Clinical Medicine: Endocrinology and Diabetes



SHORT COMMENTARY

# Insulin Resistance, Type 2 Diabetes and Chronic Liver Disease. A Deadly Trio

Amedeo Lonardo and Paola Loria

University of Modena and Reggio Emilia Department of Internal Medicine, Endocrinology, Geriatrics Nuovo Ospedale Sant'Agostino Estense di Baggiovara, Baggiovara, Modena, Italy. Email: a.lonardo@libero.it

**Abstract:** In this commentary to the paper by Donadon V. et al (*Clinical Medicine: Endocrinology and Diabetes*. 2009;2:25–33.) the association and significance of insulin resistance with chronic liver disease are shortly reviewed and the molecular mechanisms underlying the diabetogenic and oncogenic potentials of advanced liver disease are summarized. Literature studies demonstrate that hepatocellular carcinoma (HCC) can be part of the natural history of NASH. HCCs in patients with features of metabolic syndrome as the only risk factor for liver disease have distinct morphological characteristics and mainly occur in the absence of significant fibrosis in the background liver. Moreover, data indicate that the presence of diabetes carries an approximately three to four-fold increased risk of HCC and such a risk is strongly increased by concurrent viral infections. Finally, the relationship between insulin resistance, steatosis and diabetes in NAFLD and HCV infection will be commented, along with the directions for future studies.

**Keywords:** T2DM, hepatitis, cirrhosis, hepatocellular carcinoma

*Clinical Medicine: Endocrinology and Diabetes* 2009:2 81–88

This article is available from http://www.la-press.com.

## The Diabetogenic Potential of Advanced Liver Disease

Insulin resistance (IR) is a concept popular among diabetologists who, historically, have contributed to its most explicit conceptualization in the last two decades.[1] During the same time period, however, IR has also become of great current interest among hepatologists. This is essentially the result of IR playing a key-role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD)[2] and being a cofactor of progression/impaired response to treatment in chronic hepatitis C.[3] Such close links between IR and two among the most common chronic liver disorders in western countries are likely to account for why diabetes almost invariably follows most chronic liver diseases. Moreover, they explain why cirrhosis, in particular, was depicted to be an overt diabetogenic condition a few years before Reaven had conceptualized the importance of IR in human disease.[4] Closing the circle, we now are aware that increasing stages of hepatic fibrosis are associated with increasing risks of developing type 2 diabetes via increasing levels of IR. The paper by Donadon[5] is further evidence for this pathogenic cascade of events.

## The Oncogenic Potential of Advanced Liver Disease is Influenced by IR

Not only does insulin regulate glucose metabolism, but it is also directly and indirectly involved in the risk of promoting the development of cancer at various extrahepatic organ sites such as colon, prostate, and pancreas.[6] There is strong epidemiologic evidence linking the metabolic syndrome (MS) and hepatocellular carcinoma (HCC); the molecular mechanisms sustaining hepatic carcinogenesis in those with IR, however, are not completely understood.[7] Primary liver cancer might result from activation of the tumor suppressor PTEN, a phosphoinositide phosphatase regulating the PI3K/Akt signaling pathways and the dysregulated expression and activity of which critically affects hepatic insulin sensitivity, triggers the development of NAFLD and participates in the molecular pathogenesis of HCC.[8,9] The Hydroxymethyl-glutaryl-CoA inhibitors statins exert pleiotropic actions in liver physiology and particularly on cholesterol-related cell signalling pathways.[10] On this basis, the recent finding that statin use is associated with a significant reduction in the risk of HCC among patients with diabetes[11] indirectly suggests that metabolic pathways such as synthesis of bile acids, sonic Hedgehog, Kras, and the Rho family, p21 and p27 cyclin-dependent kinase inhibitors and fibrogenesis could be additional potential mechanisms involved in hepatocarcinogenesis in diabetics.[10,11]

## NASH, Cryptogenic Cirrhosis and HCC

Nonalcoholic steatohepatitis (NASH) is the most advanced histological form in the NAFLD spectrum. The association between NASH-cirrhosis—sometimes indistinguishable from cryptogenic cirrhosis—and HCC has been consistently confirmed by several studies summarized in Table 1.[12–26] Such an association comes as no surprise given that cirrhosis of various etiologies is known to be a pre-cancerous condition[27] and NASH is indeed strongly associated with IR.[28] Overall, literature studies summarized in Table 1 demonstrate that HCC can be part of the natural history of NASH.[12–26] HCCs in patients with features of MS as the only risk factor for liver disease have distinct morphological characteristics and mainly occur in the absence of significant fibrosis in the background liver.[22,23] Awareness of these specific features of disease can be exploited to implement specific strategies aimed at obtaining earlier diagnoses and more effective treatment results.[26]

## Association of Diabetes, Steatosis and HCC

Population studies from Northern Italy have shown type 2 diabetic patients to have an increased risk of death from gastrointestinal diseases, particularly from liver cirrhosis after 5 years of follow-up and a higher risk of mortality from liver cancer after 10 years of follow-up, particularly in obese patients.[29] Such findings are strongly supported by several studies, summarized in Table 2.[30–46] Data indicate that the presence of diabetes carries an approximatively three to four-fold increased risk of HCC.[32,36,45] Moreover, the metabolic risk of diabetes is strongly potentiated by concurrent viral infections.[31,37,44,45] Given that steatosis is a sensitive barometer of metabolic health, the association of steatosis with HCC risk is also biologically plausible[35,43] although a study contrasts with such a view.[38]

**Table 1.** Evidence for a relationship between NASH, cryptogenic cirrhosis and HCC.

| Author, (Ref.) | Series | Main finding |
|---|---|---|
| Powell EE[12] | 42 NASH patients. Cirrhosis was present at initial diagnosis in one subject. | The patient with cirrhosis later died of HCC. |
| Cotrim HP[13] | A patient with NASH-cirrhosis developed HCC after a 6-yr follow-up. | HCC can be part of the natural history of NASH. |
| Shimada[14] | 6 patients with NASH and HCC out of a series of 82 cases with NASH. | In patients with NASH-cirrhosis, the development of treatable HCC is sufficiently common to warrant regular screening for this grave complication. |
| Bugianesi[15] | 44/641 cryptogenic cirrhosis-associated HCCs, were identified. Of these, 23 were actively followed- up and compared in a case-control study with viral- and alcohol-associated HCC. | Hypertriglyceridemia, diabetes, and normal aminotransferases are factors independently associated with HCC arising in cryptogenic cirrhosis, suggesting that HCC may represent a late complication of NASH-related cirrhosis. |
| Regimbeau JM[16] | 18/210 HCC patients (8.6%) had no identifiable cause for the underlying liver disease. | The prevalence of obesity, diabetes, AST/ALT ratio $< 1$ , steatosis $>20\%$ and well-differentiated tumors was significantly higher in patients with cryptogenic liver disease. |
| Hai S[17] | 2/481 (0.4%) patients who underwent liver resection for HCC had associated NASH with moderate hepatic fibrosis in one patient and cirrhosis in the other. | Follow-up and screening for HCC should be done for patients with hepatic fibrosis caused by NASH. |
| Sanyal AJ[18] | 152 patients with NASH cirrhosis were compared with 150 matched patients with cirrhosis due to HCV. | Compensated NASH cirrhosis is associated with a lower mortality rate, decompensation rate, development of HCC; and greater cardiovascular mortality in patients with NASH. |
| Hashizume H[19] | Nine patients with HCC in NASH. | All patients except one met the criteria for metabolic syndrome. |
| Tsutsumi K[20] | Two cases of patients with HCC that developed into cryptogenic cirrhosis suggestive of NASH as background liver disease. | These cases progressed from NASH and fatty liver, respectively, to NASH-related cirrhosis, eventually developing HCC. |
| Guzman G[21] | Three out of 50 patients with HCC. | NAFLD may predispose patients to HCC in the absence of cirrhosis. |
| Paradis[22] | HCC patients with features of MS as the only risk factor for liver diseases (n = 31) were compared to HCC patients with overt causes of CLD (n = 81) or without causes of CLD (n = 16). | HCCs in patients with features of MS as the only risk factor for liver disease have distinct morphological characteristics and mainly occur in the absence of significant fibrosis in the background liver. |
| Hashimoto E[23] | 34 NASH patients with HCC were compared with 348 NASH without HCC. | Older age and advanced fibrosis were important risk factors for HCC. HCC was the major cause of mortality in NASH patients with advanced fibrosis. Regular screening for HCC is warranted for NASH patients with advanced fibrosis |
| Malik[24] | 17/98 patients (17%) with NASH cirrhosis were diagnosed with HCC. | Patients with NASH cirrhosis, especially men older than 50 years, should undergo surveillance imaging. |

(*Continued*)

**Table 1.** (*Continued*)

| Author, (Ref.) | Series | Main finding |
|---|---|---|
| Kawada N[25] | Eight (1%) HCC patients were diagnosed with NASH. Six (75%) of them showed non-cirrhosis in non-cancerous areas. | HCC might arise frequently from non-cirrhotic NASH. |
| Giannini EG[26] | 45 consecutive CC patients with HCC were compared with 426 consecutive patients with HCC and only HCV infection. | HCC patients with CC had similar impairments in liver function as patients with HCV infection. However, the HCC patients with CC had lower aminotransferase levels and higher platelet counts. HCC was significantly less likely to be diagnosed during surveillance and thus to be more advanced and less amenable to treatment compared with HCV patients. |

**Abbreviations:** CC, cryptogenic cirrhosis; HCC, hepatocellular carcinoma; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

## The Relationship Between Insulin Resistance, Steatosis and Diabetes in NAFLD and HCV Infection

Early stages of both NAFLD and HCV infection share steatosis as a common histologic feature and IR is a physiopathologic feature of both liver diseases. Such findings have generated interest in the possibility of transferring knowledge from one disease to the other.[47] In the transgenic mouse model expressing HCV core protein, IR anticipates the development of steatosis. Overt diabetes only occurs once these animals gain weight as a result of a high-fat diet. A high level of tumor necrosis factor-alpha, which acts by disturbing tyrosine phosphorylation of insulin receptor substrate-1 and is a common finding also in human chronic hepatitis C, is considered to be one of the bases of IR in the transgenic mice.[48] Studies conducted by short-term high fat feeding rats support the hypothesis that hepatic steatosis leads to hepatic insulin resistance by stimulating gluconeogenesis and activating PKC-epsilon and JNK1, which may interfere with tyrosine phosphorylation of IRS-1 and IRS-2 and impair the ability of insulin to activate glycogen synthase.[49] Our group recently compared the predictors of IR in HCV and NAFLD. Data show IR to be independently assso-ciated with BMI and triglyceridemia in NAFLD; male gender and fibrosis in chronic HCV infection.[50] Collectively, these animal and human studies have relevant clinical implications. On the HCV side, eradication of viral infection with combined IFN+ Ribavirin regimens, which is associated with prevention of fibrosis, has resulted in the prevention of the development of diabetes[51] although this finding has not been invariably confirmed.[52] On the NAFLD side, these patients are often glucose-intolerant or diabetics either at the first diagnosis or during follow-up.[53–56] Furthermore, in a study conducted in patients with type 2 diabetes, a weight loss of only approximately 8 kg resulted in improved basal and insulin-stimulated hepatic glucose metabolism associated with an 80% reduction in intrahepatic lipid content.[57]

## Conclusions and Research Agenda

In conclusion, data reviewed here strongly support that advanced hepatic fibrosis is associated with diabetes and that diabetes increses the risk of developing HCC. Such a view is also confirmed in the study by Donadon.[5] Asssociation, however, does not prove causality. The paper by Donadon, owing to its cross-sectional design does not show which, between IR and HCC, comes first.[5] Prospective studies are, therefore, needed to address the issue whether those chronic liver disease patients who are more insulin-resistant are at an increased risk

**Table 2.** Evidence for an association between diabetes (or steatosis) and HCC.

| Author, (Ref.) | Series | Main finding |
|---|---|---|
| Braga C[30] | 320 HCC patients and 1408 controls. | In the development of HCC, the attributable risk for diabetes was 8% compared with 40% for low vegetable and fruit consumption, 31% for low education, 18% for liver cirrhosis, 16% for hepatitis, and 7% for heavy alcohol consumption. |
| El-Serag HB[31] | 823 patients with PLC and 3459 controls. | In the multivariable logistic regression, diabetes was associated with a significant increase in the adjusted OR of PLC (OR 1.57) in the presence of HCV, HBV, or alcoholic cirrhosis. |
| Hassan MM[32] | 115 HCC patients and 230 non-liver cancer controls. | Multivariate ORs were 15.3, 12.6, 4.5, and 4.3 for anti-HCV, HBsAg, heavy alcohol consumption, and diabetes mellitus, respectively. |
| Tazawa J[33] | 279 patients were followed-up for 65.9 +/– 29.4 months until the occurrence of HCC. | With multivariate analysis, only diabetes mellitus and age were associated with the occurrence of HCC. |
| Huo TI[34] | 245 HCC patients with well-preserved liver functions undergoing resection. | Multivariate Cox regression model analysis confirmed that DM and tumor size >3 cm were independent prognostic predictors associated with the occurrence of hepatic decompensation. |
| Ohata K[35] | 161 patients with chronic HCV infection followed for up to 15 years. | Multivariate analysis identified hepatic steatosis, together with aging, cirrhosis, and no IFN treatment, as independent and significant risk factors for HCC. |
| Yuan JM[36] | 295 HCC cases and 435 age-, gender-, and race-matched control subjects among Hispanic and non-Hispanic whites and blacks. | Subjects with a history of diabetes had an OR of 2.7 for HCC compared with nondiabetic subjects. A synergistic interaction on HCC risk was observed between heavy alcohol consumption and diabetes, or between diabetes and viral hepatitis. |
| Davila JA[37] | 2061 HCC patients and 6183 non-cancer controls. | In adjusted multiple logistic regression analyses diabetes was associated with a threefold increase in the risk of HCC. A significant positive interaction between HCV and diabetes was detected. |
| Kumar D[38] | The histological severity of steatosis was compared in the index liver biopsies of 25 patients with chronic hepatitis C who subsequently developed HCC with matched controls. | This is the only negative study reporting that hepatic steatosis does not augment the risk of hepatocarcinogenesis in patients with chronic HCV infection. |
| Lai MS[39] | Out of a prospective cohort of 54,979 subjects 5,732 individuals with T2D and 138 confirmed HCC cases were identified. | After controlling for confounders, the association between type 2 diabetes and incidence of HCC was only statistically significant for those being HCV negative and those having hypercholesterolemia. |

(*Continued*)

**Table 2.** (*Continued*)

| Author, (Ref.) | Series | Main finding |
|---|---|---|
| N'Kontchou G[40] | 771 patients with well-compensated alcohol-or HCV-related cirrhosis prospectively screened for HCC. | In multivariate analysis, factors predictive for HCC were BMI, diabetes, age, sex, HCV, and mixed etiology. |
| Yu L[41] | 158 black compared to 701 white HCC patients. | Higher rates of HBV, HCV, concurrent HBV and HCV, and viral hepatitis associated with diabetes might explain the greater burden of HCC in black Americans. |
| Komura T[42] | 90 patients who had undergone curative resection for HCC. | Diabetes was a factor independently associated with HCC recurrence after treatment. |
| Pekow JR[43] | 32 patients with HCV-cirrhosis and HCC compared to 62 who had HCV-cirrhosis and no HCC. | Age, AFP and steatosis were independent predictors of HCC. |
| Chen CL[44] | 23,820 residents in Taiwan followed-up for 14 years. | Diabetes was associated with HCC in all patients. The highest risk was seen in those with HCV infection (RR 3.52) and lowest in HBV carriers (RR(a) 2.27). HBV or HCV carriers with both obesity and diabetes had more than 100-fold increased risk, indicating synergistic effects of metabolic factors and hepatitis. |
| Veldt BJ[45] | 541 HCV patients of whom 85 (16%) had diabetes mellitus. | In patients with chronic hepatitis C and advanced cirrhosis, diabetes mellitus increases the risk of developing HCC (hazard ratio, 3.28). |
| Polesel J[46] | 185 HCCs and 404 controls. | After allowance for known risk factors, BMI $>$ /= 30 and DM (OR = 3.7) were associated to HCC risk. These associations persisted among subjects without HBV and/or HCV infection. |

**Abbreviations:** BMI, body mass index (Kg/m$^2$); DM, diabetes mellitus; HCC, hepatocellular carcinoma; OR, odds ratio; RR, relative risk; PLC, primary liver cancer; T2D, type 2 diabetes.

of developing HCC or if it is the presence of HCC *per se* that aggravates pre-existent IR. Moreover, given that most studies are based on patients with HCC rather than on diabetics, it is unclear whether a stricter metabolic control might be effective in preventing the development of HCC in these patients.

## Acknowledgements

The authors are indebted to Mrs Jacqueline Mole for English editing of the manuscript.

## Disclosures

The authors report no conflicts of interest.

## References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–607.
2. Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. *Hepatology*. 2005;42:987–1000.
3. Lonardo A, Adinolfi LE, Petta S, Craxì A, Loria P, Hepatitis C and diabetes: the inevitable coincidence? *Expert Rev Anti Infect Ther*. 2009;7:293–308.
4. Cacciatore L, Cozzolino G, Giardina MG, et al. Liver cirrhosis as a diabetogenic condition. *Dig Dis Sci*. 1986;31:111.
5. Donandon V, Balbi M, Percacciante A, Casarin P, Zanette G. Insulin resistance and hyperinsulinemia in patients with chronic liver disease and hepatocellular carcinoma. *Clinical Medicine: Endocrinology and Diabetes*. 2009;2:25–33.
6. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology*. 2007;132:2208–25.
7. Siegel AB, Zhu AX. Metabolic syndrome and hepatocellular carcinoma: two growing epidemics with a potential link. *Cancer*. 2009 Oct 15.

8. Vinciguerra M, Foti M. PTEN at the crossroad of metabolic diseases and cancer in the liver. *Ann Hepatol*. 2008;7:192–9.
9. Zender L, Kubicka S. Molecular pathogenesis and targeted therapy of hepatocellular carcinoma. *Onkologie*. 2008;31:550–5.
10. El-Serag HB, Johnson ML, Hachem C, Morgana RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. *Gastroenterology*. 2009;136:1601–8.
11. Argo CK, Loria P, Caldwell SH, Lonardo A. Statins in liver disease: a molehill, an iceberg, or neither? *Hepatology*. 2008;48:662–9.
12. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology*. 1990;11:74–80.
13. Cotrim HP, Paraná R, Braga E, Lyra L. Nonalcoholic steatohepatitis and hepatocellular carcinoma: natural history? *Am J Gastroenterol*. 2000;95:3018–9.
14. Shimada M, Hashimoto E, Taniai M, et al. Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis. *J Hepatol*. 2002;37:154–60.
15. Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology*. 2002;123:134–40.
16. Regimbeau JM, Colombat M, Mognol P, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. *Liver Transpl*. 2004;10(2 Suppl 1): S69–73.
17. Hai S, Kubo S, Shuto T, et al. Hepatocellular carcinoma arising from nonalcoholic steatohepatitis: report of two cases. *Surg Today*. 2006;36:390–4.
18. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis. *C Hepatology*. 2006;43:682–9.
19. Hashizume H, Sato K, Takagi H, et al. Primary liver cancers with nonalcoholic steatohepatitis. *Eur J Gastroenterol Hepatol*. 2007;19:827–34.
20. Tsutsumi K, Nakayama H, Sakai Y, et al. Two cases of patients with hepatocellular carcinoma (HCC) that developed in cryptogenic cirrhosis suggestive of nonalcoholic steatohepatitis (NASH) as background liver disease after clinical courses of 26 years. *Nippon Shokakibyo Gakkai Zasshi*. 2007; 104:690–7.
21. Guzman G, Brunt EM, Petrovic LM, Chejfec G, Layden TJ, Cotler SJ. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? *Arch Pathol Lab Med*. 2008;132: 1761–6.
22. Paradis V, Zalinski S, Chelbi E, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. *Hepatology*. 2009;49:851–9.
23. Hashimoto E, Yatsuji S, Tobari M, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *J Gastroenterol*. 2009;44 Suppl 19:89–95. Epub 2009 Jan 16.
24. Malik SM, Gupte PA, de Vera ME, Ahmad J. Liver transplantation in patients with nonalcoholic steatohepatitis-related hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2009;7:800–6.
25. Kawada N, Imanaka K, Kawaguchi T, et al. Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. *J Gastroenterol*. 2009. DOI 10.1007/s00535-009-0112-0.
26. Giannini EG, Marabotto E, Savarino V, et al; for the Italian Liver Cancer (ITALICA) group. Hepatocellular carcinoma in patients with cryptogenic cirrhosis. *Clin Gastroenterol Hepatol*. 2009;7:580–5.
27. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127(5 Suppl 1): S35–50.
28. Loria P, Lonardo A, Carulli N. Should nonalcoholic fatty liver disease be renamed? *Dig Dis*. 2005;23:72–82.
29. Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. *Aliment Pharmacol Ther*. 2005;22 Suppl 2:24–7.
30. Braga C, La Vecchia C, Negri E, Franceschi S. Attributable risks for hepatocellular carcinoma in northern Italy. *Eur J Cancer*. 1997;33:629–34.
31. El-Serag HB, Richardson PA, Everhart JE.The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. *Am J Gastroenterol*. 2001;96:2462–7.
32. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*. 2002;36:1206–13.
33. Tazawa J, Maeda M, Nakagawa M, et al. Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. *Dig Dis Sci*. 2002;47:710–5.
34. Huo TI, Lui WY, Huang YH, et al. Diabetes mellitus is a risk factor for hepatic decompensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. *Am J Gastroenterol*. 2003;98:2293–8.
35. Ohata K, Hamasaki K, Toriyama K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer*. 2003;97:3036–43.
36. Yuan JM, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. *Cancer*. 2004;101:1009–17.
37. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut*. 2005;54:533–9.
38. Kumar D, Farrell GC, Kench J, George J. Hepatic steatosis and the risk of hepatocellular carcinoma in chronic hepatitis C. *J Gastroenterol Hepatol*. 2005;20:1395–400.
39. Lai MS, Hsieh MS, Chiu YH, Chen TH. Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. *Hepatology*. 2006;43:1295–302.
40. N'Kontchou G, Paries J, Htar MT, et al. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. *Clin Gastroenterol Hepatol*. 2006;4:1062–8.
41. Yu L, Sloane DA, Guo C, Howell CD. Risk factors for primary hepatocellular carcinoma in black and white Americans in 2000. *Clin Gastroenterol Hepatol*. 2006;4:355–60.
42. Komura T, Mizukoshi E, Kita Y, et al. Impact of diabetes on recurrence of hepatocellular carcinoma after surgical treatment in patients with viral hepatitis. *Am J Gastroenterol*. 2007;102:1939–46.
43. Pekow JR, Bhan AK, Zheng H, Chung RT. Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. *Cancer*. 2007;109:2490–6.
44. Chen CL, Yang HI, Yang WS, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology*. 2008;135:111–21.
45. Veldt BJ, Chen W, Heathcote EJ, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology*. 2008;47:1856–62.
46. Polesel J, Zucchetto A, Montella M, et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. *Ann Oncol*. 2009; 20:353–7.
47. Lonardo A, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology*. 2004;126:586–97.
48. Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology*. 2004;126:840–8.
49. Samuel VT, Liu ZX, Qu X, et al. Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *J Biol Chem*. 2004 30;279:32345–53.
50. Lonardo A, Ballestri S, Adinolfi LE, et al. Hepatitis C virus-infected patients are 'spared' from the metabolic syndrome but not from insulin resistance. A comparative study of nonalcoholic fatty liver disease and hepatitis C virus-related steatosis. *Can J Gastroenterol*. 2009;23:273–8.
51. Arase Y, Suzuki F, Suzuki Y, et al. Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C. *Hepatology*. 2009;49:739–44.
52. Giordanino C, Bugianesi E, Smedile A, et al. Incidence of type 2 diabetes mellitus and glucose abnormalities in patients with chronic hepatitis C infection by response to treatment: results of a cohort study. *Am J Gastroenterol*. 2008;103:2481–7.
53. Friis-Liby I, Aldenborg F, Jerlstad P, Rundström K, Björnsson E. High prevalence of metabolic complications in patients with non-alcoholic fatty liver disease. *Scand J Gastroenterol*. 2004;39:864–9.

54. Shibata M, Kihara Y, Taguchi M, Tashiro M, Otsuki M. Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care*. 2007;30:2940–4.
55. Kim CH, Park JY, Lee KU, Kim JH, Kim HK. Fatty liver is an independent risk factor for the development of Type 2 diabetes in Korean adults. *Diabet Med*. 2008;25:476–81.
56. Adams LA, Waters OR, Knuiman MW, Elliott RR, Olynyk JK. NAFLD as a risk factor for the development of diabetes and the metabolic syndrome: an eleven-year follow-up study. *Am J Gastroenterol*. 2009;104:861–7.
57. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes*. 2005;54:603–8.