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REVIEW

Impact of Diabetes on the Severity of Liver Disease

Ingrid J. Hickman, PhD,[a] Graeme A. Macdonald, MBBS, PhD[a,b]

[a]Diamantina Institute for Cancer, Immunology and Metabolic Medicine, and [b]Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia.

ABSTRACT

The prevalence of type 2 diabetes is higher in patients who have liver diseases, such as nonalcoholic fatty liver disease, chronic viral hepatitis, hemochromatosis, alcoholic liver disease, and cirrhosis. The development of diabetes in patients with cirrhosis is well recognized, but evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of diabetes and that diabetes plays a role in the initiation and progression of liver injury. This article provides an overview of the evidence for an increased prevalence of diabetes in a range of liver diseases; the effect of diabetes on the severity of disease; the potential mechanisms whereby coexistent diabetes exacerbates progression of hepatic fibrosis; and the impact of obesity, insulin resistance, and type 2 diabetes on clinical outcomes.

KEYWORDS: Cirrhosis; Fatty liver disease; Insulin resistance; Obesity

The prevalence of type 2 diabetes is increasing with a new diagnosis made every 21 seconds.[1] Historically, the development of diabetes in patients with cirrhosis is well documented with overt diabetes present in up to 70% of cirrhotic subjects.[2] However, evidence is emerging that the development of chronic liver disease and progression to cirrhosis may occur after the diagnosis of type 2 diabetes and that diabetes plays a role in the initiation and progression of liver injury.

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 diabetes accounts for 90% to 95% of all diagnosed cases of diabetes mellitus[3] and is responsible for the majority of the health burden attributable to diabetes. Type 2 diabetes develops from an imbalance between insulin sensitivity and insulin secretion.[4] The earliest detected abnormality in individuals who develop type 2 diabetes is impairment in the body's response to insulin.[5,6] This is described as insulin resistance. Risk factors associated with insulin resistance and type 2 diabetes include central obesity, positive calorie load, physical inactivity, age, and genetic predisposition.[7]

The liver plays a key role in the whole-body response to insulin. In the fasting state the liver releases glucose into the circulation. After a meal, as blood glucose increases, insulin is secreted from the pancreas and acts on muscle and fat to stimulate glucose uptake and on the liver to suppress glucose output. In insulin-resistant states, more insulin is required for the same effects.[7]

PREVALENCE OF TYPE 2 DIABETES IS INCREASED IN CHRONIC LIVER DISEASES

The prevalence of type 2 diabetes is higher in patients who have certain liver diseases. There is a link between the presence of type 2 diabetes and the severity of liver injury. On analysis of these studies, it is important to remember the link between diabetes and cirrhosis, because studies with an increased proportion of cirrhotic patients are more likely to find an association between type 2 diabetes and disease severity. The liver diseases associated with type 2 diabetes include nonalcoholic fatty liver disease, chronic viral hepatitis, hemochromatosis, alcoholic liver disease, and cirrhosis.

Requests for reprints should be addressed to Ingrid Hickman, PhD, Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, Ipswich Road, Woolloongabba Qld 4102, Australia.

E-mail address: ihickman@uq.edu.au

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Nonalcoholic Fatty Liver Disease

The most prevalent liver disease in developed countries is nonalcoholic fatty liver disease, which occurs when there is lipid accumulation within the hepatocytes. This can be associated with hepatocyte injury and inflammation that results in hepatic fibrosis and ultimately in cirrhosis. This more severe end of the disease spectrum is described as nonalcoholic steatohepatitis. It is estimated that up to one third of adult Americans may have nonalcoholic fatty liver disease,[8] whereas the prevalence of nonalcoholic steatohepatitis is estimated to be 2% to 3%. Nonalcoholic fatty liver disease is considered the most common cause of cryptogenic cirrhosis.[9] It is associated with central obesity, and virtually all patients have evidence of insulin resistance.[10] It is therefore not surprising that type 2 diabetes is present in 21% to 45% of patients with nonalcoholic fatty liver disease[11] and is associated with a 2 to 5-fold increased risk for nonalcoholic fatty liver disease.[12]

CLINICAL SIGNIFICANCE

- Patients with nonalcoholic fatty liver disease, hepatitis C, hemochromatosis, alcoholic liver disease, or cirrhosis have an increased risk of type 2 diabetes.
- Patients with type 2 diabetes and liver disease have an increased risk of severe complications, such as cirrhosis, liver failure, and hepatocellular carcinoma.
- Patients with type 2 diabetes should be monitored for underlying liver disease.
- The prevalence of severe chronic liver disease is expected to increase as obesity and type 2 diabetes rates increase.

Viral Hepatitis

Evidence has accumulated regarding the association between glucose metabolism and chronic hepatitis C virus (HCV) infection. The National Health and Nutrition Examination Survey identified a 3-fold increased risk of type 2 diabetes in subjects who were aged more than 40 years and had chronic HCV, compared with HCV-negative participants.[13] Knobler et al[14] showed the prevalence of type 2 diabetes to be 33% in noncirrhotic patients with HCV compared with 5.6% in a control group. The reason for the link between HCV infection and type 2 diabetes may relate to viral effects because specific HCV genotypes (particularly genotype 1) have been linked to insulin resistance,[15] and in vitro studies have demonstrated HCV proteins inhibiting insulin signaling.[16]

In hepatitis B virus (HBV) infection, there is conflicting evidence as to whether there is an increased prevalence of type 2 diabetes. Knobler et al[14] found that the prevalence of diabetes was twice as high in noncirrhotic subjects with HBV infection compared with controls without liver disease (12% vs 5.6%), although this difference was not statistically significant.[14] Two other studies failed to show an association between type 2 diabetes and HBV.[17,18]

Hemochromatosis

Hereditary hemochromatosis type 1 is the most prevalent cause of iron accumulation in populations with Northern European ancestry and is caused by mutations of *HFE*. Its association with diabetes is well recognized. Up to 23% of probands and 13% of family members with previously undiagnosed hemochromatosis have diabetes.[19] The pathogenesis of diabetes in hemochromatosis relates in part to the deposition of iron in the pancreas. This iron accumulation occurs predominantly in exocrine cells; however, iron-containing granules can be shown to accumulate in islet cells, particularly in insulin-secreting beta-cells.[20] Similar findings are present in the pancreas of iron-loaded animals.[21] It might therefore be expected that hemochromatosis would be more prevalent in subjects with diabetes. Conte et al[22] found an increased prevalence of hemochromatosis in individuals with type 2 diabetes. Others have detected an increased prevalence of *HFE* mutations in type 2 diabetes,[23] but this has not been universal. Dubois-Laforgue et al[24] found that although the prevalence of *HFE* mutations was not increased in type 2 diabetes, type 2 diabetic patients with *HFE* mutations had greater iron stores and were less likely to be obese.[25]

Alcoholic Liver Disease

Patients with alcoholic liver disease have been shown to be at increased risk for type 2 diabetes.[26] In a prospective follow-up study of 8663 men, heavy drinking (>270 g/wk) was associated with a 2-fold increased risk of developing type 2 diabetes compared with moderate drinking (60-120 g/wk).[27] This association was independent of other risk factors, such as age, obesity, smoking history, family history of diabetes, and blood pressure.[28] It is noteworthy that similar studies have not shown the same relationship in women.[28-30] Excessive alcohol intake may have a direct effect on the development of type 2 diabetes by decreasing insulin-mediated glucose uptake in the acute situation and by damaging pancreatic islet cells with chronic use.

CIRRHOSIS AND DIABETES

The term "hepatogenous" diabetes is used to describe the association between cirrhosis and impaired glucose metabolism. Up to 96% of patients with cirrhosis have diabetes or impaired glucose tolerance.[2] Hepatogenous diabetes differs from type 2 diabetes in that there is less association with risk factors such as age, body mass index, and family history of diabetes.[2] Cirrhosis may contribute to the development of type 2 diabetes through numerous factors. With the development of portal hypertension, blood shunting redirects blood away from hepatocytes and results in re-

duced insulin clearance with peripheral hyperinsulinemia.[31] This systemic hyperinsulinemia may contribute to the development of insulin resistance through the down-regulation of insulin receptors.[32]

However, cirrhosis alone does not always induce diabetes, and the cause of liver disease and environmental factors may play a role. Zein et al[26] found that the prevalence of diabetes was increased in HCV cirrhosis (25%) and alcoholic liver disease (19%) but not in cholestatic liver disease (1.3%).

This association among diabetes, insulin resistance, and liver disease has implications with respect to treatment. The peroxisome proliferator-activated receptor-gamma agonists pioglitazone and rosiglitazone have shown promise in small studies of patients with nonalcoholic steatohepatitis, including cirrhotic patients[33-35]; however, there are concerns about their use in patients with alanine aminotransferase 2.5 times or more the upper limit of normal or with decompensated cirrhosis.[36] Long-term efficacy studies have not been completed. Similarly, metformin has shown some promise in the treatment of nonalcoholic steatohepatitis,[37] although there are concerns about its use in advanced liver disease.

THE LINK BETWEEN OBESITY AND INSULIN RESISTANCE AND LIVER INJURY

Hepatic steatosis, obesity, and insulin resistance seem to act as cofactors for liver injury in a range of liver diseases.[38] In patients with nonalcoholic fatty liver disease, older age, obesity, and the presence of type 2 diabetes are independent risk factors for more severe fibrosis.[39] Obesity-related insulin resistance plays a clear role in the production of reactive oxygen species and altered adipokine production, which in turn leads to up-regulation of proinflammatory cytokines. Insulin resistance results in enhanced hepatic gluconeogenesis and impaired hepatic lipid metabolism, which results in hepatic steatosis and liver injury.[40]

Obesity and steatosis are associated with more severe fibrosis in chronic HCV.[41] Although steatosis in HCV is linked to genotype-specific viral effects, steatosis is more prevalent and worsened in obese, insulin-resistant patients irrespective of viral genotype.[42] Emerging evidence supports the hypothesis that altered metabolic profiles associated with insulin resistance contribute to liver injury in HCV.[43] Insulin resistance is an independent predictor for the rate of fibrosis progression,[15] and elevated fasting insulin[44,45] and glucose[46] independently seem to contribute to fibrosis in HCV.

Hemochromatosis is another liver disease for which coexistent obesity and steatosis seem to contribute to liver injury.[47] In a retrospective study of patients with hemochromatosis before de-ironing, obesity was independently associated with the presence of steatosis, which in turn was associated with more severe fibrosis.[47] The prevalence of diabetes or degree of insulin resistance was not reported in this study.

In a study of 1604 alcoholic patients, Naveau et al[48] found that being overweight was associated with a greater prevalence of alcoholic hepatitis and cirrhosis (60% vs 35% in lean patients).[48] The mechanisms whereby obesity and insulin resistance may exacerbate liver injury in alcoholic liver disease are still debated. Alterations in cytokine production (leptin, adiponectin, and tumor necrosis factor-α), caused by both obesity and alcohol, may work synergistically to activate hepatic stellate cells, resulting in hepatic fibrosis.[49]

TYPE 2 DIABETES MELLITUS AND THE SEVERITY OF LIVER DISEASE

There is evidence from a range of liver diseases linking obesity with insulin resistance and hepatic steatosis, which in turn contribute to liver injury. In nonalcoholic fatty liver disease, a range of studies have consistently identified type 2 diabetes as an independent predictor of fibrosis,[39,50-52] faster fibrosis progression,[51] and increased mortality.[53] This relationship is maintained when analysis is restricted to noncirrhotic patients.[51] Younossi et al[54] demonstrated that patients with type 2 diabetes were at greater risk for the development of adverse outcomes such as cirrhosis or liver-related mortality.[54]

Scrutiny of the impact of type 2 diabetes in HCV has identified a role for insulin resistance and type 2 diabetes in disease progression. Hyperinsulinemia,[42] hyperglycemia,[46] and insulin resistance[55] have all been associated with more severe fibrosis in HCV. Again, an important observation is that the onset of insulin resistance occurs early, before the development of cirrhosis.[56]

The effect of type 2 diabetes on the histologic severity of alcoholic liver disease has not been widely studied. Raynard et al[57] showed that obesity and increased fasting glucose levels were associated with increased severity of hepatic fibrosis in alcoholic liver disease, independently of daily alcohol intake and duration of alcohol abuse.[57] Although the prevalence of type 2 diabetes was not reported in this study, the link with elevated serum glucose suggests that type 2 diabetes may also be correlated with more severe disease.

TYPE 2 DIABETES AND COMPLICATIONS OF LIVER CIRRHOSIS

Type 2 diabetes seems to be associated with an increased risk of cirrhosis complications. The Verona Diabetes Study, a population-based study on more than 7000 subjects with type 2 diabetes, found an increased risk of death from chronic liver disease and cirrhosis compared with the general population (standardized mortality ratio after 5 years of 2.52, 95% confidence interval [CI], 1.96-3.2).[58] In addition, there was an increased risk of mortality from hepatocellular carcinoma (standardized mortality ratio after 10 years of 1.86, 95% CI, 1.43-2.38).[58] Insulin treatment of type 2 diabetes, perhaps as a marker of more severe diabetes, was associated with a particularly high risk of mortality in cirrhotic patients (relative risk 6.84).[59]

Similar observations have been made in smaller cohort studies. Younossi et al[54] found that in nonalcoholic fatty liver disease, patients with type 2 diabetes had an overall mortality twice that of nondiabetic subjects. After adjustment for potential confounders, including cirrhosis, the risk ratio was 22.83 (95% CI, 2.97-175.03) for liver-related mortality in those with type 2 diabetes and 3.30 (95% CI, 1.76-6.18) for overall mortality.[54] Nishida et al[60] also found that the survival rates of cirrhotic patients with type 2 diabetes were significantly lower than those with normal glucose tolerance.

Several studies have demonstrated an increased incidence of diabetes among patients with hepatocellular carcinoma ranging from 2- to 4-fold.[11] Type 2 diabetes seems to play an etiologic role in hepatocellular carcinoma cirrhosis independently of alcohol, viral hepatitis, or demographic features,[61,62] although the risk of hepatocellular carcinoma increases up to 10-fold when viral hepatitis and hazardous alcohol consumption are combined with type 2 diabetes.[63]

HOW MIGHT TYPE 2 DIABETES MELLITUS MAKE LIVER DISEASE WORSE?

The pathogenic mechanisms underlying the relationship between type 2 diabetes and chronic liver disease remain to be elucidated. Generalized peripheral insulin resistance and altered β-cell function are usually present. The role of increased proinflammatory cytokines, reduction in protective cytokines, hyperinsulinemia and hyperglycemia in the activation of hepatic stellate cells, and stimulation of collagen production are prime focuses of research in this area.

There seems to be cross-talk between adipose tissue and other tissues mediated in part by the release of cytokines from adipose tissue, known collectively as adipokines. Adipokines, such as leptin and tumor necrosis factor-α, activate inflammatory pathways that may exacerbate liver injury.[40]

The serum concentration of most adipokines is increased in obesity and type 2 diabetes. An exception to this is adiponectin, a key regulator of insulin sensitivity and tissue inflammation.[64] Plasma concentrations of adiponectin and hepatic adiponectin receptor expression[65] are reduced in nonalcoholic fatty liver disease, and it has been hypothesized that hypoadiponectinemia may play a role in disease progression. Xu et al[66] demonstrated a potent protective effect of adiponectin in animal models of both alcoholic liver disease and nonalcoholic fatty liver disease. Administration of recombinant adiponectin to a mouse model of alcoholic liver disease reduced hepatic steatosis and significantly reduced hepatic inflammation and serum alanine aminotransferase. Adiponectin had similar effects in the *ob/ob* mouse model of nonalcoholic fatty liver disease.[66] To date, studies in humans of the role of adiponectin in liver disease have produced conflicting results, with some studies reporting a protective effect against hepatic steatosis,[67,68] necroinflammation, and fibrosis,[69,70] and others reporting no correlation with disease severity.[71,72] Data regarding a link among adiponectin, steatosis, and disease progression in chronic HCV are emerging with evidence of genotype-specific interactions with adiponectin.[73,74]

Insulin stimulates the proliferation of hepatic stellate cells and induces production of collagen, resulting in hepatic fibrosis.[75] Connective tissue growth factor is produced by activated hepatic stellate cells and has been implicated in the development and progression of hepatic fibrogenesis. Hyperglycemia and hyperinsulinemia stimulate connective tissue growth factor synthesis in hepatic stellate cell cultures, and connective tissue growth factor has been found to be overexpressed in liver tissue from patients with nonalcoholic steatohepatitis.[76]

SIGNIFICANCE

Patients with type 2 diabetes seem more likely to have a range of liver diseases, and patients with liver disease and diabetes are at risk of severe liver disease, cirrhosis, liver failure, and hepatocellular carcinoma. This has obvious implications for the clinical management. The increasing incidence of obesity and type 2 diabetes in children means we may see more severe chronic liver disease occurring at younger ages. Awareness of type 2 diabetes as a significant risk factor for liver injury may improve diagnosis and interventions to minimize the progression of chronic liver disease.

Our understanding of the links between type 2 diabetes and the development and progression of chronic liver disease has benefited from the mainly retrospective studies performed to date, but prospective studies are needed to fully elucidate the cause and effect of type 2 diabetes in liver injury. Identifying the mechanisms whereby type 2 diabetes increases disease severity could offer new insights into the treatment of chronic liver disease, including the role of weight reduction and pharmacologic interventions with insulin sensitizers.

CONCLUSIONS

Type 2 diabetes is prevalent in a range of liver diseases, particularly nonalcoholic fatty liver disease, chronic HCV, hemochromatosis, and alcoholic liver disease. Coexistent type 2 diabetes seems to be associated with more severe liver injury before the onset of cirrhosis and more severe complications and higher mortality once cirrhosis is established. There is evidence that the metabolic disturbances associated with type 2 diabetes contribute to liver injury, but this relationship is made more complex by the association of cirrhosis with hepatogenous diabetes. It is unclear whether treatment of coexistent diabetes and improved glycemic control will benefit chronic liver disease. Clinicians should be aware that patients with type 2 diabetes may have underlying chronic liver disease. In the setting of type 2 diabetes and cirrhosis, consideration should be given to surveillance for life-threatening complications of liver disease, such as hepatocellular carcinoma. A better understanding of the factors that modulate liver disease progression is

critical to identify patients who require more aggressive monitoring, lifestyle interventions, and pharmacotherapy.

References

1. The American Diabetes Association. Available at: http://www.diabetes.org/home.jsp. Accessed July 30, 2007.
2. Holstein A, Hinze S, Thiessen E, et al. Clinical implications of hepatogenous diabetes in liver cirrhosis. *J Gastroenterol Hepatol.* 2002; 17:677-681.
3. US Department of Health and Human Services. Trends in the prevalence and incidence of self-reported diabetes mellitus—United States, 1980-1994. *MMWR Morb Mortal Wkly Rep.* 1997;46:1014-1018.
4. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care.* 1992;15:318-368.
5. Martin BC, Warram JH, Krolewski AS, et al. Role of glucose and insulin resistance in development of type 2 diabetes mellitus. Results of a 25-year follow-up study. *Lancet.* 1992;340:925-929.
6. Kahn BB. Type 2 diabetes: when insulin secretion fails to compensate for insulin resistance. *Cell.* 1998;92:593-596.
7. Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev.* 1995;75:473-486.
8. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology.* 2004;40:1387-1395.
9. Caldwell SH, Oelsner DH, Iezzoni JC, et al. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology.* 1999;29:664-669.
10. Chitturi S, Abeygunasekera S, Farrell G, et al. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology.* 2002;35:373-379.
11. Harrison SA. Liver disease in patients with diabetes mellitus. *J Clin Gastroenterol.* 2006;40:68-76.
12. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. *Gastroenterology.* 2002;122:1649-1657.
13. Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med.* 2000;133:592-599.
14. Knobler H, Schihmanter R, Zifroni A, et al. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc.* 2000;75:355-359.
15. Hui JM, Sud A, Farrell GC, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology.* 2003;125:1695-1704.
16. Kawaguchi T, Yoshida T, Harada M, et al. Hepatitis C virus down-regulates insulin receptor substrates 1 and 2 through up-regulation of suppressor of cytokine signaling 3. *Am J Pathol.* 2004;165:1499-1508.
17. Fraser GM, Harman I, Meller N, et al. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. *Isr J Med Sci.* 1996;32:526-530.
18. Papatheodoridis GV, Chrysanthos N, Savvas S, et al. Diabetes mellitus in chronic hepatitis B and C: prevalence and potential association with the extent of liver fibrosis. *J Viral Hepatol.* 2006;13:303-310.
19. Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. *Am J Med.* 1991;90:445-449.
20. Rahier J, Loozen S, Goebbels RM, Abrahem M. The haemochromatotic human pancreas: a quantitative immunohistochemical and ultrastructural study. *Diabetologia.* 1987;30:5-12.
21. Iancu TC, Ward RJ, Peters TJ. Ultrastructural changes in the pancreas of carbonyl iron-fed rats. *J Pediatr Gastroenterol Nutr.* 1990;10:95-101.
22. Conte D, Manachino D, Colli A, et al. Prevalence of genetic hemochromatosis in a cohort of Italian patients with diabetes mellitus. *Ann Intern Med.* 1998;128:370-373.
23. Kwan T, Leber B, Ahuja S, et al. Patients with type 2 diabetes have a high frequency of the C282Y mutation of the hemochromatosis gene. *Clin Invest Med.* 1998;21:251-257.
24. Dubois-Laforgue D, Caillat-Zucman S, Djilali-Saiah I, et al. Mutations in HFE, the hemochromatosis candidate gene, in patients with NIDDM. *Diabetes Care.* 1998;21:1371-1372.
25. Dubois-Laforgue D, Caillat-Zucman S, Boitard C, Timsit J. Clinical characteristics of type 2 diabetes in patients with mutations of HFE. *Diabetes Metab.* 2000;26:65-68.
26. Zein NN, Abdulkarim AS, Wiesner RH, et al. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol.* 2000;32:209-217.
27. Wei M, Gibbons LW, Mitchell TL, et al. Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care.* 2000;23:18-22.
28. Holbrook TL, Barrett-Connor E, Wingard DL. A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus. *Am J Epidemiol.* 1990;132:902-909.
29. Stampfer MJ, Colditz GA, Willett WC, et al. A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol.* 1988;128:549-558.
30. Balkau B, Randrianjohany A, Papoz L, Eschwege E. Re: A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus. *Am J Epidemiol.* 1991;134:1469-1470.
31. Deschenes M, Somberg KA. Effect of transjugular intrahepatic portosystemic shunt (TIPS) on glycemic control in cirrhotic patients with diabetes mellitus. *Am J Gastroenterol.* 1998;93:483.
32. Picardi A, D'Avola D, Gentilucci UV, et al. Diabetes in chronic liver disease: from old concepts to new evidence. *Diabetes Metab Res Rev.* 2006;22:274-283.
33. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med.* 2006;355:2297-2307.
34. Promrat K, Lutchman G, Uwaifo GI, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology.* 2004;39: 188-196.
35. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, et al. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology.* 2003;38:1008-1017.
36. Waugh J, Keating GM, Plosker GL, et al. Pioglitazone: a review of its use in type 2 diabetes mellitus. *Drugs.* 2006;66:85-109.
37. Bugianesi E, Gentilcore E, Manini R, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol.* 2005;100:1082-1090.
38. Powell EE, Jonsson JR, Clouston AD. Steatosis: co-factor in other liver diseases. *Hepatology.* 2005;42:5-13.
39. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology.* 1999;30:1356-1362.
40. Roden M. Mechanisms of disease: hepatic steatosis in type 2 diabetes—pathogenesis and clinical relevance. *Nat Clin Pract Endocrinol Metab.* 2006;2:335-348.
41. Hourigan LF, Macdonald GA, Purdie D, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology.* 1999;29:1215-1219.
42. Hickman IJ, Powell EE, Prins JB, et al. In overweight patients with chronic hepatitis C, circulating insulin is associated with hepatic fibrosis: implications for therapy. *J Hepatol.* 2003;39:1042-1048.
43. Prati D, Shiffman ML, Diago M, et al. Viral and metabolic factors influencing alanine aminotransferase activity in patients with chronic hepatitis C. *J Hepatol.* 2006;44:679-685.
44. Hickman I, Powell E, Clouston A, et al. Fibrosis in chronic hepatitis C correlates significantly with circulating insulin levels. *J Hepatol.* 2002; 36(Suppl 1):172.
45. Maeno T, Okumura A, Ishikawa T, et al. Mechanisms of increased insulin resistance in non-cirrhotic patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol.* 2003;18:1358-1363.
46. Ratziu V, Munteanu M, Charlotte F, et al. Fibrogenic impact of high serum glucose in chronic hepatitis C. *J Hepatol.* 2003;39:1049-1055.
47. Powell EE, Ali A, Clouston AD, et al. Steatosis is a cofactor in liver injury in hemochromatosis. *Gastroenterology.* 2005;129:1937-1943.

48. Naveau S, Giraud V, Borotto E, et al. Excess weight risk factor for alcoholic liver disease. *Hepatology.* 1997;25:108-111.
49. Diehl AM. Obesity and alcoholic liver disease. *Alcohol.* 2004;34:81-87.
50. de Ledinghen V, Ratziu V, Causse X, et al. Diagnostic and predictive factors of significant liver fibrosis and minimal lesions in patients with persistent unexplained elevated transaminases. A prospective multicenter study. *J Hepatol.* 2006;45:592-599.
51. Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol.* 2005;42:132-138.
52. Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology.* 1990; 12:1106-1110.
53. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology.* 2005;129:113-121.
54. Younossi ZM, Gramlich T, Matteoni CA, et al. Nonalcoholic fatty liver disease in patients with type 2 diabetes. *Clin Gastroenterol Hepatol.* 2004;2:262-265.
55. Taura N, Ichikawa T, Hamasaki K, et al. Association between liver fibrosis and insulin sensitivity in chronic hepatitis C patients. *Am J Gastroenterol.* 2006;101:2752-2759.
56. Petit JM, Bour JB, Galland-Jos C, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *J Hepatol.* 2001;35:279-283.
57. Raynard B, Balian A, Fallik D, et al. Risk factors of fibrosis in alcohol-induced liver disease. *Hepatology.* 2002;35:635-638.
58. 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):24-27.
59. de Marco R, Locatelli F, Zoppini G, et al. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes Care.* 1999;22:756-761.
60. Nishida T, Tsuji S, Tsujii M, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. *Am J Gastroenterol.* 2006; 101:70-75.
61. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology.* 2004;126:460-468.
62. Kaczynski J, Hansson G, Wallerstedt S. Diabetes: one of few remarkable differences in clinicopathologic features between cirrhotic and noncirrhotic Swedes with hepatocellular carcinoma. *Dig Dis Sci.* 2006; 51:796-802.
63. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology.* 2002;36:1206-1213.
64. Whitehead JP, Richards AA, Hickman IJ, et al. Adiponectin—a key adipokine in the metabolic syndrome. *Diabetes Obes Metab.* 2006;8: 264-280.
65. Kaser S, Moschen A, Cayon A, et al. Adiponectin and its receptors in non-alcoholic steatohepatitis. *Gut.* 2005;54:117-121.
66. Xu A, Wang Y, Keshaw H, et al. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest.* 2003;112:91-100.
67. Mendez-Sanchez N, Chavez-Tapia NC, Villa AR, et al. Adiponectin as a protective factor in hepatic steatosis. *World J Gastroenterol.* 2005; 11:1737-1741.
68. Bajaj M, Suraamornkul S, Piper P, et al. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab.* 2004;89:200-206.
69. Musso G, Gambino R, Biroli G, et al. Hypoadiponectinemia predicts the severity of hepatic fibrosis and pancreatic beta-cell dysfunction in nondiabetic nonobese patients with nonalcoholic steatohepatitis. *Am J Gastroenterol.* 2005;100:2438-2446.
70. Hui JM, Hodge A, Farrell GC, et al. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology.* 2004;40:46-54.
71. Bugianesi E, Pagotto U, Manini R, et al. Plasma adiponectin in nonalcoholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity. *J Clin Endocrinol Metab.* 2005;90:3498-3504.
72. Jonsson JR, Moschen AR, Hickman IJ, et al. Adiponectin and its receptors in patients with chronic hepatitis C. *J Hepatol.* 2005;43: 929-936.
73. Petit JM, Minello A, Jooste V, et al. Decreased plasma adiponectin concentrations are closely related to steatosis in hepatitis C virus-infected patients. *J Clin Endocrinol Metab.* 2005;90:2240-2243.
74. Wang AY, Hickman IJ, Richards AA, et al. High molecular weight adiponectin correlates with insulin sensitivity in patients with hepatitis C genotype 3, but not genotype 1 infection. *Am J Gastroenterol.* 2005; 100:2717-2723.
75. Svegliati-Baroni G, Ridolfi F, Di Sario A, et al. Insulin and insulin-like growth factor-1 stimulate proliferation and type I collagen accumulation by human hepatic stellate cells: differential effects on signal transduction pathways. *Hepatology.* 1999;29:1743-1751.
76. Paradis V, Perlemuter G, Bonvoust F, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. *Hepatology.* 2001;34:738-744.