

Impact of non-alcoholic fatty liver disease on accelerated metabolic complications

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Insulin resistance is the basis of both non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MetS), the two conditions are often found in the same individual. The mortality of patients with NAFLD is significantly higher than that among the general population and cardiovascular risk may compete with liver-related risk in dictating the final outcome. Recent prospective studies have reported that NAFLD is associated with an increased incidence of MetS and type 2 diabetes mellitus, independent of obesity and other components of MetS. Thus, NAFLD may not only be a liver disease but also an early mediator of type 2 diabetes mellitus and MetS. The biological mechanisms by which NAFLD contributes to a higher risk of developing metabolic disorders are not

fully understood. However, the fatty liver could contribute in the same way as visceral adipose tissue to insulin resistance, systemic inflammation and oxidative stress, while the decreased serum adiponectin concentrations might also be part of the mechanism. In contemporary clinical practice, it has become mandatory to evaluate the metabolic risk factors in NAFLD patients and to consider careful surveillance and aggressive treatment, not only of the resultant liver disease, but also of the possible underlying metabolic and vascular complications. Future studies might address the question whether earlier adjustment to a more efficient lifestyle or a pharmacological treatment that mobilizes fat out of the liver could reduce these risks.

KEY WORDS: alanine aminotransferase, gamma-glutamyltransferase, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, type 2 diabetes mellitus.

Non-alcoholic fatty liver disease (NAFLD) is currently a common cause of chronic liver disease in clinical practice. Insulin resistance (IR) and oxidative stress play important roles in the development and progression of NAFLD.¹⁻⁴ Mortality in patients with NAFLD is significantly higher than that in the age and gender-matched general population, with malignancy, cardiovascular disease, liver-related complications being the

most common causes of death.^{1,3,5} Liver-related morbidity and mortality in NAFLD occur only when the disease has progressed to advanced fibrosis and cirrhosis, but significant fibrosis is rarely encountered in patients with simple steatosis, whereas non-alcoholic steatohepatitis (NASH) has a real potential for fibrosis progression.^{1,2,5} Disease progressing to NASH and cirrhosis appears to be very slow, and only a few patients develop life-threatening advanced liver disease. As an indolent form of liver disease, NAFLD may be secondary to primary biliary cirrhosis, and patients are expected to have cirrhosis only in late life. In many cases of NAFLD, competing risks may take a heavier toll on chances of survival and quality of life than the hepatic disease.⁶ Although excessive hepatic fat accumulation is the starting point and prerequisite for liver injury in

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IR, it may also be a condition with far-reaching metabolic consequences, from controlled diabetes to increased cardiovascular morbidity.^{2,6}

RELATIONSHIP OF NAFLD WITH METABOLIC SYNDROME

The term metabolic syndrome (MetS) refers to a cluster of cardiovascular risk factors associated with IR. An association between NAFLD and MetS has been finally established in some retrospective and prospective studies.^{1,2,4} MetS is a strong predictor of NAFLD and NAFLD is less likely to regress in those participants with the MetS at the baseline.⁷ Abdominal obesity, hypertension, dyslipidemia and type 2 diabetes mellitus are pathological conditions frequently associated with NAFLD, and their coexistence in the same individual increases the likelihood of having more advanced forms of liver disease.^{1,2,4,8} Compared with the abdominal obesity and overall obesity, fatty liver has the highest frequency of clustering, greater specificity, higher positive predictive value and most attributable risk as a percentage for detecting risk factors clustering.⁹ IR is almost a universal finding in patients with NAFLD, and NAFLD is considered the hepatic manifestation of MetS.^{1,2,4}

The correlation of liver fat content with insulin sensitivity independent of body fat content is found in the absence of clinical steatosis individuals,¹⁰ and most patients with NAFLD are hyperinsulinemic and more IR compared with non-steatotic healthy subjects. While the relevance of NAFLD and IR is invariable, their potential relationship has been reviewed elsewhere.¹¹ However, what is becoming evident experimentally is that the more severe the steatosis, the more likely is the hepatic pathology to be steatohepatitis rather than simple steatosis.^{1–4} On the other hand, patients with NASH are older and exhibit more advanced IR and more marked metabolic complications than those with simple steatosis.^{2–4}

Although there is a nearly universal association between NAFLD and MetS irrespective of obesity, NAFLD is not rare in non-obese, non-diabetic adults at the initial diagnosis.^{12–17} This group appears to consist of relatively younger men with milder histology, abdominal adiposity and hyperinsulinemia.^{12–17} Fatty liver itself is an IR status, not only in subjects with additional metabolic disorders, but also in lean subjects with normal glucose tolerance, and since hepatic fat accumulation can lead to hepatic IR, the latter may occur before any alternation in peripheral insulin action, and this may induce peripheral IR.^{2,4} Hence, these results have

stimulated interest in the possible role of NAFLD in the development of metabolic complications.

ELEVATED LIVER ENZYMES PREDICT THE ONSET OF NEW METABOLIC DISORDERS

The presence of mildly raised serum liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT), are the most frequent and sometimes the only laboratory abnormality found in NAFLD patients.^{1,4,18} In subjects without viral hepatitis or excessive alcohol consumption, the persistent elevation of liver enzymes is only regarded as a surrogate marker of NAFLD.^{1–4,19,20} Recently, a number of prospective cohort studies showed that this marker predicted the development of metabolic complications independently.^{21–27}

In the West of Scotland Coronary Prevention Study, a total of 139 men (2.5%) developed new diabetes mellitus over 5 years of follow up. The levels of ALT but not of AST increased progressively with the increasing number of MetS components, and only a sustained increase in ALT predicted a higher risk for type 2 diabetes mellitus than other liver enzymes. In a stepwise regression incorporating ALT and C-reactive protein (CRP) together with MetS criteria, elevated ALT (≥ 29 U/L) and CRP (≥ 3 mg/L) predicted incident type 2 diabetes mellitus. Even elevated ALT levels within normal range could predict incident diabetes mellitus, suggesting that hepatic fat accumulation is a contributing factor for conversion to diabetes mellitus in men at risk.^{21,22}

Serum GGT was found to be specifically associated with abdominal visceral adipose tissue and hepatic fat content, but not with the abdominal subcutaneous fat area in patients with type 2 diabetes mellitus.²⁸ In order to investigate the association between serum GGT and risk of MetS and type 2 diabetes mellitus, Nakanishi *et al.* followed up 2957 MetS-free men and 3260 non-diabetic men at an age range of 35–59 years. With adjustments for age, family history of diabetes, body mass index (BMI), alcohol intake, cigarette smoking, regular physical activity and white blood cell count, the risk of MetS and type 2 diabetes mellitus increased in correlation with the levels of serum GGT, ALT, AST and alkaline phosphatase over a 7-year period. Additional adjustment for all the other liver enzymes attenuated these associations, but serum GGT remained a significant risk factor for both MetS and type 2 diabetes mellitus. Although mild elevations in liver enzymes are associated with features of MetS, only raised GGT is an independent predictor of deterioration of metabolic disorders.²³ A similar result,

recently found in the Bogalusa Heart Study,²⁹ may reflect the role of GGT in the dynamics of free radical generation, a factor involved in the pathogenesis of metabolic risk.^{23,24,28}

However, these studies have not measured insulin sensitivity, which is important in associations with obesity and NAFLD. In the IR Atherosclerosis Study of subjects aged 40–69 years, a total of 127 (20%) and 148 individuals (16%) developed MetS and type 2 diabetes mellitus, respectively, after 5 years of follow up. Hanley *et al.* found that ALT and the AST to ALT ratio at baseline predicted MetS independently of potential confounding variables, including directly measured insulin sensitivity and acute insulin response. In addition, AST and ALT were positively associated with incident type 2 diabetes mellitus after excluding the former and moderately heavy drinkers.^{25,26} Thus, elevations in ALT and GGT are considered to be part of the MetS. However, one should remember that the liver enzyme levels have a poor sensitivity and negative prediction of NAFLD, and the entire histological spectrum of NAFLD can be seen in patients with normal liver function tests.^{1,4,18}

NAFLD INCREASES INCIDENCE OF ONSET OF NEW METABOLIC DISORDERS

NAFLD is considered to be the liver component of the MetS and is frequently associated with obesity, dyslipidemia and type 2 diabetes mellitus. Fris-Liby *et al.* determined the development of liver function tests and metabolic complications in patients previously diagnosed as NAFLD. A total of 102 patients in whom NAFLD had been diagnosed during 1994–2001 were identified in this study. Eighty were brought in for investigations, including liver function tests, blood pressure, BMI, lipid profile, blood glucose and insulin, and the original liver biopsy was re-evaluated. The results showed that 62 patients (77%) were men (median age 46 years; mean follow-up period 2.8 ± 1.2 years). Fifty-four patients (68%) were mild to moderate overweight with a BMI of 25–30 kg/m². The mean BMI (28.2 kg/m²) was the same during diagnosis and follow-up (28.3 kg/m²). At the new examination, 18 patients (23%) had developed type 2 diabetes mellitus ($n = 6$) or had impaired fasting glucose (IFG) ($n = 12$), compared to only two patients at the original diagnosis. Hyperinsulinemia was observed in 19 patients (24%) and dyslipidemia with elevated triglycerides and/or hypercholesterolemia was now present in 65 patients (81%). Twenty-two patients (27%) had hypertension compared to nine (11%) at the original diagnosis. A liver biopsy was performed in 24%, and 89% of those

fulfilled the criteria of NASH. However, mild inflammation and fibrosis were observed, and none had cirrhosis. This study demonstrated that a significant proportion of patients with both clinical and histological diagnosis of NAFLD had developed metabolic problems soon after diagnosis and that these patients should therefore be screened regularly for metabolic disorders.³⁰

Recently, Fan *et al.* followed up 358 patients with NAFLD and 788 of their counterparts matched for age, sex, and occupation for 6 years. Both at baseline and follow up, MetS components were present at a greater frequency among those with NAFLD than that among the controls. The prevalence of MetS was not formally assessed by predefined criteria at entry of the study, but the authors found that 26% of the NAFLD group and 12% of the controls had three or more metabolic abnormalities at baseline. The corresponding figures for the follow-up study were 68 and 22%, respectively. Subjects with NAFLD were also more likely to develop new metabolic disorders than the controls. A new diagnosis of type 2 diabetes mellitus was made in 20%, hypertriglyceridemia in 39%, obesity in 48%, and hypertension in 70% of patients with NAFLD. Furthermore, in an attempt to establish the separate effect of fatty liver on the incidence of metabolic disorders other than those having common associations with overall obesity, a separate analysis was performed according to the characteristics of participants on entry of the study. The incidence of hypertension, hypertriglyceridemia, hypercholesterolemia, impaired fasting glucose and type 2 diabetes mellitus were significantly higher in the NAFLD group without obesity than that among the controls with neither fatty liver nor obesity.³¹

In order to determine the association between NAFLD and the risk of development of diabetes, Shibata and his colleagues conducted an observational cohort study among middle-aged male workers in a Japanese company from 1997 to 2005.³² The workers who had a daily alcohol intake of more than 20 g and those with impaired glucose tolerance by a 75 g oral glucose tolerance test were excluded. The remaining 3189 workers were classified into fatty liver and non-fatty liver groups based on the findings of abdominal ultrasonography. Both groups were followed for the development of diabetes mellitus. The hazard ratio (HR) was determined in a Cox proportional hazard analysis. A nested case-control study was conducted to determine the odds ratio (OR), the results showed that the average age of the participants was 48 years at entry of the study, and the average follow-up period was 4 years. The incidence of diabetes mellitus in the fatty

liver group was 2073 per 100 000 person-years (65 cases), whereas it was 452 per 100 000 person-years (44 cases) in the non-fatty liver group. The age- and BMI-adjusted HR of diabetes mellitus associated with fatty liver was 5.5 [95% confidence interval (CI) 3.6–8.5, $P < 0.001$]. In the nested case-control analysis, the OR adjusted for age and BMI was 4.6 (95% CI 3.0–6.9, $P < 0.001$). These results suggested that NAFLD significantly increased the risk of diabetes mellitus in middle-aged Japanese men. Therefore, NAFLD is a better predictor of the development of metabolic disorders than obesity itself, and it can be considered to be an early predictor of MetS and type 2 diabetes mellitus.

NAFLD AND INCREASED RISK OF CARDIOVASCULAR DISEASE

The importance of NAFLD and its relationship with the MetS are increasingly recognized, and this has stimulated the interest in the possible role of NAFLD in the development of cardiovascular disease. Indeed, the impact of NAFLD on cardiovascular disease risk deserves particular attention, in view of the implications for screening/surveillance strategies in this growing number of patients. Recent studies have reported an association of NAFLD with multiple classical and non-classical risk factors for cardiovascular disease. Moreover, there is a strong association between the severity of hepatic histopathology in NAFLD patients and greater carotid artery intima-media thickness and plaque, and lower endothelial flow-mediated vasodilation (as markers of subclinical atherosclerosis) independent of obesity and other MetS components. Finally, it has recently been demonstrated that NAFLD is associated with an increased risk of all causes of death and predicts future cardiovascular disease events independently of other prognostic factors, including MetS components. Overall, the current body of evidence strongly suggests that NAFLD is likely to be associated with an increased risk of cardiovascular disease and raises the possibility that NAFLD may not only be a marker but also an early mediator of atherosclerosis. Relationships between NAFLD and the risk of cardiovascular disease have been suggested by Targher *et al.* and have been reviewed elsewhere.^{6,24,29,33–36}

In summary, patients with NAFLD and/or unexplained liver enzymes elevation are associated with a future high incidence of metabolic and cardiovascular complications, suggesting that NAFLD is inclined to be more than a hepatic disease confined to classical boundaries.^{2,6,29,37,38} Although the presence of multiple features of MetS is associated with a more advanced and more progressive NAFLD, cardiovascular risk may

compete with liver-related complications in dictating the final outcome. It has become mandatory to evaluate diabetic and cardiovascular risk in NAFLD patients and to consider careful surveillance and aggressive treatment not only of their liver disease, but also of the possible underlying metabolic complications.^{4,37,39,40} The adverse influences of NAFLD on accelerated metabolic complications may be the consequence of liver fat accumulation and underlying visceral adipose tissue, the resultant hepatic and peripheral IR, chronic subclinical systemic inflammation and increased oxidative stress. In addition, decreased adiponectin concentrations might also be part of the mechanism.^{2,6,29} However, it is not known whether an intervention in lifestyle and pharmacotherapy on NAFLD/NASH will ultimately prevent the development of metabolic complications.

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REFERENCES

- 1 Angulo P. GI epidemiology: nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2007; 25: 883–9.
- 2 Fan JG, Saibara T, Chitturi S *et al.* What are the risk factors and settings for non-alcoholic fatty liver disease in Asia–Pacific? *J Gastroenterol Hepatol* 2007; 22: 794–80.
- 3 Farrell GC, Larter CZ. Nonalcoholic fatty liver: from steatosis to cirrhosis. *Hepatology* 2006; 43: S99–112.
- 4 Chitturi S, Farrell GC, Hashimoto E *et al.* Non-alcoholic fatty liver disease in the Asia–Pacific region: Definitions and overview of proposal guidelines. *J Gastroenterol Hepatol* 2007; 22: 778–87.
- 5 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: 113–21.
- 6 Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: The plot thickens. *Diabet Med* 2007; 24: 1–6.
- 7 Hamauchi M, Kojima T, Takeda N *et al.* The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005; 143: 722–8.
- 8 Fan JG, Zhu J, Li XJ *et al.* Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. *J Hepatol* 2005; 43: 508–14.
- 9 Fan JG, Zhu J, Li XJ *et al.* Fatty liver and the metabolic syndrome among Shanghai adults. *J Gastroenterol Hepatol* 2005; 20: 1825–32.
- 10 Thamer C, Machann J, Haap M *et al.* Reduced insulin effect in subclinical fatty liver. *Dtsch Med Wochenschr* 2004; 129: 872–5.
- 11 Larter CZ, Farrell GC. Insulin resistance, adiponectin, cytokines in NASH: Which is the best target to treat? *J Hepatol* 2006; 44: 253–61.
- 12 Kotronen A, Westerbacka J, Bergholm R *et al.* Liver fat in the metabolic syndrome. *J Clin Endocrinol Metab* 2007; 92: 3490–7.

- 13 Pacifico L, Celestre M, Anaania C *et al.* MRI and ultrasound for hepatic fat quantification: relationships to clinical and metabolic characteristics of pediatric nonalcoholic fatty liver disease. *Acta Paediatrica* 2007; **96**: 542–7.
- 14 Kim HJ, Kim HJ, Lee KE *et al.* Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch Intern Med* 2004; **164**: 2169–75.
- 15 Chien KL, Hsu HC, Chao CL *et al.* Interaction of obesity, metabolic syndrome and Framingham risk on steatohepatitis among healthy Taiwanese: Population-based nested case-control study. *Cardiovasc Diabetol* 2006; **5**: 12.
- 16 Chen CH, Huang MH, Yang JC *et al.* Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: Metabolic significance of nonalcoholic fatty liver disease in nonobese adults. *J Clin Gastroenterol* 2006; **40**: 745–52.
- 17 Wong VW, Hui AY, Tsang SW *et al.* Prevalence of undiagnosed diabetes and postchallenge hyperglycaemia in Chinese patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2006; **24**: 1215–22.
- 18 Wieckowska A, McCullough AJ, Feldstein AE. Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: Present and future. *Hepatology* 2007; **46**: 582–9.
- 19 Ioannou GN, Weiss NS, Boyko EJ *et al.* Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. *Hepatology* 2006; **43**: 1145–51.
- 20 Hanley AJ, Wagenknecht LE, Festa A *et al.* Alanine aminotransferase and directly measured insulin sensitivity in a multiethnic cohort: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2007; **30**: 1819–27.
- 21 Sattar N, McCannachie A, Ford I *et al.* Serial metabolic measurements and conversion to type 2 diabetes in the west of Scotland coronary prevention study: Specific elevations in alanine aminotransferase and triglycerides suggest hepatic fat accumulation as a potential contributing factor. *Diabetes* 2007; **56**: 984–91.
- 22 Sattar N, Scherbakova O, Ford I *et al.* Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland coronary prevention study. *Diabetes* 2004; **53**: 2855–60.
- 23 Nakanishi N, Suzuki K, Tatara K. Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2004; **27**: 1427–32.
- 24 Patel DA, Srinivasan SR, Xu JH *et al.* Persistent elevation of liver function enzymes within the reference range is associated with increased cardiovascular risk in young adults: The Bogalusa heart study. *Metabolism Clin Exp* 2007; **56**: 792–8.
- 25 Hanley AJ, Williams K, Festa A *et al.* Liver markers and development of the metabolic syndrome: the insulin resistance atherosclerosis study. *Diabetes* 2005; **54**: 3140–7.
- 26 Hanley AJ, Williams K, Festa A *et al.* Elevations in markers of liver injury and risk of type 2 diabetes: The insulin resistance atherosclerosis study. *Diabetes* 2004; **53**: 2623–32.
- 27 Nannipieri M, Gonzales C, Baldi S *et al.* Liver enzymes, the metabolic syndrome, and incident diabetes: The Mexico City diabetes study. *Diabetes Care* 2005; **28**: 1757–62.
- 28 Iwasaki T, Yoneda M, Kawasaki S *et al.* Hepatic fat content-independent association of the serum level of gamma-glutamyltransferase with visceral adiposity, but not subcutaneous adiposity. *Diabetes Res Clin Pract* 2007; **79**: e13–14.
- 29 Fan JG, Peng YD. Metabolic syndrome and non-alcoholic fatty liver disease: Asian definitions and Asian studies. *Hepatobiliary Pancreat Dis Int* 2007; **6**: 572–8.
- 30 Friis-Liby I, Aldenborg F, Jerlstad P *et al.* High prevalence of metabolic complications in patients with non-alcoholic fatty liver disease. *Scand J Gastroenterol* 2004; **39**: 864–9.
- 31 Fan JG, Li F, Cai XB *et al.* Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. *J Gastroenterol Hepatol* 2007; **22**: 1086–91.
- 32 Shibata M, Kihara Y, Taguchi M *et al.* Nonalcoholic fatty liver disease is a risk factor for type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 2007; **30**: 2940–4.
- 33 Targher G, Zenari L, Bertolini L *et al.* Relationships between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. *Diabetes Care* 2006; **29**: 1325–30.
- 34 Loria P, Lonardo A, Bellentani S *et al.* Non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease: An open question. *Nutr Metab Cardiovasc Dis* 2007; **17**: 684–98.
- 35 Fan J, Xu M. Relationship between fatty liver and atherosclerosis, and coronary atherosclerotic heart disease. *Zhonghua Gan Zang Bing Za Zhi* 2002; **10**: 150–1.
- 36 Chitturi S, Farrell GC. Fatty liver now, diabetes and heart attack later? The liver as a barometer of metabolic health. *J Gastroenterol Hepatol* 2007; **22**: 967–9.
- 37 Qian Y, Fan JG. Obesity, fatty liver and liver cancer. *Hepatobiliary Pancreat Dis Int* 2007; **4**: 173–7.
- 38 Fan JG. Non-alcoholic fatty liver disease: Its past, present and future. *Zhonghua Gan Zang Bing Za Zhi* 2007; **15**: 641–3.
- 39 Farrell GC, Chitturi S, Lau GKK *et al.* Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: Executive summary. *J Gastroenterol Hepatol* 2007; **22**: 775–7.
- 40 Chen HL-Y, de Silva HJ, Leung NW-Y *et al.* How should we manage patients with non-alcoholic fatty liver disease in 2007? *J Gastroenterol Hepatol* 2007; **22**: 801–8.