Int J Clin Exp Med 2018;11(8):8608-8614
www.ijcem.com /ISSN:1940-5901/IJCEM0067370

Original Article

Effect of metabolic syndrome and nonalcoholic fatty liver disease on asymptomatic carotid atherosclerosis

Chia-Ying Tsai[1], Lee-Ching Hwang[1,2], Chun-Yuan Huang[3], Hsin-Yin Hsu[1], Hsin-Lung Chan[1]

[1]*Department of Family Medicine, Mackay Memorial Hospital, Taipei, Taiwan, China;* [2]*Mackay Medical College, New Taipei City, Taiwan, China;* [3]*Department of Family Medicine, China Medical University Hospital Taipei Branch, Taipei, Taiwan, China*

Received October 17, 2017; Accepted May 24, 2018; Epub August 15, 2018; Published August 30, 2018

Abstract: Objective: Asymptomatic carotid atherosclerosis is a risk equivalent factor for cardiovascular disease (CVD). Nonalcoholic fatty liver disease (NAFLD) has a high prevalence in the general population and is a critical risk factor of CVD. We investigated the effect of NAFLD and metabolic syndrome (MetS) on asymptomatic carotid atherosclerosis. Method: This cross-sectional study included 3,147 participants in a health examination center based population over the preceding 10 years. Differences in participants with and without carotid atherosclerosis were compared using ANCOVA with adjustment for age. The multivariable logistic regression models were performed to determine whether components of MetS and NAFLD are associated with carotid atherosclerosis. Results: The prevalence of carotid atherosclerosis was considerably higher in individuals with both NAFLD and MetS compared with individuals with one of or neither NAFLD or MetS. In a multivariable logistic regression model, age, sex, smoking status and exercise status were included. The patients with moderate-severe NAFLD (odds ratio [OR]=1.53, 95% confidence interval [CI]=1.19-1.96) had a notably higher risk of carotid atherosclerosis than did those with mild NAFLD (OR=1.30, 95% CI=1.06-1.58). In the combined groups, the patients with MetS and NAFLD (OR=1.91, 95% CI=1.47-2.47) had a higher risk of carotid atherosclerosis than did those with NAFLD (OR=1.37, 95% CI=1.08-1.74) or MetS (OR=1.64, 95% CI=1.01-2.65). Conclusion: NAFLD and MetS are independent risk factors of carotid atherosclerosis. The patients with moderate-severe NAFLD had a notably higher risk of carotid atherosclerosis than did those with mild NAFLD. The patients with NAFLD and MetS had the highest risk of carotid atherosclerosis.

Keywords: Fatty liver, atherosclerosis, cardiovascular risk, metabolic syndrome

Introduction

Cardiovascular disease (CVD), including coronary heart disease, cerebrovascular disease and peripheral vascular disease, is the most common disease in the general population, and is the leading cause of mortality and morbidity [1]. Well-established risk factors for atherosclerotic CVD are age, hypertension, hyperlipidemia, diabetes mellitus, smoking and obesity [2]. Non-coronary atherosclerotic disease, including carotid artery disease, peripheral artery disease and abdominal aortic aneurysm, is also associated with cardiovascular risk for CVD [3].

Studies have demonstrated that asymptomatic carotid atherosclerosis is a risk equivalent factor for ischemic stroke and coronary artery disease [4, 5]. Risk factors for carotid plaque are older age, male sex, obesity, smoking (current/past) and metabolic syndrome (MetS) [6]. Hence, we used carotid atherosclerosis as a surrogate marker for predicting CVD risk.

Nonalcoholic fatty liver disease (NAFLD) is defined as follows: (a) evidence of hepatic steatosis, either by imaging or by histology; and (b) no causes for secondary hepatic fat accumulation [7]. NAFLD is increasing in prevalence worldwide and affects 5%-35% (median 20%) of the population [8]. NAFLD and the components of MetS are critical risk factors for CVD, the progression of carotid atherosclerosis, and all-cause-mortality [9].

Few studies have investigated associations among NAFLD, MetS, and asymptomatic carotid atherosclerosis. To predict CVD early in asymptomatic patients, we evaluated the rela-

Table 1. Basic characteristics of the study sample

	All subjects (n=3,147)
Age (years)	51.7 ± 7.4
Sex (male, %)	2,521 (80.1)
BMI (kg/m^2)	24.8 ± 3.2
Low BMI (< 18.5)	57 (1.8)
Normal BMI (18.5 ≤ BMI < 24)	1,255 (39.9)
Overweight (24 ≤ BMI < 27)	1,134 (36.0)
Obesity (≥ 27)	701 (22.3)
Waist circumference (cm)	86.7 ± 9.4
Fasting plasma glucose (mg/dL)	107.1 ± 24.5
Triglyceride (mg/dL)	148.3 ± 103.5
LDL (mg/dL)	122.8 ± 30.4
HDL (mg/dL)	53.7 ± 13.8
Systolic blood pressure (mmHg)	118.3 ± 15.1
Diastolic blood pressure (mmHg)	76.1 ± 10.2
Diabetes mellitus (%)	422 (13.4)
Hypertension (%)	941 (29.9)
Smoking every day (%)	302 (9.6)
Exercise habit (%)	876 (30.7)
Carotid atherosclerosis	
Normal	1,046 (33.2)
Mild	2,028 (64.5)
Moderate to severe	73 (2.3)
Nonalcoholic fatty liver disease	
Normal	750 (23.8)
Mild	1,725 (54.8)
Moderate to severe	672 (21.4)
Metabolic syndrome	
No	1,830 (58.2)
Yes	1,317 (41.8)

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

tionships among MetS, grading of NAFLD, and severity of asymptomatic carotid atherosclerosis.

Materials and methods

This retrospective study included patients between 40 and 69 years of age who underwent a check-up at a health examination center in the preceding 10 years. We began by excluding participants with incomplete or missing laboratory data, individuals with a history of alcohol consumption of more than three days per week or history of hepatitis B or hepatitis C infection. The final study population comprised 3,147 participants.

The following study variables were obtained for all participants: age, sex, diabetes mellitus, hypertension, cigarette smoking, exercise habits, systolic blood pressure (SBP) and diastolic blood pressure (DBP), body mass index (BMI), waist circumference, lipid profiles, and fasting plasma glucose.

The definition of MetS was based on revised adult treatment panel III of the National Cholesterol Education Program, and diagnosis was based on the presence of three or more of the following components: (1) waist circumference of >90 cm in men and >80 cm in women; (2) fasting glucose of ≥ 100 mg/dl or known treatment for diabetes mellitus; (3) blood pressure of ≥ 130/85 mmHg or receiving antihypertensive treatment; (4) serum triglycerides of ≥ 150 mg/dL; (5) high density lipoprotein (HDL)-cholesterol levels < 40 mg/dL in men and < 50 mg/dL in women [10]. Carotid atherosclerosis was measured by carotid duplex ultrasound. The severity of carotid atherosclerosis was defined as intima-media thickness: normal (< 1 mm), mild (1-2 mm), moderate (2-4 mm) and severe (≥ 4 mm) [11].

NAFLD was defined when abdominal ultrasound revealed fatty liver, that was diagnosed based on known standard ultrasound criteria. NAFLD was subdivided into normal, mild and moderate-severe according to the severity of the fatty liver status. We excluded participants with alcohol consumption of more than 3 days per week and history of hepatitis B or hepatitis C infection.

All statistical analysis was performed using SAS 9.2 software (SAS Institute, Inc., Cary, NC, USA). Categorical variables were expressed as numbers and percentages, and were compared using an chi-squared (X^2-) test. Continuous variables were expressed as mean ± standard deviation by using a Student's t-test. The differences in participants with mild, moderate-severe, and without carotid atherosclerosis were compared using ANCOVA. The multiple logistic regressions were performed to analyze whether MetS and carotid atherosclerosis are independently associated with carotid atherosclerosis, after adjustment for age, sex, and smoking and exercise habits. *P* values of < 0.05 were considered significant.

Results

Basic characteristics

The basic characteristics of the group are shown in **Table 1**. The mean age was 51.7 years and most individuals were male (80.1%). A total of 302 participants were current smokers (9.6%). Approximately 13% of participants (n=422, 13.4%) had diabetes mellitus and approximately 30% (n=941, 29.9%) had hypertension at baseline. A third of the participants (n=876, 30.7%) had regular exercise habits. A total of 2,397 participants were diagnosed with NAFLD (mild: 54.8%; moderate-severe: 21.4%). Only a third of the participants (n= 1,046, 33.2%) did not have carotid atherosclerosis, whereas 64.5% (n=2,028) and, 2.3% participants (n=73) had mild and, moderate-severe carotid atherosclerosis, respectively. Approximately 1,317 participants (41.8%) had MetS.

Relationship of severity of asymptomatic carotid atherosclerosis and cardio-metabolic risk factors

We classified all cohorts into three groups: normal (n=1,046), mild (n=2,028) and moderate-severe (n=73) according to the severity of carotid atherosclerosis (**Table 2**). The participants in the mild and moderate-severe groups had greater age, BMI, waist circumference, fasting plasma glucose, triglyceride, low-density lipoprotein, SBP and DBP level compared with the normal group. Moreover, considerable differences in diabetes mellitus and hypertension were observed among the three groups. Prevalence of moderate-severe NAFLD and MetS progressively increased according to the severity of carotid atherosclerosis. NAFLD and MetS were independent predictors of carotid atherosclerosis. When individuals were grouped according to status of NAFLD and MetS, the presence of carotid atherosclerosis notably increased in individuals with NAFLD and MetS (mild carotid atherosclerosis: n=837, 70.4%; moderate-severe carotid atherosclerosis: n= 33, 2.8%) compared with individuals with one of the two factors but not NAFLD or MetS (mild carotid atherosclerosis: n=378, 56.4%; moderate-severe carotid atherosclerosis: n= 12, 1.8%).

Multivariable logistic regression models for asymptomatic carotid atherosclerosis

The multivariable logistic regression models of age, gender, smoking status (none, past, or current), exercise status (none, seldom, or regular) were included. Individuals with NAFLD or MetS had a significantly higher risk of asymptomatic carotid atherosclerosis compared with normal individuals (**Table 3**).

The patients with moderate-severe NAFLD (odds ratio [OR]=1.53, 95% confidence interval [CI]=1.19-1.96) had a considerably higher risk of carotid atherosclerosis than did those with mild NAFLD (OR=1.30, 95% CI=1.06-1.58). The patients with only MetS had a higher risk of carotid atherosclerosis (OR=1.44, 95% CI= 1.21-1.71). In model 3 of the combined groups, the patients with either NAFLD (OR=1.37, 95% CI=1.08-1.74) or MetS (OR=1.64, 95% CI=1.01-2.65) had an increased risk of carotid atherosclerosis; those patients with MetS and NAFLD (OR=1.91, 95% CI=1.47-2.47) had a highest risk of carotid atherosclerosis.

Discussion

In this study, we examined the association between asymptomatic carotid atherosclerosis, NAFLD, and MetS for predicting risks of cardiovascular events. NAFLD and MetS are independent predictors of carotid atherosclerosis.

NAFLD is a crucial factor in carotid atherosclerosis and has received attention because of the increasing risk of mortality and morbidity of CVD [12]. A meta-analysis review showed that NAFLD was notably associated with increased carotid intima thickness and carotid plaque [11]. The risk of carotid plaque for an NAFLD patient was 3.73 times higher than that for a non-NAFLD patient [13]. Another meta-analysis review involving 27 cross-sectional studies showed that NAFLD was associated with increased carotid intima thickness, increased coronary calcification, increased endothelial dysfunction and increased arterial stiffness [14]. Our study was in agreement with previous studies and indicated, that patients with moderate-severe NAFLD (OR=1.53) had a no-

Table 2. Relationship of severity of carotid atherosclerosis and cardiometabolic risk factors

	Carotid intima-media thickness			p
	Normal (N=1046)	Mild (N=2028)	Moderate-Severe (N=73)	
Age (years)	46.9 ± 5.4	54.1 ± 7.1	54 ± 6.7	< 0.0001
BMI (kg/m^2)	24.7 ± 3.5	24.9 ± 3.1	25.2 ± 3.0	0.04
Low BMI	27 (2.6)	30 (1.5)	0	0.0191
Normal BMI	449 (42.9)	777 (38.3)	29 (39.7)	
Overweight	340 (32.5)	766 (37.8)	28 (38.4)	
Obesity	230 (22.0)	455 (22.4)	16 (21.9)	
Waist circumference (cm)	85.7 ± 9.9	87.1 ± 9.1	89.1 ± 6.6	0.0032
Fasting plasma glucose (mg/dL)	103.3 ± 19.9	109.0 ± 26.5	109.0 ± 19.4	0.0004
Triglyceride (mg/dL)	147.9 ± 102.9	148.4 ± 104.5	149.1 ± 84.1	0.08
LDL (mg/dL)	116.8 ± 28.8	125.7 ± 30.8	129.9 ± 30.9	< 0.0001
HDL (mg/dL)	54.7 ± 14.2	53.3 ± 13.7	51.3 ± 11.4	< 0.0001
SBP (mmHg)	115.1 ± 14.3	119.8 ± 15.2	121.4 ± 16.2	0.0002
DBP (mmHg)	74.9 ± 10.5	76.7 ± 10	77.6 ± 10.7	< 0.0001
Diabetes (%)	76 (7.3)	334 (16.5)	12 (16.4)	< 0.0001
Hypertension (%)	206 (19.7)	714 (35.2)	21 (28.8)	< 0.0001
Current smoking (%)	90 (8.6)	205 (10.1)	7 (9.6)	0.4066
Exercise habit (%) n=2,853	237 (25.9)	621 (33.1)	18 (29.0)	0.0004
Nonalcoholic fatty liver				
Normal	303 (28.9)	433 (21.4)	14(19.2)	< 0.0001
Mild	546 (52.2)	1,142 (56.3)	37 (50.7)	
Moderate to severe	197 (18.8)	453(22.3)	22 (30.1)	
Metabolic syndrome				
No	690 (65.9)	1,103 (54.4)	37 (50.7)	< 0.0001
Yes	356 (34.0)	925 (45.6)	36 (49.3)	
Groups				
Non MetS and non NAFLD	280 (41.8)	378 (56.4)	12 (1.8)	< 0.0001
NAFLD without MetS	410 (35.3)	725 (62.5)	25 (2.2)	
MetS without NAFLD	37 (28.9)	88 (68.8)	3 (2.3)	
MetS with NAFLD	319 (26.8)	837 (70.4)	33 (2.8)	

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease. Values are expressed as mean ± standard deviation or number (%). All parameters were adjusted for age.

tably higher risk of asymptomatic carotid atherosclerosis than did those with mild NAFLD (OR=1.30).

The association between NAFLD and CVD has been consistent in several studies. NAFLD has increased all-cause mortality, CVD mortality and nonfatal CVD events [15-19]. A SMART study including 2,684 patients with clinical manifestations of arterial disease or type 2 diabetes mellitus, but without a history of cerebral ischemia, showed that patients with asymptomatic carotid atherosclerosis of 50% or greater increased by 12.3% (95% CI=10.7-13.9) in subsequent vascular events after 5 years, by 2.2% (95% CI=1.4-2.8) in cerebral infarction, and by 8.0% (95% CI=6.6-9.4) in myocardial infarction [4]. The pathogenesis of NAFLD is linked to insulin resistance due to increased hepatic lipogenesis, decreased fatty acid oxidation and decreased release of lipids from hepatocytes into circulation [20, 21].

Although participants with NAFLD typically meet the criteria of MetS, strong evidence suggested that elevated risk of CVD in NAFLD

Table 3. Odds ratios for carotid atherosclerosis according to multivariate logistic regression models

	OR (95% CI)
Model 1 with fatty liver	
No fatty liver	1.00
Mild fatty liver	1.30 (1.06-1.58)
Moderate to severe fatty liver	1.53 (1.19-1.96)
Model 2 with metabolic syndrome (yes v.s. non)	
No	1.00
Yes	1.44 (1.21-1.71)
Model 3 with combined groups	
Non MetS and non NAFLD	1.00
NAFLD without MetS	1.37 (1.08-1.74)
MetS without NAFLD	1.64 (1.01-2.65)
MetS with NAFLD	1.91 (1.47-2.47)

OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease. The variables included in multivariable analysis were age (years), sex, smoking status (none, past, or current), and exercise status (none, seldom, or regular).

patients is independent of the risk of MetS [22]. A study reported that carotid-intimal medial thickness was greater in patients with NAFLD than in healthy control, with all data adjusted for age, sex, MetS components and insulin resistance [23]. A prospective cohort study, where patients who underwent coronary angiogram had ultrasound screening for fatty liver, revealed that fatty liver (adjusted OR=2.31; 95% CI=1.46-3.64) was independently associated with coronary artery disease after adjustment for demographic characteristics and MetS [24]. Hence, in our study, we directly investigated the influence of MetS and NAFLD on carotid atherosclerosis and discovered that patients with MetS but without NAFLD (OR=1.64) had a higher risk of carotid atherosclerosis than did those with only NAFLD (OR=1.37).

A previous study of 37,799 asymptomatic adults aged 20 years or older who underwent a health check-up examination in the Republic of Korea, revealed that NAFLD (Sensitivity: 44%; Specificity: 60%) was more sensitive than MetS (Sensitivity: 27%; Specificity: 81%) regarding carotid plaque but was less specific. The presence of NAFLD plus MetS (Sensitivity: 53%; Specificity: 55%) improved sensitivity. There may have been some benefit from NAFLD screening for carotid plaque but with limited sensitivity and specificity. NAFLD has more a prominent association with carotid plaque in young adults (< 60 years) without MetS than old adults (≥ 60 years) or adults with MetS [6]. In our study, the population was young and apparently metabolically healthy (e.g. approximately 13.1% of the participants had diabetes mellitus and 41% had MetS). These findings suggested that NAFLD could be another tool to predict CVD risks early in young adults.

Our study had several strengths and limitations. We included a large study population without major CVD; this enabled us to test for interactions and generalize the results to the entire population. However, the limitations were as follows. First, the participants were mostly men undergoing a routine health check-up. Therefore, the association between NAFLD and carotid atherosclerosis in woman required further evaluation. Second, this study was a cross-sectional study; further longitudinal studies are required to determine whether early intervention of NAFLD could decrease CVD risk. Third, NAFLD was diagnosed by ultrasonography-an operator-dependent examination, which may need to incorrect diagnosis in 10%-30% of cases [25]. However, ultrasonography is still the most frequently used tool for diagnosing NAFLD because of its noninvasiveness and acceptable accuracy, and is recommended by several guidelines on the diagnosis and management of NAFLD [7].

In conclusion, this study demonstrated that NAFLD and MetS are independent risk factors of subclinical carotid atherosclerosis. The risk of carotid atherosclerosis is proportional to the severity of NAFLD. Furthermore, the patients with NAFLD and MetS had highest risk of carotid atherosclerosis. Thus, NAFLD and MetS could be a valuable tool for early prediction of CVD risk in asymptomatic patients in the general population.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hsin-Lung Chan, Department of Family Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, Chung-Shan North Road, Taipei 10449, Taiwan, China. Tel: 886-2-2543-3535; E-mail: hunter5770@gmail.com

References

[1] Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M and Murray CJ. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation 2015; 132: 1667-1678.

[2] Patel SA, Winkel M, Ali MK, Narayan KM and Mehta NK. Cardiovascular mortality associated with 5 leading risk factors: national and state preventable fractions estimated from survey data. Ann Intern Med 2015; 163: 245-253.

[3] Shah AM, Banerjee T and Mukherjee D. Coronary, peripheral and cerebrovascular disease: a complex relationship. Herz 2008; 33: 475-480.

[4] Goessens BM, Visseren FL, Kappelle LJ, Algra A and van der Graaf Y. Asymptomatic carotid artery stenosis and the risk of new vascular events in patients with manifest arterial disease: the SMART study. Stroke 2007; 38: 1470-1475.

[5] Chimowitz MI, Weiss DG, Cohen SL, Starling MR and Hobson RW 2nd. Cardiac prognosis of patients with carotid stenosis and no history of coronary artery disease. Veterans Affairs Cooperative Study Group 167. Stroke 1994; 25: 759-765.

[6] Sinn DH, Cho SJ, Gwak GY, Cho J, Gu S, Seong D, Kang D, Kim H, Yi BK and Paik SW. Nonalcoholic fatty liver disease for identification of preclinical carotid atherosclerosis. Medicine (Baltimore) 2016; 95: e2578.

[7] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M and Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012; 142: 1592-1609.

[8] Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ and Goh KL. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? J Gastroenterol Hepatol 2007; 22: 788-793.

[9] Galassi A, Reynolds K and He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006; 119: 812-819.

[10] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA and Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112: 2735-2752.

[11] Sookoian S and Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol 2008; 49: 600-607.

[12] Calori G, Lattuada G, Ragogna F, Garancini MP, Crosignani P, Villa M, Bosi E, Ruotolo G, Piemonti L and Perseghin G. Fatty liver index and mortality: the Cremona study in the 15th year of follow-up. Hepatology 2011; 54: 145-152.

[13] Cai J, Zhang S and Huang W. Association between nonalcoholic fatty liver disease and carotid atherosclerosis: a meta-analysis. Int J Clin Exp Med 2015; 8: 7673-7678.

[14] Oni ET, Agatston AS, Blaha MJ, Fialkow J, Cury R, Sposito A, Erbel R, Blankstein R, Feldman T, Al-Mallah MH, Santos RD, Budoff MJ and Nasir K. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis 2013; 230: 258-267.

[15] Treeprasertsuk S, Leverage S, Adams LA, Lindor KD, St Sauver J and Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. Liver Int 2012; 32: 945-950.

[16] Zhou YJ, Li YY, Nie YQ, Huang CM and Cao CY. Natural course of nonalcoholic fatty liver disease in southern China: a prospective cohort study. J Dig Dis 2012; 13: 153-160.

[17] Targher G and Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007; 191: 235-240.

[18] Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, Kawahito Y, Yoshida N, Suetsugu A, Kato T, Okuda J, Ida K and Yoshikawa T. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol 2007; 13: 1579-1584.

[19] Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C and Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007; 30: 1212-1218.

[20] Bhatia LS, Curzen NP and Byrne CD. Nonalcoholic fatty liver disease and vascular risk. Curr Opin Cardiol 2012; 27: 420-428.

[21] Kopec KL and Burns D. Nonalcoholic fatty liver disease: a review of the spectrum of disease, diagnosis, and therapy. Nutr Clin Pract 2011; 26: 565-576.

[22] Targher G, Day CP and Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010; 363: 1341-1350.

[23] Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, Cigolini M, Falezza G and

Arcaro G. Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006; 29: 1325-1330.
[24] Wong VW, Wong GL, Yip GW, Lo AO, Limquiaco J, Chu WC, Chim AM, Yu CM, Yu J, Chan FK, Sung JJ and Chan HL. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. Gut 2011; 60: 1721-1727.
[25] Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E and Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011; 54: 1082-1090.