to meet the demands of erythrocyte production[2]. The synthesis of hepcidin in the liver is modulated by upstream regulators. Transferrin receptor2, Hfe, the juvenile hemochromatosis gene product, Hjv, and bone morphogenetic protein 6 are positive regulators of hepcidin expression[112-118]. On the other hand, TMPRSS6 (matriptase 2), a transmembrane serine protease, is the negative regulator of liver hepcidin expression[119,120]. Patients expressing TMPRSS6 mutations exhibit iron-refractory iron deficiency anemia due to elevated hepcidin production[119].

HEPCIDIN, SEX DIFFERENCES AND LIVER DISEASES

Human hepcidin gene (*HAMP, HEPC*, OMIM 606464) is located on the long arm of chromosome 19 at position 13.1[2,100]. Unlike humans or rats, mice have 2 hepcidin genes, *hepc1* and *hepc2*, and both genes are located on mouse chromosome 7[106,121]. Hepcidin expression in the liver has been reported to differ by gender[122]. Female mice express significantly higher hepcidin levels in the liver than males[122,123]. Both hepcidin1 and hepcidin2 respond to iron. The higher level of hepcidin expression in female mice is also associated with elevated liver and spleen iron concentrations[122,123]. However, it is unclear whether the elevated expression of hepcidin in female mice is due to the increase in iron stores. It is also not known whether women and men differ in the level of hepcidin expression in the liver. Women usually have lower iron stores than men mainly due to the physiological loss of blood. A study utilizing enzyme-linked immunoabsorbent assay reported lower serum hepcidin levels in healthy female volunteers compared to those measured in males[124]. The level of serum hepcidin has been postulated to correlate with that of serum ferritin levels[124]. However, it should be noted that besides iron, hepcidin is also regulated by other stimuli which may also play a role in sex-specific expression of hepcidin in the liver.

Accumulating evidence suggests hepcidin as the modifier gene in genetic hemochromatosis. Hepcidin mRNA expression is reduced in patients with GH and in Hfe knockout mice[125,126]. Some patients with Hfe C282Y homozygosity have been reported to carry additional mutations in hepcidin gene (*HAMP*)[127-129]. GH patients subjected to acute oral iron challenge have been shown to display a blunted hepcidin response compared to healthy control subjects[130]. Constitutive expression of hepcidin has been shown to prevent iron overload in Hfe knockout mice[131]. Hepcidin is also altered in other non-Hfe-related forms of hemochromatosis. Hemochromatosis patients harboring mutations in transferrin receptor 2 gene have lower urinary hepcidin levels[112]. Mutations in the hepcidin gene and the juvenile hemochromatosis gene, hemojuvelin (*Hjv*), have been identified in juvenile hemochromatosis patients[114,132]. In contrast to hepcidin, *Hjv* does not respond to iron levels but its inactivation results in hepcidin deficiency[114,132-134]. *Hjv* acts as a bone morphogenic protein (BMP) co-receptor[118]. Furthermore, BMP6 regulates hepcidin expression[115,116].

Hepcidin expression is also altered in other liver diseases. Patients with alcoholic liver disease or chronic hepatitis C and animal models of alcohol and HCV display reduced hepcidin expression[35,56-58,135,136]. Hepcidin has been reported to be expressed in adipose tissue and the expression was increased in obese patients; correlating with the body mass index (BMI)[137]. The pathogenesis of nonalcoholic steatohepatitis is associated with insulin resistance and metabolic syndrome[59,60,79]. However, hepcidin expression in the livers of these patients was unchanged[137]. High levels of leptin accompany insulin resistance which is suggested to play a role in the progression

of NAFLD to NASH[138-140]. Interestingly, an *in vitro* study performed with Huh7 human hepatoma cells showed that the adipokine, leptin, increased the expression of hepcidin through the Jak2/Stat3 signaling pathway[141].

The liver is sensitive to the action of sex hormones including estrogens[142-144]. There is some evidence that estrogens can increase the production of reactive oxygen species in the liver[145]. Recently, oxidative stress has been reported to regulate hepcidin transcription in the liver[55]. It is therefore possible that estrogens may play a role in sex-specific regulation of hepcidin expression in the liver. A study of patients with chronic hepatitis reported higher c-myc expression in the livers of patients in which the liver expressed a variant form of the estrogen receptor that exhibits constitutive transcriptional activity compared to patients in whom the liver expressed wild type estro gen receptor[145,146]. Estrogen has also been reported to cause c-myc overexpression in hamster kidneys[147]. c-myc belongs to the basic helix-loop-helix/leucine zipper (bHLH/zip) family of transcription factors which also includes upstream stimulatory factor (USF) and transcription factor E (TFE)[148]. These transcription factors bind to E-Box motifs in the regulatory elements of promoter sequences of target genes[148]. Hepcidin genes are located directly downstream of the *Usf2* gene. An involvement of USF1, USF2 and c-myc in the transcriptional regulation of human and mouse hepcidin genes has been postulated[106,107,149]. Moreover, the mutation of E-box motifs in the human hepcidin gene promoter has been shown to abolish the transcriptional regulation by USF1, USF2 or c-myc[149]. However, it remains to be seen whether estrogen plays a role in the transcriptional regulation of hepcidin and in sex-based differences observed regarding the expression of hepcidin in the liver.

CONCLUSION

Iron is essential for many biological processes. However, excess iron is harmful and can lead to tissue injury. The liver acts as a storage depot for iron and plays a central role in the regulation of iron metabolism. The key iron re gulatory hormone, hepcidin, is synthesized in the liver. Genetic hemochromatosis (GH) is a prevalent iron overload disorder in the Caucasian population. Patients with non-hemochromatotic liver diseases such as alcoholic liver disease, chronic hepatitis C and non-alcoholic steatohepatitis also frequently exhibit evidence of iron overload. Hepcidin is suggested to play a role in GH and has been shown to be modulated by alcohol, hepatitis C viral proteins and obesity. Genotypic and sex differences have been shown to be involved in the regulation of liver hepcidin expression in mice. Men and women exhibit clinical differences in the severity of various liver diseases. Women of childbearing age usually have lower iron stores compared to men mainly due to the physiological loss of blood. However, an association between body iron levels and the gender-specific differences observed in the progression of chronic liver diseases has yet to be established. Gender-specific regulation of hepcidin synthesis in the liver may play a role in this process. Further understanding of the mechanisms underlying the gender-based differences in the pathophysiology of chronic liver diseases may lead to the development of novel diagnostic markers and treatment strategies.

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