MJMR

Hepatitis C and Iron Over Load

Sandeep Poddar

Research Director, Lincoln University College, Malaysia

Corresponding Author Email: sandeeppoddar@lincoln.edu.my; drsandeeppoddar@gmail.com

ABSTRACT

Hepatitis C is a liver disease caused by the hepatitis C virus: the virus can cause both acute and chronic hepatitis infection. Patients with chronic hepatitis C virus (HCV) infection appear to have an excellent chance of responding to 6 months of standard therapy with interferon (IFN) and frequently develop systemic iron overload, which exacerbates morbidity. The iron excess in hepatitis C may be due to hereditary hemochromatosis, hematologic diseases, multiple transfusions, porphyria cutanea tarda and chronic alcohol abuse. Different mechanisms proposed to explain the relation between HCV infection and hepatic iron overload. Some revealed that hepatic iron accumulation results from release of iron from damaged liver cells. Consumption of coffee, tea also reduces iron absorption and thereby decrease iron overload in Liver and thereby reduces the oxidative stress of iron overload in liver. The global scenario of this problem has been discussed in the article.

Keywords: Iron, HCV, Tea, Liver, IFN, Phlebotomy

INTRODUCTION

Iron overload in the liver has been associated with the genetic disorders like hereditary hemochromatosis, thalassemia and with unusual dietary habits mildly increased amounts of iron in the liver can increase hepatic injury, particularly if combined with other hepatotoxic factors, such as use of alcohol, porphyrogenic drugs, or chronic viral hepatitis. More recently, elevated hepatic iron levels also have been observed in chronic hepatitis C virus (HCV) infection (Isom *et al*. 2009). Hepatitis C virus (HCV) infection, which affects nearly 2% of the human population, is a major cause of liver disease worldwide (Lauer *et al*. 2001). Association of a low-iron diet to phlebotomy has an additional effect in removing iron-induced oxidative stress in HCV patients is demonstrated. Consumption of Tea or, Coffee reduces the iron intake and thereby iron overload in liver.

DISCUSSION

The following works have been carried out globally and is summarized as follows.

Insulin, HCV and Iron Overload:

Lliver fibrosis, hyperglycemia and hyperinsulinemia will lead to increased levels of insulin resistance and the development of glucose abnormalities. Furthermore, iron depletion by phlebotomy removes liver iron content and reduces serum glucose and insulin resistance in NAFLD patients. Therefore, it seems that iron overload participates in those glucose abnormalities associated with NAFLD. Concerning chronic HCV infection, it has been classically assumed that iron overload contributes to insulin resistance associated with virus infection.(Lecube *et al*. 2009). Iron depletion therapy has shown efficacy at reducing serum aminotransferase levels and improving insulin sensitivity in subjects with NAFLD (Nelson *et al* 2012).

HCV-induced IR, oxidative stress, and changes in lipid and iron metabolism lead to glucose intolerance, arterial hypertension, hyperuricemia, and atherosclerosis, resulting in increased cardiovascular mortality (Kralij *et al* 2016).

Coffee and Tea consumption and Iron Overload in Hepatitis:

Inoue *et al*. (2009) conducted a cohort study among a large Japanese population, and found that coffee and green tea consumption differed in their association with the risk of liver cancer. Specifically, coffee consumption reduced the risk of liver cancer in all subjects as well as in those who were either or both HCV and HBV infection positive. In contrast, green tea consumption showed no significant association with the risk of liver cancer overall or by HCV or HBV status.

The relationship of green tea consumption on serum ALT level has been inconsistently reported in previous studies. Two studies in Japan showed that consumption of green tea did not materially influence the serum ALT level (Tanaka *et al* 1998, Honjo *et al* 2001). On the other hand, one study reported that heavy green tea

consumption (≥10 cups per day) was related to decreased concentrations of serum ALT levels (Imai and Nakachi 1995). Sasaki *et al* 2013 in their study has showed a beneficial effect consumption of black tea/oolong tea on serum ALT level after 12 months, both among patients with normal baseline ALT levels and among those with higher ALT levels and reported a favorable association between consumption of black tea/oolong tea and serum ALT level.

Earlier works have shown that polyphenols of mate tea and green tea extracts significantly inhibit iron induced calcium homeostatic changes in liver tissue suspension (Anghileri & Thouvenot 2000) due to chelating effect. The findings of Poddar(2004)also show that the addition of ferrous sulphate to the diet for a long-term does not synergistically increase the protective action of black tea against arsenic damage in the mice bone marrow system. Consumption of tea within one hour of food consumption has been shown to reduce iron absorption by 85% (Disler *et al*., 1975).

Serum Iron markers and IFN:

Vagu *et al*. (2013) demonstrated that serum iron markers (especially ferritin and transferrin) might be used as surrogate markers for both liver fibrosis and necroinflammatory activity. Patients with chronic hepatitis C (CHC) often have elevated serum iron markers, which may worsen liver injury. Alexander and colleagues (Alexander *et al*. 20007) found that iron depletion was associated with a biochemical response in 22% of patients who did not respond to interferon (IFN) monotherapy and that, among patients with serum Alanine Aminotransferase (ALT) normalization, there was a significant reduction of serum markers of liver fibrosis (procollagen III peptide). Kaito *et al*. (2006) found that iron-reduction therapy by phlebotomy significantly reduced lipid peroxidation and oxidative stress, which mediate the deleterious effect of iron overload on the liver.

Iron Deposition, Diet with IFN therapy in HCV:

The association of a low-iron diet to phlebotomy has an additional effect in removing iron-induced oxidative stress (Kimura *et al*. 2005; Kato *et al* 2001). Indeed, in a study conducted by Kato and colleagues (Kato *et al* 2001), 34 patients with chronic HCV infection unresponsive to IFN therapy were maintained in an iron-depleted state with phlebotomy and a low-iron diet for 6 years. This therapy was associated with a high rate of biochemical response (65%), improvement in liver histology, and reduction in hepatic levels of 8-OHdG, a marker of oxidant stress. In a recent cohort study, the same authors demonstrated that long-term phlebotomy with a low-iron diet therapy reduced the risk of progression of chronic HCV infection to hepatocellular carcinoma (Kato *et al*. 2007).

HCV-infected patients who have large accumulations of hepatic iron have not responded well to interferon therapy, compared to patients with normal hepatic iron stores. Physicians who treat patients infected with HCV should be aware of the detrimental effect of excess liver iron on interferon therapy. The degree of hepatic iron overload should be assessed and the reason for the excess iron should be investigated. Phlebotomy is the most practical method for iron removal and is well tolerated by patients with HCV infection (Roeckel I E 2000).

Numerous studies in humans and in animal models revealed that the alteration of iron homeostasis is closely associated with various HCV-induced pathologies including liver fibrosis (Martinelli *et al*. 2004, Casaril *et al*. 2000), steatosis (Sebastiani *et al* 2006; Nishina *et al*. 2010; Furutani *et al* 2006), insulin resistance (Sumida *et al* 2007), diabetes mellitus (D'Souza *et al*. 2007), porphyria cutanea tarda (Darwich *et al*. 2013), and HCC occurrence (Furutani *et al* 2006). In contrast, iron deposition in liver does not correlate with rates of Sustained Virologic Response (SVR) during interferon/ribavirin therapy (Hofer *et al*. 2004; Pianko *et al*. 2002), although there is some evidence of a negative correlation between SVR and the level of serum ferritin (Hofer *et al*. 2004). At the same time several studies reported the same relationship between alterations of iron metabolism and interferon monotheraly (Pianko *et al*. 2002, Carlo *et al*. 2003, Fargion *et al*. 1997). Phlebotomy in CHC patients leads to a decrease in hepcidin expression (Fujita *et al*. 2007) and to a marked reduction of serum transaminases ALT and Aspartate Aminotransferase (AST) and liver injury (Carlo *et al*. 2003; Yano *et al*. 2004, Kaito *et al*. 2006). However, it is considered that reduction of iron overload does not lead to increase in SVR rate (Guyader *et al*. 1999, Herrera J L 1999, Di Bisceglie *et al*. 2000, Iwasa *et al*. 2002), although opposite has also been reported (Fontana *et al*. 2000). Iron overload and oxidative stress during HCV infection are closely related to each another. There is a strong correlation between serum ferritin levels and lipid peroxydation markers in CHC patients (Barbaro *et al*. 1999).

8-OHdG content, a DNA oxidation marker, also correlates with hepatic iron storage markers including serum ferritin, hepatic total iron score and hepcidin mRNA levels (Fujita *et al*. 2007). In addition, transgenic mice expressing an HCV polyprotein and subjected to iron-rich diet also exhibit signs of oxidative stress in liver (lipid peroxydation, 8oxoG), accompanied by alterations of mitochondrial ultrastructure (Furutani *et al*. 2006). Currently there is no consensus on which of them is a trigger of another. On one hand, suppression of hepcidin expression is mediated by Reactive Oxygen Species (ROS) (Miura *et al*. 2008).

On the other hand, phlebotomy or dietary iron restriction reduces oxidative stress and lipid peroxidation in CHC patients (Kaito *et al*. 2006, Fujita *et al*. 2007).

Iron overload in chronically HCV-infected patients was uncommon and hepatic iron content seemed not to be related to the liver damage process. In the eventuality of iron overload, histochemical liver iron is a useful marker to estimate hepatic iron concentration (HIC) (Ivonete *et al* 2005)

Most of the hepatitis C virus (HCV)-infected patients develop a chronic slowly progressive liver disease that may result in cirrhosis and hepatocarcinoma. Several factors have been proposed to explain this unfavorable evolution such as male gender, age at infection and alcohol abuse (Poynard *et al* 2001).

Recently, the role of iron has been pointed out as an important element in the natural history of hepatitis C. In fact, serum iron stores are frequently increased in chronic HCV-infected carriers but little is known about the significance of these abnormalities. (Di Bisceglie *et al* 1992, Haque *et al* 1996)

The iron excess in hepatitis C may be due to hereditary hemochromatosis, hematologic diseases, multiple transfusions, porphyria cutanea tarda and chronic alcohol abuse (Di Marco *et al*. 1997, Ganne-Carrie *et al* 2000, Martinelli *et al*. 2000a, 2000).

Iron overload is a condition when the body iron stores increases as a result of iron administration, repeated blood transfusions or disorders that increase the rate of iron absorption within the body. The known impacts of iron overload are mainly Cirrhosis (a liver disease which leads to a progressive loss of liver function), and some types of carcinoma, tuberculosis and other infections. In Indian populations, there have not been any links established as yet to detect Iron overload (Poddar, 2006),

Recent investigations have found that hepatic iron concentration does not influence the response to antiviral therapy with IFN plus ribavirin (Hofer *et al*. 2004; Pianko *et al*. 2002)

However, if these factors are absent the mechanisms involved in iron overload remain unclear.

Over the last few years, there has been much interest in the study of iron in hepatitis C because some studies have shown that iron accumulation in chronic HCV carriers is related to a poor response to interferon therapy (Van Thiel *et al* 1994, Fargion *et al* 1997). In addition, others have suggested that hepatic iron overload in hepatitis C may worsen liver damage by still unrecognized mechanisms. (Andant *et al* 1996, Hezode *et al*. 1999).

Iron overload is often assessed using indirect parameters of iron stores such as serum iron, serum ferritin and transferrin saturation, which are frequently increased in chronic viral hepatitis (Di Bisceglie *et al* 1992,) as well as by the histological determination of stainable iron in liver samples (Deugnier YM *et al* 1993).

CONCLUSION

The evidence exists that iron overload, is a common finding associated with chronic hepatitis C virus (HCV) infection, plays a vital role in the pathophysiology of this disease. Some aspects of excess iron and liver damage along with the benefit of iron depletion in patients with chronic HCV infection have been discussed in this review. As a future scope we should focus on reduction of iron overload to HCV infected persons to get a good response to interferon antiviral therapy.

REFERENCES

Alexander, J., Tung, B. Y., Croghan, A., Kowdley, K. V. (2007) Effect of iron depletion on serum markers of fibrogenesis, oxidative stress, serum liver enzymes in chronic hepatitis C: results of a pilot study. Liver Int. 27, pp. 268–273.

Andant, C., Lamoril, J., Edery, J. et al. (1996). Hepatic iron concentration (HIC) and serum iron parameters in patients with chronic hepatitis C, Hepatology. 26, pp. 478A.

Anghileri, L. J. and Thouvenot, P. (2000). Natural

polyphenols-iron interaction its biological importance, Biol Trace Element Res. 73, pp.251.

Barbaro, G., Di Lorenzo, G., Ribersani, M., Soldini, M., Giancaspro, G., Bellomo, G., Belloni, G., Grisorio, B., Barbarini, G. (1999). Serum ferritin and hepatic glutathione concentrations in chronic hepatitis C patients related to the hepatitis C virus genotype, J. Hepatol. 30, pp.774–782.

Carlo, C., Daniela, P., Giancarlo, C. (2003). Iron depletion and response to interferon in chronic hepatitis C, Hepatogastroenterology, 50, pp.1467–1471.

Casaril, M., Stanzial, A.M., Tognella, P., Pantalena, M., Capra, F., Colombari, R., Corrocher, R. (2000). Role of iron load on fibrogenesis in chronic hepatitis C, Hepatogastroenterology, 47, pp.220–225.

Darwich, E., To-Figueras, J., Molina-Lopez, R. A., Deulofeu, R., Olbina, G., Westerman, M., Sanchez-Tapias, J. M., Munoz-Santos, C., Herrero, C. (2013). Increased serum hepcidin levels in patients with porphyria cutanea tarda, J. Eur. Acad. Dermatol. Venereol., 27, pp.68–74.

Deugnier, Y. M., Turlin, B., Powell, L. W. et al. (1993). Differentiation between heterozygotes and homozygotes in genetic hemochromatosis by means of a histological hepatic iron index: a study of 192 cases, Hepatology, 17, pp. 30-4.

Di Bisceglie, A. M., Bonkovsky, H. L., Chopra, S., Flamm, S., Reddy, R. K., Grace, N., Killenberg, P., Hunt, C., Tamburro, C., Tavill, A. S., et al.(2000). Iron reduction as an adjuvant to interferon therapy in patients with chronic hepatitis C who have previously not responded to interferon: A multicenter, prospective, randomized, controlled trial, Hepatology, 32, pp.135–138.

Di Bisceglie, A. M., Axiotis, C. A., Hoofnagle, J. H., Bacon, B. R. (1992). Measurements of iron status in patients with chronic hepatitis, Gastroenterology, 102, pp. 2108-13.

Di Marco, V., Lo Iacono, O., Almasio, P. et al. (1997). Long-term efficacy of alpha-interferon in beta-thalassemics with chronic hepatitis C, Blood, 90, pp.2207-12.

Disler, P. B., Lynch, S. R. and Chalton, R. W., (1975). The effect of tea on iron absorption, Gut, 16, pp.193.

D'Souza R.F., Feakins R., Mears L., Sabin C. A., Foster, G. R. (2005). Relationship between serum ferritin, hepatic iron staining, diabetes mellitus and fibrosis progression in patients with chronic hepatitis C, Aliment. Pharmacol. Ther. 21, pp.519–524.

Fargion, S., Fracanzani, A. L., Sampietro, M. et al. (1997). Liver iron influences the response to interferon alpha therapy in chronic hepatitis C, Eur. J. Gastroenterol. Hepatol, 9, pp. 497-503.

Fontana, R. J., Israel, J., LeClair, P., Banner, B. F., Tortorelli, K., Grace, N., Levine, R. A., Fiarman, G., Thiim, M., Tavill, A. S., et al. (2000). Iron reduction before and during interferon therapy of chronic hepatitis C: Results of a multicenter, randomized, controlled trial, Hepatology, 31, pp.730–736.

Fujita, N., Horiike, S., Sugimoto, R., Tanaka, H., Iwasa, M., Kobayashi, Y., Hasegawa, K., Ma, N., Kawanishi, S., Adachi, Y., et al. (2007). Hepatic oxidative DNA damage correlates with iron overload in chronic hepatitis C patients, Free Radic. Biol. Med. 42, pp.353–362.

Fujita, N., Sugimoto, R., Urawa, N., Tanaka, H., Konishi, M., Kobayashi, Y., Iwasa, M., Watanabe, S., Kaito, M. (2007). Influence of phlebotomy on iron-related gene expression levels in the livers of patients with chronic hepatitis C, J. Gastroenterol. 42, pp.326–327.

Furutani, T., Hino, K., Okuda, M., Gondo, T., Nishina, S., Kitase, A., Korenaga, M., Xiao, S.Y., Weinman, S. A., Lemon, S. M., et al.(2006). Hepatic iron overload induces hepatocellular carcinoma in transgenic mice expressing the hepatitis C virus polyprotein, Gastroenterology, 130, pp.2087–2098.

Ganne-Carrie, N., Christidis, C., Chastang, C. et al. (2000). Liver iron is predictive of death in alcoholic cirrhosis: a multivariate study of 229 consecutive patients with alcoholic and/or hepatitis C virus cirrhosis: a prospective follow up study, Gut, 46, pp. 277-82.

Guyader, D., Boucher, E., Andre, P., Even, C., Cottereau, J., Bianchi, A., Gasser, P., Mendler, M. H., Deugnier, Y., Brissot, P. (1999). A pilot study of iron depletion as adjuvant therapy in chronic hepatitis C patients not responding to interferon, Am J Gastroenterol, 94, pp.1696–1698.

Haque, S., Chandra, B., Gerber, M. A., Lok, A. S. (1996). Iron overload in patients with chronic hepatitis C: a clinicopathologic study, Hum. Pathol, 27, pp.1277-81.

Herrera, J. L. (1999). Iron depletion is not effective in inducing a virologic response in patients with chronic

hepatitis C who failed to respond to interferon therapy, Am. J. Gastroenterol. 94, pp.3571–3575.

Hezode, C., Cazeneuve, C., Coue, O. et al. (1999). Liver iron accumulation in patients with chronic active hepatitis C: prevalence and role of hemochromatosis gene mutations and relationship with hepatic histological lesions, J. Hepatol. 31, pp. 979-84.

Hofer, H., Osterreicher, C., Jessner, W., Penz, M., Steindl-Munda, P., Wrba, F., et al. (2004). Hepatic iron concentration does not predict response to standard and pegylated-IFN/ribavirin therapy in patients with chronic hepatitis C, J Hepatol, 40, pp.1018–1022.

Honjo, S., Kono, S., Coleman, M. P., Shinchi, K., Sakurai, Y. et al. (2001). Coffee consumption and serum aminotransferases in middle-aged Japanese men, J Clin Epidemiol, 54, pp. 823-829.

Imai, K., Nakachi, K. (1995). Cross sectional study of effects of drinking green tea on cardiovascular and liver diseases, BMJ, 310, pp.693-696.

Inoue, M., Kurahashi, N., Iwasaki, M., Shimazu, T., Tanaka, Y., Mizokami, M., Tsugane, S. (2009). Effect of Coffee and Green Tea Consumption on the Risk of Liver Cancer: Cohort Analysis by Hepatitis Virus Infection Status. Cancer Epidemiology, Biomarkers and Prevention,18(6), pp. 1744-1753.

Isom, H. C., McDevitt, E. I., Moon, M.S. (2009). Elevated hepatic iron: a confounding factor in chronic hepatitis C, Biochim Biophys Acta, 1790(7), pp.650-62.

Ivonete, S. S., Silva, Renata, M. Perez, Pedro V. Oliveira, Maria, Inês Cantagalo, Elizabete Dantas, Cristina, Sisti, Cláudio, Figueiredo-Mendes, Valeria, P. Lanzoni, Antonio, E.B. Silva, Maria, Lucia, G. Ferraz, (2005). Iron Overload in Patients with Chronic Hepatitis C Virus Infection: Clinical and Histological Study, J Gastroenterol Hepatol, 20(2), pp.243-248.

Iwasa, M., Kaito, M., Ikoma, J., Kobayashi, Y., Tanaka, Y., Higuchi, K., Takeuchi, K., Iwata, K., Watanabe, S., Adachi, Y. (2002). Dietary iron restriction improves aminotransferase levels in chronic hepatitis C patients, Hepatogastroenterology, 49, pp.529–531.

Kaito, M., Iwasa, M., Kobayashi, Y., Fujita, N., Tanaka, H., Gabazza, E. C., et al. (2006) Iron reduction therapy by phlebotomy reduces lipid peroxidation and oxidative stress in patients with chronic hepatitis C, J Gastroenterol, 41, pp.921–922.

Kato, J., Kobune, M., Nakamura, T., Kuroiwa, G., Takada, K., Takimoto, R., et al.(2001). Normalization of elevated hepatic 8-hydroxy-2'-deoxyguanosine levels in chronic hepatitis C patients by phlebotomy and low iron diet, Cancer Res, 61, pp.8697–8702.

Kato, J., Miyanishi, K., Kobune, M., Nakamura, T., Takada, K., Takimoto, R., et al. (2007). Long-term phlebotomy with low-iron diet therapy lowers risk of development of hepatocellular carcinoma from chronic hepatitis C, J Gastroenterol, 42, pp.830–836.

Kimura, F., Hayashi, H., Yano, M., Yoshioka, K., Matsumura, T., Fukuda, T., et al. (2005). Additional effect of low iron diet on iron reduction therapy by phlebotomy for chronic hepatitis C, Hepato-gastroenterology, 52, pp.563–566.

Kralj, D., Jukić, L. V., Stojsavljević, S., Duvnjak, M., Smolić, M., & Čurčić, I. B. (2016). Hepatitis C Virus, Insulin Resistance, and Steatosis, Journal of Clinical and Translational Hepatology, 4(1), pp. 66–75.

Lauer GM, Walker BD. (2001). Hepatitis C virus infection, N Engl J Med, 345, pp.41–52.

Lecube, A., Hernández, C., Simó, R. (2009). Glucose abnormalities in non-alcoholic fatty liver disease and chronic hepatitis C virus infection: the role of iron overload, 25(5), pp. 403-10.

Martinelli, A. L., Ramalho, L. N., Zucoloto, S. (2004). Hepatic stellate cells in hepatitis C patients: relationship with liver iron deposits and severity of liver disease, J. Gastroenterol. Hepatol,19, pp. 91–98.

Martinelli, A. L., Franco, R. F., Villanova, M. G. et al. (2000a). Are haemochromatosis mutations related to the severity of liver disease in hepatitis C virus infection?, Acta Haematol, 102, pp. 152-6.

Martinelli, A. L., Zago, M. A., Roselino, A. M. et al. (2000). Porphyria cutanea tarda in Brazilian patients: association with hemochromatosis C282Y mutation and hepatitis C virus infection, 95, pp.3516-21.

Miura, K., Taura, K., Kodama, Y., Schnabl, B., Brenner, D. A. (2008). Hepatitis C virus-induced oxidative stress suppresses hepcidin expression through increased histone deacetylase activity, Hepatology, 48, pp.1420–1429.

Nelson, J. E., Klintworth, H., Kowdley, K.V. (2012). Iron metabolism in Nonalcoholic Fatty Liver Disease, Curr

Gastroenterol Rep, 14(1), pp.8-16.

Nishina, S., Korenaga, M., Hidaka, I., Shinozaki, A., Sakai, A., Gondo, T., Tabuchi, M., Kishi, F., Hino, K. (2010). Hepatitis C virus protein and iron overload induce hepatic steatosis through the unfolded protein response in mice, Liver Int, 30, pp.683–692

Pianko, S., McHutchison, J. G., Gordon, S. C., Heaton, S., Goodman, Z. D., Patel, K., et al. (2002) Hepatic iron concentration does not influence response to therapy with interferon plus ribavirin in chronic HCV infection, J Interf Cytokine Res, 22, pp.483–489.

Poddar, S. (2006). Hereditary Hemachromatosis – special reference to Indian scenario, Int. Jou. Hum. Genetics, 6(1), pp. 73-79.

Poddar, S. (2004). Dietary intervention with iron and black tea infusion in reducing cytotoxicity of arsenic, Indian Journal of Experimental Biology, 42, pp. 900-903.

Poynard, T., Ratziu, V., Charlote, F., Goodman, Z., McHutchison, J., Albrecht, J. (2001). Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C, J. Hepatol. 34, pp.730-9.

Roeckel, I. E. (2000). Commentary: Iron metabolism in hepatitis C infection, Ann Clin Lab Sci., 30(2), pp.163-5.

Sasaki, Y., Ohfuji, S., Fukushima, W., Tamori, A., Enomoto, M., et al. (2013). Effect of Caffeine-Containing Beverage Consumption on Serum Alanine Aminotransferase Levels in Patients with Chronic Hepatitis C Virus Infection: A Hospital-Based Cohort Study, PLOS ONE, 8(12), pp. e83382.

Sebastiani, G., Vario, A., Ferrari, A., Pistis, R., Noventa, F., Alberti, A. (2006). Hepatic iron, liver steatosis and viral genotypes in patients with chronic hepatitis C, J. Viral. Hepat., 13, pp.199–205.

Sumida, Y., Kanemasa, K., Fukumoto, K., Yoshida, N., Sakai, K. (2007). Hepatic iron accumulation may be associated with insulin resistance in patients with chronic hepatitis C, Hepatol. Res., 37, pp. 932–940.

Tanaka, K., Tokunaga, S., Kono, S., Tokudome, S., Akamatsu, T. et al. (1998). Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers, Int J Epidemiol, 27, pp.438-443.

Vagu, C., Sultana, C., and Ruta, S. (2013). Serum Iron Markers in Patients With Chronic Hepatitis C Infection, Hepatitis Monthly, 13(10), e13136. http://doi.org/10.5812/hepatmon.13136

Van, Thiel D. H., Friedlander, L., Fagiuoli, S., Wright, H. I., Irish, W., Gavaler, J. S. (1994). Response to interferon alpha therapy is influenced by the iron content of the liver, J. Hepatol, 20, pp. 410-15.

Yano, M., Hayashi, H., Yoshioka, K., Kohgo, Y., Saito, H., Niitsu, Y., Kato, J., Iino, S., Yotsuyanagi, H., Kobayashi, Y., et al. (2004). A significant reduction in serum alanine aminotransferase levels after 3-month iron reduction therapy for chronic hepatitis C: A multicenter, prospective, randomized, controlled trial in Japan, J. Gastroenterol, 39, pp.570–574.