



Iron-Induced Hepatocarcinogenesis — Preventive Effects of Nutrients

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The liver is a primary organ that stores body iron, and plays a central role in the regulation of iron homeostasis. Hepatic iron overload (HIO) is a prevalent feature among patients with chronic liver diseases (CLDs), including alcoholic/nonalcoholic liver diseases and hepatitis C. HIO is suggested to promote the progression toward hepatocellular carcinoma because of the pro-oxidant nature of iron. Iron metabolism is tightly regulated by various factors, such as hepcidin and ferroportin, in healthy individuals to protect the liver from such deteriorative effects. However, their intrinsic expressions or functions are frequently compromised in patients with HIO. Thus, various nutrients have been reported to regulate hepatic iron metabolism and protect the liver from iron-induced damage. These nutrients are beneficial in HIO-associated CLD treatment and eventually prevent iron-mediated hepatocarcinogenesis. This mini-review aimed to discuss the mechanisms and hepatocarcinogenic risk of HIO in patients with CLDs. Moreover, nutrients that hold the potential to prevent iron-induced hepatocarcinogenesis are summarized.

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INTRODUCTION

Iron is an essential micronutrient that is utilized as a co-factor for various proteins, including heme and Fe-S proteins (1, 2). However, iron facilitates hydroxyl radical production *via* a well-established mechanism, the Fenton reaction (3). Hydroxyl radical is one of the most potent reactive oxygen species, which harshly damages cellular components, including nucleic acids, proteins, and lipids, leading to the collapse of cellular homeostasis. Moreover, excessive cellular iron causes ferroptosis, a nonapoptotic programmed cell death, which is recently suggested to be involved in the development of a broad range of diseases, including chronic liver diseases (CLDs) (4). Thus, iron metabolism is precisely controlled by various factors, such as hepcidin and ferroportin (1, 2, 4).

Body iron is mainly stored in the liver; thus, compromised function and expression of these iron metabolism-related factors readily cause hepatic iron overload (HIO). Hereditary hemochromatosis, which leads to massive iron accumulation not only in liver, but also in many other organs, such as heart and pancreas, etc., is caused by genetic defects in the iron metabolism-related factors that frequently result in diabetes mellitus, cardiomyopathy, and liver cancer (5). Moreover, nonhereditary, secondary HIO is prevalent among patients with CLDs, such as chronic hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD), all of which are important etiologies of hepatocellular carcinoma (HCC) (6). As mentioned above, excessive iron severely impairs normal tissue functions by aggravating oxidative stress; thus, HIO is suggested to promote the development and progression of these CLDs and even predispose them to HCC.

Contrastingly, several lines of evidence indicate that the correction of dysregulated iron metabolism significantly improves liver functions and ameliorates pathologies related to CLDs associated with HIO. Therefore, HCC is reasonably expected to arise from HIO-associated CLDs, which can be prevented by interventions that target iron metabolism.

The present mini-review briefly described the current knowledge on HIO associated with CLDs, focusing on mechanisms and hepatocarcinogenesis. Moreover, nutritional interventions with protective effects against HIO by correcting iron dysmetabolism are concisely summarized.

HIO IN CLDS

HIO is attributable to both genetic and nongenetic causes. Hemochromatosis results from genetic defects of iron-metabolism-related genes, including *HFE*, *HAMP* (encoding hepcidin), *HJV* (hemojuvelin), *TFR2* (transferrin receptor 2), and *SLC40A1* (ferroportin) genes (5), whose functions are described below. Moreover, thalassemia is a severe hereditary anemia that is caused by genetic defects of globin genes and is prevalently associated with HIO. Contrastingly, the pathogenic mechanisms of nonhereditary HIO are yet to be fully elucidated. However, several molecular mechanisms underlying HIO in CLDs have been postulated based on clinical and basic research and are herein presented, followed by a summary of the hepatocarcinogenic potential of HIO.

Hepcidin-Mediated Regulation of Systemic Iron Metabolism

Hepcidin is a central player in iron metabolism in humans and is mainly expressed and secreted from hepatocytes and binds to ferroportin, a cellular iron exporter, which is present in the cellular membrane of all types of cells involved in systemic iron metabolism, including hepatocytes, macrophages, and enterocytes (7, 8). Upon binding to hepcidin, ferroportin is taken up by endocytosis and degraded in lysosomes (7, 8).

The primary physiological function of hepcidin is to decrease circulating iron levels by inhibiting cellular iron efflux. Dietary iron absorbed by enterocytes is released to the circulation *via* ferroportin and stored mainly in the liver, skeletal muscle, and reticuloendothelial cells. Whereas, aged or injured red blood cells were phagocytosed by liver Kupffer cells and spleen red pulp macrophages (9). Moreover, hepatocytes and Kupffer cells take up hemoglobin released from hemolytic red blood cells (9). The intracellularly stored iron is exported to the circulation *via* ferroportin and utilized for erythropoiesis. Thus, hepcidin obstructs dietary iron absorption, while it also suppresses the release of stored iron, leading to cellular iron accumulation. Thus, hepcidin decreases body iron storage and systemic iron mobilization, and, in some cases, causes iron-deficiency anemia (10).

Hepcidin expression in the liver is tightly regulated by several factors. HFE is a membrane protein that binds to TFR1, competing with holo-transferrin (11). Increased transferrin saturation facilitates the dissociation of HFE from TFR1 and binding of HFE to TFR2, resulting in transferrin-induced hepcidin upregulation

(11, 12). Hemojuvelin is a BMP co-receptor required for BMP6-induced hepcidin expression (13, 14). Iron overload upregulates BMP6 in the liver, thereby inducing iron-dependent hepcidin expression *via* the BMP6/hemojuvelin/SMAD pathway (14, 15). It is demonstrated that HFE also binds to BMP type I receptor ALK3 and induces hepcidin expression *via* the SMAD pathway (16). Thus, it is suggested that the BMP/SMAD pathway is a critical regulator of iron metabolism by regulating hepcidin expression. In addition to iron, hepatic hepcidin expression is also induced by inflammatory stimuli, such as interleukin-6 and lipopolysaccharide (17, 18). The increase in hepcidin expression upon inflammation leads to the development of inflammatory anemia, which is characterized by decreases in serum iron and erythropoiesis, despite of increased cellular iron stores in the reticuloendothelial system (10).

Molecular Mechanisms

HIO is found in 10–36% of patients with chronic hepatitis C, and the hepatic iron amount is associated with a disease severity and decreased by interferon therapy (19, 20). In healthy individuals, hepatic iron accumulation induces hepcidin expression in hepatocytes *via* the BMP pathway to inhibit dietary iron uptake (13, 21). However, patients with chronic hepatitis C show lower hepcidin expression than patients with hepatitis B and nonviral hepatitis despite HIO (22). Moreover, although hepatic inflammation is evident, chronic hepatitis C virus (HCV) infection was shown to downregulate hepcidin (23). This might be due to the impairment of the BMP6/hemojuvelin pathway by TNF α , which suppresses the transcription of hemojuvelin (24). Contrastingly, hepcidin expression was reported to increase in culture cells and experimental animal models of HCV infection (25, 26). At a molecular level, HCV core protein activates the *HAMP* gene promoter while nonstructural protein 5A suppresses it (25, 27, 28). Thus, hepcidin levels in HCV-infected patients might be altered by infection status (acute/chronic, inflammation status, virus load, infection period, etc.) (29).

Alcohol intake is a trigger of systemic iron overload and concomitantly reduces the risk of iron-deficient anemia (30). Increased serum ferritin and transferrin saturation were observed (31, 32) and approximately half develop HIO in patients with alcoholic liver disease (33). Alcohol was shown to suppress hepcidin transcription in cultured cells and laboratory animals, possibly by inhibiting C/EBP α (34, 35). Likewise, decreased serum hepcidin levels and increased intestinal ferroportin expression were depicted in patients with alcoholic liver disease (36, 37), and intestinal iron absorption was consistently increased two-fold in chronic alcoholics (38). Thus, excessive dietary iron absorption due to the decreased hepcidin expression might occur in patients with alcoholic liver disease as well as chronic hepatitis C.

Like chronic hepatitis C, approximately one-third of patients with NAFLD are associated with HIO (39). Iron metabolism alteration results in hyperferritinemia, which is significantly associated with patients with NAFLD (40). Variants of *HFE*, *TM6SS6*, *HBB*, and *CP* have been reported as genetic factors associated with HIO in patients with NAFLD (41–44); however, nongenetic factors remain unclear. We and other groups have determined hepatic expression levels of iron metabolism-related genes in patients or rats with NAFLD and found the upregulation of

hepcidin (45–47). Moreover, hepatic ferroportin expression was downregulated in NAFLD (45, 47, 48). Based on these observations, dysregulated hepcidin expression might suppress hepatic iron export *via* ferroportin in patients with NAFLD. Interestingly, amelioration of HIO, concomitant with the upregulation of hepatic ferroportin expression, was observed in mice fed with a high-fat diet after a fibroblast growth factor 21 treatment (48).

Hepatocarcinogenic Risk

Hepatic neoplastic nodules were found in 5 of 8 rats fed with an iron-supplemented diet for 32 months and one of the rats with neoplastic nodule developed a HCC, while only 1 of 9 control rats developed neoplastic nodules (49). This iron challenge significantly exacerbated hepatic oxidative stress and DNA damage (50). Adult males in sub-Saharan Africa are often affected with dietary iron overload from a traditional home-brewed beer fermented in steel drums (51). Several lines of studies suggest that there is an association between HCC and dietary iron overload in black Africans (52–54). Consistently, two retrospective studies demonstrated that HCC prevalence in patients with nonalcoholic steatohepatitis (NASH)- or HCV-related cirrhosis is significantly associated with the presence of HIO (55, 56). In particular, iron deposition in the portal tract was significantly associated with poor survival of patients with HCC after curative resection (57). Whereas, phlebotomy with a low-iron diet effectively reduced the risk of development of HCC in chronic hepatitis C patients (58). Thus, HIO has a hepatocarcinogenic potential and is considered a risk factor for HCC development while interventions targeting iron metabolism, such as iron reduction therapy, are promising for prevention of HCC. However, there remains a need for more robust evidence of the hepatocarcinogenic risk of HIO, for example, through long-term follow-up studies.

Liver fibrosis is known as a major risk factor for HCC development (59). Hyperferritinemia in NAFLD patients with HIO independently predicts the risk of advanced liver fibrosis (60). Consistently, predominant parenchymal iron deposition was associated with advanced fibrosis stages in patients with NAFLD (61). However, a contradictory report demonstrated that nonparenchymal iron deposition in patients with NAFLD was more associated with advanced histological features, including fibrosis and inflammation (39). A recent study of 299 patients with NAFLD with a mean follow-up period of 8.4 years demonstrated that nonparenchymal iron deposition more likely leads to fatal hepatic or cardiac disease development (62). However, this study did not show the association between HIO and HCC, possibly due to the insufficient sample size and follow-up period. The clinical significances of parenchymal and nonparenchymal iron depositions remain elusive; however, liver fibrosis could be a key factor in HIO-induced hepatocarcinogenesis.

PREVENTION OF IRON-INDUCED LIVER DAMAGE BY NUTRIENTS

HIO would be a therapeutic target to prevent CLD progression. Phlebotomy, indeed, improves disease severity in patients with chronic hepatitis C and reduces the risk of HCC development (58,

63). However, the clinical benefit of phlebotomy has not been established in patients with NAFLD (64). Contrastingly, the dietary iron restriction is shown effective in attenuating liver fibrosis and steatosis in diet-induced NAFLD/NASH model animals (65, 66). Whereas, a negative correlation of hepatic iron contents was observed with dietary intake of vitamins C and E and zinc in patients with thalassemia (67), implying a close relationship between nutritional status and hepatic iron accumulation. Furthermore, several nutrients have been reported to protect the liver from iron-induced damage (**Figure 1**), as discussed below. Therefore, nutritional interventions can be a promising strategy not only for CLD amelioration but also for preventing HIO-induced HCC development.

Vitamin A

Retinoids are compounds that exert physiological actions of vitamin A. In its active form, retinoic acids, including all-*trans* and other isomers, bind to the retinoic acid receptor and retinoid X receptor and regulate the expression of various target genes. However, we and another group have reported that retinoid signals are metabolically suppressed in NAFLD livers of humans and mice (68, 69). Moreover, retinoid signals are suggested to be epigenetically silenced in HCC by histone lysine-specific demethylase 1 (70). These results suggest that the downregulation of hepatic retinoid signals might be a causative factor for the

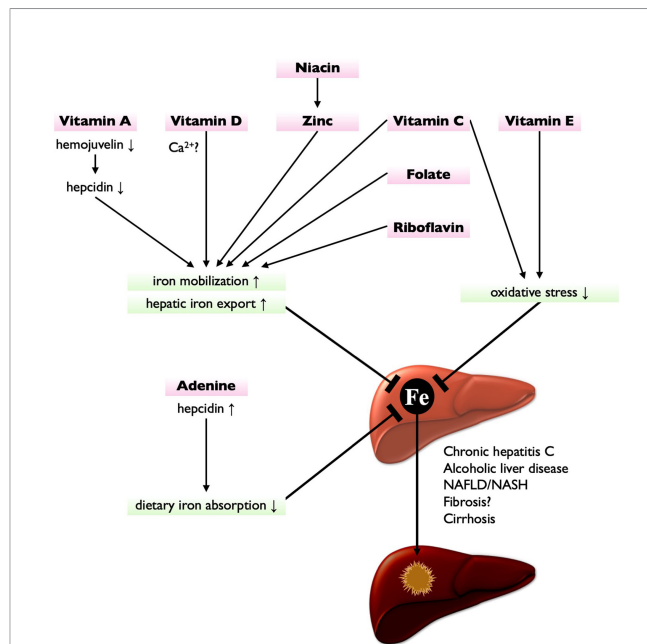


FIGURE 1 | Nutritional interventions targeting iron metabolism for HCC prevention. Vitamin A suppresses hepcidin expression by downregulating hemojuvelin, leading to the enhancement of hepatic iron export. Vitamin D (possibly *via* Ca²⁺ homeostasis), niacin (*via* zinc), vitamin C, folate, and riboflavin also enhance hepatic iron export and iron mobilization, thereby reducing hepatic iron contents. Vitamin C and vitamin E are potent antioxidant, thereby protecting liver from HIO-induced injury. Adenine increases hepcidin expression, thereby suppressing dietary iron absorption. These nutrients have potential to treat or prevent HIO and may reduce the risk of hepatocarcinogenesis.

development and progression of CLDs. Contrastingly, supplementation of all-*trans*-retinoic acid and a synthetic retinoid, tamibarotene, significantly suppressed HIO and hepatic oxidative stress in iron-challenged mice (71, 72). Mechanistically, these retinoids downregulate the hepatic expression of hemojuvelin through retinoic acid receptor α , leading to hepatic hepcidin downregulation and hepatic and intestinal ferroportin upregulation (71, 72). Consequently, hepatic iron export was significantly enhanced (71, 72). Moreover, we observed that the erythroid colony formation unit of bone marrow cells was increased in the presence of all-*trans*-retinoic acid (71). Consistently, retinoids are suggested to have an ability to promote erythropoiesis while their deficiency is associated with anemia (73). Thus, erythropoietic action, at least in part, contributes to HIO amelioration by retinoids. Additionally, retinoids significantly ameliorated hyperglycemia, insulin resistance, and hepatic steatosis in a mouse model of NAFLD (74, 75). Hyperglycemia and hyperinsulinemia, which are frequently complicated with NAFLD, are also risk factors for HCC (76). Thus, from dual aspects, retinoid supplementation would be an efficient strategy to prevent HCC development in patients with NAFLD.

Vitamin C

Vitamin C is a water-soluble antioxidant required for duodenal cytochrome b to reduce Fe^{3+} to Fe^{2+} . This process is necessary for dietary nonheme iron absorption through divalent metal transporter 1 (DMT1) (77). Likewise, vitamin C increased hemoglobin synthesis in patients on hemodialysis with anemia refractory to erythropoietin (78). An observational study with >8,000 Chinese adults showed that dietary vitamin C intake was associated with lower plasma ferritin level (79). These data suggest that vitamin C suppress iron accumulation by enhancing systemic iron mobilization. Contrastingly, in an animal model of alcoholic liver disease, vitamin C supplementation restored the decreased hepcidin expression in the liver and concomitantly downregulated intestinal ferroportin expression, leading to alcohol-induced HIO amelioration (80). Based on these findings, vitamin C is expected to reduce dietary iron absorption in patients with HIO associated with hepcidin downregulation, such as alcoholic liver disease and chronic hepatitis C. However, the nutritional effect of vitamin C on hepatic hepcidin expression and iron mobilization is required further investigation. Moreover, vitamin C was shown to improve glycemic control in patients with type 2 diabetes and NAFLD (81, 82). It is also observed that dietary vitamin C intake was associated with lower HbA1c level (79). Considering its antioxidant effects, vitamin C holds a high potential to prevent HCC development.

Vitamin D

Vitamin D is a fat-soluble vitamin essential for calcium homeostasis and is produced by ultraviolet light in the dermis or epidermis and activated by successive 25- and 1-hydroxylations in the liver and kidney, respectively (83). 1,25-dihydroxyvitamin D was shown to protect zebrafish liver cells from ferroptosis, concomitant with decreases in hepcidin expression and cellular iron contents (84). Moreover, it was demonstrated that vitamin D receptor activation inhibits ferroptotic cell death in human renal proximal tubule cells and

mouse hippocampal cells (85, 86). However, the protective effects of vitamin D in the liver remains elusive.

Decreased 25-hydroxyvitamin D levels are frequently observed and are associated with diseased severity in patients with CLDs (87–90). The possible explanation of this is that HIO suppresses 25-hydroxyvitamin D production, as its serum levels were negatively correlated with hepatic iron contents in patients with thalassemia major (91–93). Likewise, a negative correlation was found in patients with hereditary hemochromatosis, and 25-hydroxyvitamin D levels were significantly restored after phlebotomy (94). These results suggest that iron is a negative regulator of metabolic activation of vitamin D although its precise mechanism remains unknown. Moreover, vitamin D depletion exacerbated HIO in *hemojuvelin*-knockout mice (95), suggesting that there is a vicious cycle exacerbating HIO by suppressing vitamin D signals. However, 1,25-dihydroxyvitamin D supplementation failed to ameliorate HIO in the *hemojuvelin*-knockout mice (95). Contrastingly, verapamil, a calcium channel blocker, treatment significantly decreased hepatic iron contents and ameliorated HIO-induced liver fibrosis (95, 96). These results suggest that the physiological link between iron and calcium may exist, and that blockade of cellular calcium influx would be relevant for treating HIO. The transport systems of these ions are totally different; however, the involvement of DMT1 is suggested (96, 97). Moreover, duodenum calcium absorption is inversely correlated with duodenum iron absorption and is activated by hepcidin and vitamin D (98). The therapeutic effects of vitamin D supplementation on CLDs are still under debate; however, it is recently suggested that impaired calcium signaling plays a critical role in the development of NAFLD (90, 99). Vitamin D and calcium homeostasis would provide new insights into the pathogenic mechanisms of HIO in CLDs.

Vitamin E

Tocopherol is a lipophilic antioxidant known as vitamin E, which has been reported to ameliorate steatosis, inflammation, ballooning, and fibrosis in patients with NASH (100, 101). Thus, tocopherol is clinically used for the treatment of NASH. Although its clinical effects on HIO has not been investigated, α -tocopherol significantly reduced hepatic oxidative stress in rats with HIO (102). As its safety and efficacy have been established, it should be investigated whether α -tocopherol also provides clinical benefit for the treatment of HIO in patients with NASH. However, α -tocopherol did not decrease hepatic iron contents in rats with diabetes or with iron overload (102, 103) while it suppressed lipid peroxidation and ferroptosis induced by hepatic ischemia-reperfusion in rats (104). Therefore, the hepatoprotective effects of tocopherol are likely attributable solely to its antioxidant properties.

It was revealed that HIO downregulates miR-122 while upregulating its target gene, CCL-2, leading to hepatic inflammation in iron-challenged rats (102). In contrast to patients with NASH (100), α -tocopherol did not improve inflammation in the iron-challenged rats, possibly because miR-122 and CCL-2 expressions were not restored by α -tocopherol in those rats (102). Thus, α -tocopherol might have a species-specific therapeutic efficacy, suggesting the importance of clinical studies in patients with HIO. Moreover, the suppression of ferroptosis by tocopherol remained to be clarified in patients with CLDs.

Adenine

Zhang et al. identified adenine as a potent hepatic hepcidin expression inducer from a commercially available vitamin library and found that adenine regulates hepcidin expression *via* the protein kinase A/SMAD pathway (105). Interestingly, adenine significantly ameliorated blood iron parameters and suppressed HIO in mice fed with an iron-enriched diet and *Hfe*-knockout mice, in which hepcidin expression is suppressed (105). Because adenine is clinically used for the treatment of leukopenia, its clinical application for HIO treatment is expected. However, dietary adenine supplementation rapidly induces experimental chronic kidney disease in rodents (106, 107). These animals also develop anemia although serum erythropoietin, which is produced in the kidney, was not altered (107). Whereas, hepcidin was upregulated concomitant with increased serum ferritin and decreased serum iron levels (107). These findings are in agreement with clinical characteristics of inflammatory anemia induced by hepcidin, suggesting that adenine supplementation inhibits iron mobilization by the upregulation of hepcidin. Therefore, the clinical application of adenine for HIO treatment requires optimal dosage determination.

Zinc

Zinc is a hepatoprotective micronutrient, and its deficiency is suggested to be involved in CLD development and eventually HCC (108). Rats fed with a zinc-deficient diet for 7 weeks developed HIO associated with an increased plasma ferritin level, while zinc intervention returned hepatic iron contents to the normal level (109). The zinc-deficient diet increased plasma hepcidin level, consistent with reduced intestinal iron absorption (109). There might be a physiological crosstalk between iron and zinc in erythropoiesis because clinical studies revealed that patients with iron deficiency anemia were significantly associated with zinc deficiency (110, 111). Moreover, zinc supplementation stimulates erythropoiesis while zinc plus iron more efficiently ameliorated anemia than iron alone (112, 113). These results suggest that zinc ameliorates HIO by enhancing iron mobilization and utilization. The therapeutic effects of zinc on CLDs have been established (108); however, the benefit of zinc supplementation for HIO in patients with CLDs remained unclear.

Niacin

Dietary nicotinic acid intake was shown to increase intestinal zinc uptake, hepatic zinc and iron contents, and blood hemoglobin levels in weanling rats, thereby promoting their growth (114). Nicotinic acid supplementation restored hepatic zinc to the normal level in rats fed with a low-zinc diet, while depletion of nicotinic acid the low-zinc diet significantly lowered hepatic zinc level (115). These results suggest that nicotinic acid promotes zinc bioavailability; thus, it may ameliorate HIO in patients with CLDs *via* zinc. This point has not been investigated so far. However, nicotinic acid suppresses lipid peroxidation and protects the liver from oxidative stress (115). Thus, nicotinic acid would provide some benefit for patients with CLDs.

Koppe, et al. found that hepatic nicotinamide levels were significantly increased by a dietary iron challenge in mice (116). This was possibly due to iron-induced downregulation of

nicotinamide *N*-methyltransferase (NNMT) in hepatocytes (116). Additionally, hepatic NNMT expression was negatively correlated with serum iron parameters in obese individuals (116). Interestingly, NNMT knockdown exacerbated iron-induced damages while its overexpression protected hepatocytes from iron overload (116). NNMT stabilizes NAD⁺-dependent deacetylase SIRT1 by producing N¹-methylnicotinamide (117). SIRT1 regulates various metabolic pathways, and its overexpression ameliorates perturbations of glucose, lipid, and cholesterol metabolisms (117). Thus, N¹-methylnicotinamide is expected as a new nutritional intervention for the treatment of HIO and metabolic syndrome. However, N¹-methylnicotinamide is rapidly inactivated in the liver by aldehyde oxidase. It is demonstrated that the combination of N¹-methylnicotinamide and an aldehyde oxidase inhibitor, hydralazine, significantly ameliorated liver steatosis while N¹-methylnicotinamide alone failed to decrease hepatic triglyceride contents (118).

Clinical research of niacin as a therapeutic for NAFLD is ongoing (119); however, whether niacin ameliorates HIO in patients with CLDs and prevents HCC needs to be addressed by future studies.

Folate

A recent finding provided a new clue for hepatic heme uptake. Solute carrier family 46 member 1 (SLC46A1) has been suggested to mediate intestinal heme and folate uptake (120). Li et al. investigated its physiological roles by liver-specific SLC46A1 knockdown because its expression is also abundant in the liver (121). In that study, SLC46A1 was shown to uptake heme also in the liver and contribute to the development of HIO in an experimental setting (121). Because SLC46A1 expression was negatively regulated by iron (120, 121), intestinal and hepatic SLC46A1 expression is worth to be determined in patients with CLDs. Interestingly, heme inhibited folate uptake by downregulating SLC46A1 expression while folate did not affect heme uptake and SLC46A1 expression (121), suggesting that folate deficiency is caused by secondary hepatic heme uptake excess. Although folate supplementation unlikely suppressed heme-induced HIO, it promotes iron utilization and mobilization for erythropoiesis. Indeed, it was demonstrated that tissue iron contents including liver and spleen in female rats were significantly lowered by a combined administration of iron and folate, compared with administration of iron alone (122). Therefore, folate supplementation is expected to prevent HIO because of its hematopoietic action.

Riboflavin

Riboflavin deficiency was shown to reduce intestinal iron absorption and utilization, leading to anemia in humans and rats (123, 124). Consequently, hepatic iron contents were significantly reduced by riboflavin deficiency. Thus, riboflavin antagonists, such as galactoflavin (124), would be expected as a novel therapeutic agent for HIO, unlike other nutrients whose agonistic actions are desired therapeutically. However, there are contradictory studies on the effect of riboflavin on anemia (125–127). Despite that, these findings suggest that riboflavin is a

confounder of the systemic iron mobilization. The physiological effects of riboflavin on iron metabolism and its mechanism remain as unanswered questions.

CONCLUSIONS

Considering its potent pro-oxidant nature, dysmetabolism of iron has been suggested as a risk factor for CLD development and progression. Moreover, accumulating evidence indicates that iron also has intrinsic functions that exacerbate CLDs, for example, HCV replication/translation promotion and macrophage activation in NAFLD (29, 128–130). Therefore, iron metabolism is an ideal target for CLD treatment, and eventually, HCC prevention. Nutritional interventions are, in general, considered to provide several benefits for patients, including not only therapeutic effects, but also cost-effectiveness. Therapies targeting iron metabolism with nutrients are expected as an alternative approach to prevent the development of HCC.

PERSPECTIVES

This study has the following limitations: 1. Although several nutrients that are beneficial for HIO amelioration were introduced, there remain many other nutrients that are potentially useful for iron metabolism correction. 2. Clinical efficacies of most nutrients are yet to be clarified, in part because the preventive effects of nutrients on hepatocarcinogenesis require long-term follow-up to confirm them. 3. The concerns that side effects such as iron deficiency and anemia could be caused by nutrients were not sufficiently considered. 4. The nutritional effects were discussed in the same way for all CLD patients even though their HIO could arise from different mechanisms.

The clarification of molecular mechanisms underlying HIO development is quite necessary for each etiology of CLD.

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Whereas, ferroptosis is currently attracting much attention because of its involvement in the development and progression of many diseases including CLDs and HCC (4). However, research focusing on hepatic ferroptosis has not been undertaken for most of nutrients. Moreover, most nutrients have been studied in their sole use; however, combination of nutrients would show synergistic or additive effects on HIO. These points should be investigated in future studies.

As mentioned above, most nutrients still need robust evidence because of the limited number of clinical and biochemical research. Particularly, their HIO amelioration mechanism needs to be studied to provide a scientific rationale for clinical studies. On this point, hepcidin is an ideal target because of its central role in iron metabolism. However, hepcidin has dual aspects on HIO, namely, it suppresses dietary iron absorption while inhibiting systemic iron mobilization. Therefore, hepcidin upregulation could be useful for HIO prevention while its downregulation could ameliorate or treat HIO. Taking this point into consideration, future studies should be undertaken.

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The author conceived the review, wrote and reviewed the manuscript, and approved it for submission.

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