Original Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_28_16

Nonalcoholic fatty liver disease as an independent risk factor for carotid atherosclerosis

Abid Rasool, Waseem Dar, Muzamil Latief, Imtiyaz Dar, Najeebullah Sofi, Mushtaq Ahmad Khan

Abstract:

PURPOSE: Nonalcoholic fatty liver disease (NAFLD) is a frequently encountered clinical condition in clinical practice, particularly in obese and diabetic patients. Carotid atherosclerosis is regarded as surrogate marker of coronary atherosclerosis. We aimed to know whether evaluation for carotid atherosclerosis should be done in all patients of NAFLD.

MATERIALS AND METHODS: A total of 200 NAFLD patients and 100 age- and sex-matched controls were enrolled into the study. Ultrasound was done to document fatty liver and carotid intimal thickness, and relation between these two was observed.

RESULTS: Grade 1 fatty liver was seen in 36% patients while Grade 2 fatty liver was found in 39% and Grade 3 fatty liver in 25%. Patients with Grade 1 fatty liver had left intima-media thickness (IMT) in the range of 0.4–0.6 mm (mean IMT - 0.69 mm) and had right IMT in the range of 0.5–0.8 mm (mean IMT - 0.71 mm). In patients with Grade 2 fatty liver, left IMT was in the range of 0.6–1.0 mm (mean IMT - 0.80 mm) and right IMT in the range of 0.7–1.0 mm (mean IMT - 0.84 mm), while in patients with Grade 3 fatty liver, left IMT was in the range of 0.8–1.2 mm (mean IMT - 0.93 mm) and right IMT in the range of 0.9–1.4 mm (mean IMT - 0.99 mm). Among controls, the mean left IMT was 0.579 mm and mean right IMT was 0.575 mm.

CONCLUSION: The level of carotid intimomedial thickness was more in cases than in controls and progressively increased with the grade of fatty liver which was statistically significant.

Keywords:

Atherosclerosis, fatty liver, intimomedial thickness

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological condition characterized by a wide spectrum of histological abnormalities and clinical outcomes. The underlying histological abnormality is hepatic steatosis, characterized by fat accumulation, which may progress to nonalcoholic steatohepatitis (NASH), characterized in turn by steatosis, periportal inflammation, and ballooning degeneration, with or without fibrosis.[1] Ultrasonography is the most widely used imaging technique for the detection of fatty liver, but the reported accuracy and reliability have been inconsistent across studies. The overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of ultrasound for the detection of moderate-severe fatty liver, compared to histology (gold standard), are 84.8% (95% confidence interval: 79.5–88.9), 93.6% (87.2–97.0), 13.3 (6.4–27.6), and 0.16 (0.12–0.22), respectively. The true prevalence of NAFLD remains to be established. In general population studies, its prevalence ranges between 10% and 39%.[2] Patients with hepatic steatosis alone or steatosis with nonspecific inflammation appear to have a mild clinical course.[3] In contrast, 50% of patients with NASH may

Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India

Address for correspondence:
Dr. Waseem Dar, Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India.
E-mail: drwaseem.mw@gmail.com

Submission: 25-12-2016
Revised: 30-01-2017
Accepted: 21-02-2017

How to cite this article: Rasool A, Dar W, Latief M, Dar I, Sofi N, Khan MA. Nonalcoholic fatty liver disease as an independent risk factor for carotid atherosclerosis. Brain Circ 2017;3:35-40.

progress to fibrosis or cirrhosis.[4,5] One retrospective study of 30 NASH patients reported a 67% 5-year survival rate and a 59% 10-year survival rate.[6] NASH-related cirrhosis has been recognized as a distinct entity that can cause severe liver disease and death. The majority of patients with NAFLD are asymptomatic although generalized fatigue, mild epigastric, or right upper quadrant pain may occur. The most common laboratory abnormality is the elevation of alanine aminotransferase (ALT) while aspartate aminotransferase (AST) may be the predominantly elevated aminotransferase in cases with advanced liver fibrosis. Several studies have demonstrated that an AST/ALT ratio > 1 is correlated with increasing fibrosis stage in patients with steatohepatitis. Recent studies have pointed out the association between NAFLD and high cardiovascular risk. This association is independent of classical risk factors, liver enzyme levels, or the presence of the metabolic syndrome and is strongly correlated with NAFLD. Furthermore, patients with fatty liver have more components of the metabolic syndrome and carotid atherosclerosis, as expressed by higher carotid intima-media thickness (CIMT) than controls. Finally, a relation was found between carotid artery wall thickness and the severity of liver histological lesions in patients with NAFLD. Specifically, CIMT was strongly associated with the degree of hepatic steatosis, necroinflammation, and fibrosis. Arterial stiffness, endothelial function of the brachial artery, and intima-media thickness (IMT) of carotid arteries have all been identified as markers of cardiovascular disease and predictors of the corresponding risk.

Aims and objectives

The aim of this study was to study the relation of carotid intimal thickness with different grades of fatty liver in a North Indian population.

Materials and Methods

The study was conducted in the Department of Gastroenterology at Sher-i-Kashmir Institute of Medical Sciences, Kashmir, India, a tertiary care center that serves around 5 million people. This prospective study was cleared by the Ethical Committee of the Institute and included a total of 200 cases and 100 age- and sex-matched controls. NAFLD was diagnosed on the basis of ultrasonography. NAFLD was diagnosed if at least two of the following three features were present on ultrasonography:

1. Increased liver echogenicity with evident contrast between kidney and liver
2. Blurring of vessels
3. Deep attenuation of the ultrasound signal.

Abdominal ultrasonography was performed using Aloka Prosound SSD-3500 SX USG machine and fatty liver was graded as 1, 2, and 3 depending on ultrasonographic features [Figure 1].

1. Mild (Grade 1): Minimal diffuse increase in hepatic echogenicity, diaphragm, and intrahepatic vessel contours seems normal
2. Medium (Grade 2): Medium grade diffuse increase in hepatic echogenicity, mild deterioration in the image of diaphragm and intrahepatic vessels
3. Severe (Grade 3): Apparent increase in echogenicity. Posterior segment of the right hepatic lobe is difficult to display. Intrahepatic vessel structure and diaphragm contours are vague or not seen.

Protocol

Detailed history and clinical findings were recorded from each patient according to defined protocol. History of alcohol intake was documented and patients who had history of ingestion of alcohol more than 20 g/day were planned to exclude from the study. Fortunately, in our study, there was no history of alcoholism in any patient. Each patient was subjected to a battery of investigations including complete hemogram, liver function tests, lipid profile, hepatitis serology, and carotid ultrasonography. Three measurements of intimal medial thickness were obtained from the right and left common carotid artery (CCA) proximal to the bifurcation with a 1-cm interval. Largest values among the three measurements of each side were taken for calculating the mean. IMT was taken as mean of left and right IMT. The values of IMT were taken as follows:

1. Normal IMT (0.6–0.8 mm)
2. Moderately thickened (1.0–1.5 mm).

Exclusion criteria

1. Chronic liver disease
2. Portal hypertension
3. Chronic hepatitis B and C
4. Any chronic debilitating diseases
5. Diabetes mellitus.

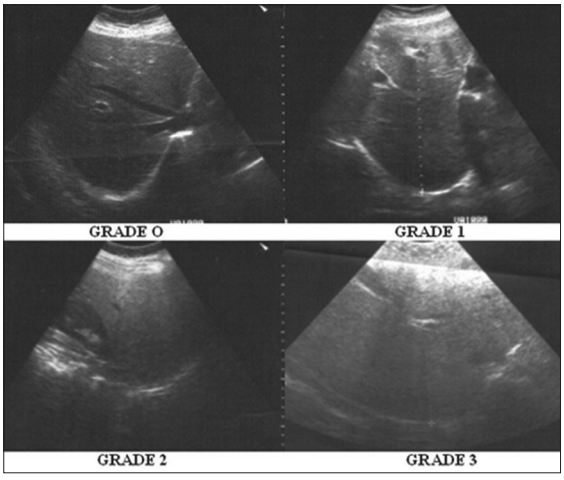

Figure 1: Grades of fatty liver

Statistical analysis

SPSS 17 Statistical Software (IBM) was used to perform statistical analysis of the results. Independent *t*-test was used to see a significant difference of means. *P* value (<0.05) was considered statistically significant.

Results

Baseline characteristics

Our study included 300 patients who were divided into two groups. Two hundred patients were in the study group while control group had 100 patients. The baseline characteristics of both the groups are given in Table 1.

Grade of fatty liver

In our study, Grade 1 fatty liver was seen in 36% patients while Grade 2 fatty liver was found in 39% and Grade 3 fatty liver in 25% patients [Figures 2 and 3].

Correlation of nonalcoholic fatty liver disease with liver function tests

The mean ALT in Grade 1 fatty liver was 55 IU/dl and in Grade 2 and 3 fatty liver was 75 IU/dl and 103 IU/dl, respectively [Table 2].

Carotid intimal thickness in different grades of nonalcoholic fatty liver disease

Patients with Grade 1 fatty liver had left IMT in the range of 0.4–0.6 mm (mean IMT - 0.69 mm) and had right IMT in the range of 0.5–0.8 mm (mean IMT - 0.71 mm). In patients with Grade 2 fatty liver, left IMT was in the range of 0.6–1.0 mm (mean IMT - 0.80 mm) and right IMT in the range of 0.7–1.0 mm (mean IMT - 0.84 mm), while in patients with Grade 3 fatty liver, left IMT was in the range of 0.8–1.2 mm (mean IMT - 0.93 mm) and right IMT in the range of 0.9–1.4 mm (mean IMT - 0.99 mm). Among controls, the mean left IMT was 0.579 mm and mean right IMT was 0.575 mm. The level of carotid intimomedial thickness was more in cases than in controls and progressively increased with the grade of fatty liver which was statistically significant [Tables 3 and 4].

Discussion

Sedentary lifestyle, aging population, and better access to food have given rise to a new era of lifestyle associated illnesses that continue to plague our population despite

Table 1: Baseline characteristics

Baseline characteristic	Cases, *n* (%)	Controls, *n* (%)
Mean age (years)	42.63	41.38
Sex		
Male	86 (43)	40 (40)
Female	114 (57)	60 (60)
Residence		
Rural	154 (77)	84 (84)
Urban	46 (23)	16 (16)
Comorbidity		
Hypertension	26 (13)	10 (10)
Diabetes mellitus	0	0
Mean BMI (kg/m^2)	22.3	21.6

BMI: Body mass index

Table 2: Level of liver enzymes in different grades of fatty liver

Parameter	Grade 1	Grade 2	Grade 3	Control
Serum ALT (U)	49-61	55-95	88-118	
Mean (U)	55	75	103	28.6

ALT: Alanine aminotransferase

Table 3: Carotid intima-media thickness in cases versus controls

	Mean	*n*	SD	SEM	*P*
Left IMT					
Cases	0.80202	200	0.15517	0.01560	0.0001
Controls	0.5818	100	0.10820	0.01087	
Right IMT					
Cases	0.84566	200	0.14650	0.01472	0.0001
Controls	0.5768	100	0.09349	0.00940	

IMT: Intima-media thickness, SD: Standard deviation, SEM: Standard error of mean

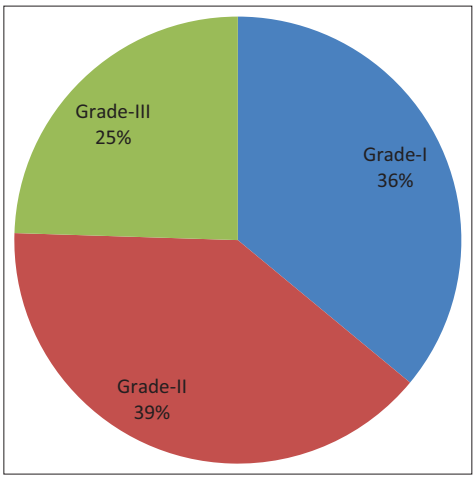

Figure 2: Grades of fatty liver in the studied population

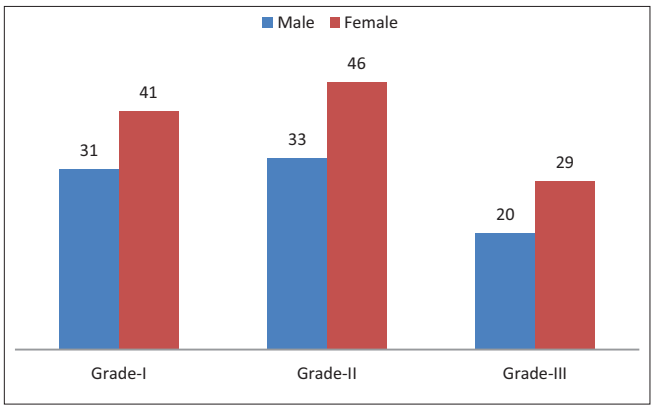

Figure 3: Sex matched distribution of fatty liver grades in our study

Table 4: Relation of carotid intima-media thickness with different grades of fatty liver

USG abdomen	*n*	Mean	SD	SE	95% CI for mean		Minimum	Maximum	*P*
					Lower bound	Upper bound			
Left carotid IMT									
1	72	0.6972	0.12215	0.01440	0.6685	0.7259	0.50	0.90	≤0.0001
2	79	0.8025	0.14498	0.01631	0.7701	0.8350	0.50	1.10	
3	49	0.9347	0.16014	0.02288	0.8887	0.9807	0.50	1.30	
Total	200	0.7970	0.16743	0.01184	0.7737	0.8203	0.50	1.30	
Right IMT (mm)									
1	72	0.7194	0.12177	0.01435	0.6908	0.7481	0.50	0.90	≤0.0001
2	79	0.8405	0.14634	0.01646	0.8077	0.8733	0.50	1.20	
3	49	0.9939	0.16634	0.02376	0.9461	1.0417	0.60	1.40	
Total	200	0.8345	0.17725	0.01253	0.8098	0.8592	0.50	1.40	

IMT: Intima-media thickness, SD: Standard deviation, SE: Standard error, CI: Confidence interval, USG: Ultrasonography

interventions at multiple levels. As the spectrum of these diseases broadens with time, newer indicators are invented to allow physicians to detect early and act early. Cardiovascular disease is usually the common end-point of these conditions and most common cause of morbidity and mortality in these illnesses. As a result, several different markers are being added continuously to the current armamentarium to allow early diagnosis and timely treatment or better prevention.

Carotid atherosclerosis as measured by intimal thickness is regarded as a surrogate marker of cardiovascular disease and hence a risk factor for stroke and myocardial infarction.[7] CIMT is the area of tissue starting at the luminal edge of the artery and ending at the boundary between the media and the adventitia. It is measured using B-mode ultrasound as the composite thickness of the intima and media. The "double-line pattern" is thus the distance between the two echogenic lines that represent the lumen–intima interface and the media–adventitia interface. CIMT in healthy middle-aged adults measures 0.6–0.7 mm and >1.20 mm is considered abnormal.[8] CIMT is age-dependent and increases at a rate of 0.005–0.010 mm/year. Thus, in younger individuals, a CIMT of > 1.00 mm would be considered abnormal.[9] In ARYA study, Oren *et al*. evaluated the relationship between conventional risk factors and increased CIMT in 750 healthy young adults, aged 27–30 years. They found that the estimated absolute risk, based on the Framingham risk function, for the development of coronary heart disease within 20 years was 2.5 times higher in individuals with mean CCIMT in the highest quartile compared with those in the lowest quartile of the distribution.[10] Similarly, Bots *et al*. conducted case–control study (Rotterdam Study) on 7983 individuals aged more than 55 years. The odds ratio for stroke per standard deviation increase (0.163 mm) was 1.41 (95% confidence interval [CI], 1.25–1.82). For myocardial infarction, an odds ratio of 1.43 (95% CI, 1.16–1.78) was found. They concluded that increased common CIMT is associated with future cerebrovascular and cardiovascular events.[11] In another study, in 146 men 40–59 years of age who had undergone CABG for coronary artery disease, preintrusive atherosclerosis in the CCA was evaluated every 6 months with B-mode ultrasonography, and intrusive atherosclerosis in the coronary arteries was evaluated at baseline and at 2 years with quantitative coronary angiography. After the trial, the incidences of coronary events were documented. For each 0.03-mm increase per year in carotid arterial IMT, the relative risk for nonfatal myocardial infarction or coronary death was 2.2 (95% CI, 1.4–3.6) and the relative risk for any coronary event was 3.1 (CI, 2.1–4.5) ($P < 0.001$). Absolute IMT was also related to risk for clinical coronary events ($P < 0.02$). Absolute thickness and progression in thickness predicted risk for coronary events beyond that predicted by coronary arterial measures of atherosclerosis and lipid measurements ($P < 0.001$). The authors concluded that noninvasive B-mode ultrasonographic measurement of progression of IMT in the distal CCA is a useful surrogate end-point for clinical coronary events.

Another outcome of this unhealthy lifestyle is increased prevalence of NAFLD. This disease is commonly found in patients who are obese, have metabolic syndrome or diabetes mellitus.[12] In a study of 40 NAFLD patients against 40 healthy controls, Brea *et al*. found that metabolic syndrome and all its individual traits, including elevated C-reactive protein, were significantly ($P < 0.005$) more frequent in NAFLD patients than in control subjects. Patients with NAFLD showed more carotid atherosclerosis than controls, with mean IMT of 0.70 ± 0.20 mm and 0.54 ± 0.13 mm ($P < 0.0001$) and plaque prevalence of 50% and 25% ($P = 0.021$), respectively.[13] Cai *et al*. did a meta-analysis of case–control studies about the relationship between NAFLD and CIMT published from 2004 to 2014. Nine studies were involved totally including 2446 subjects (925 patients and 1521 controls). We found that there was a significant heterogeneity between NAFLD and CIMT. By the random effects model, we calculated and combined the mean value of CIMT. The mean difference was 0.16 mm with

95% CI (0.11, 0.21). Studies showed that there was also heterogeneity between carotid artery plaque and NAFLD. By the random effects model, the calculated and combined OR value was 3.73 with 95% CI (2.42, 5.74). The publication bias of the included studies did not exist. The IMT in NAFLD patients increased 0.16 mm compared with the control group, and risk of carotid plaque was 3.73 times than that of the controls. In our study also, the carotid intimal thickness was more in cases than in controls. Besides, the degree of carotid intimal thickness was significantly associated with the grade of fatty liver. The degree of intimal thickness also correlates well with the histological grade of fatty liver, being lower in simple steatosis and higher in NASH.[14] Targher *et al*. compared CIMT, as assessed by ultrasonography, in 85 consecutive patients with biopsy-proven NAFLD and 160 age-, sex-, and body mass index-matched healthy controls. NAFLD patients had a markedly greater CIMT (1.14 ± 0.20 vs. 0.82 ± 0.12 mm; $P < 0.001$) than controls. Notably, CIMT was strongly associated with degree of hepatic steatosis, necroinflammation, and fibrosis among NAFLD patients ($P < 0.001$ for all). Similarly, by logistic regression analysis, the severity of histological features of NAFLD independently predicted CIMT ($P < 0.001$) after adjustment for all potential confounders.

In pediatric population also, obesity has been shown to have poor long-term cardiovascular outcomes. In such population also, NAFLD is strongly associated with carotid atherosclerosis and hence increased incidence of cardiovascular events in adulthood.[15] Pacifico *et al*. did a study that involved 29 obese children with NAFLD, 33 obese children without liver involvement, and 30 control children. Obese children with NAFLD had significantly increased CIMT (mean 0.58 [95% CIs 0.54–0.62 mm]) than obese children without liver involvement (0.49 [0.46–0.52] mm; $P = 0.001$) and control children (0.40 [0.36–0.43] mm; $P < 0.0005$). In diabetics, however, the results are different from nondiabetic population and in fact reverse.[16] One hundred and forty-four prospectively enrolled patients with type 2 diabetes underwent liver fat content measurement using H-magnetic resonance spectroscopy and carotid plaque assessment using ultrasound. Mean ± SD liver fat content was 9.86 ± 8.12%. Carotid plaque prevalence was 52.1% (75/144). Patients without plaque were younger ($P = 0.006$) and had a smaller visceral fat area ($P = 0.015$), lower reported prevalence of previous cardiovascular events or current statin therapy ($P = 0.002$), and higher liver fat content than those with plaque ($P = 0.009$). This study suggests that increased liver fat content could be associated with a relative protection against carotid atherosclerosis in patients with type 2 diabetes mellitus (T2DM). However, multiple longitudinal studies are needed to assess this hypothesis and propose any theory.

Several agents have been employed to reduce carotid intimal thickness and hence atherosclerosis.[17] Rizvi *et al*. used liraglutide to improve CIMT in patients with type 2 diabetes and NAFLD. In this 8-month prospective study, 29 subjects with type 2 diabetes and NAFLD were matched for age and gender with 29 subjects with T2DM without NAFLD. Liraglutide 0.6 mg/day for 2 weeks, followed by 1.2 mg/day, was given in addition to metformin. Glycated hemoglobin reduced significantly in both groups. No significant changes were found in body weight, waist circumference, and lipids. CIMT decreased significantly in the T2DM patients with NAFLD (from 0.96 ± 0.27 to 0.82 ± 0.17 to 0.85 ± 0.12 mm, $P = 0.0325$) but not in the T2DM patients without NAFLD (from 0.91 ± 0.23 to 0.88 ± 0.17 to 0.85 ± 0.15 mm, $P = 0.4473$). In another study, Bhatia *et al*.[18] employed 15–18 months trial of n-3 polyunsaturated fatty acid (docosahexaenoic acid and eicosapentaenoic acid) versus placebo in 92 patients of NAFLD with increased CIMT. In the treatment group ($n = 45$), CIMT progressed by 0.012 mm (interquartile range [IQR] 0.005–0.020 mm) compared to 0.015 mm (IQR 0.007–0.025 mm) in the placebo group ($n = 47$) ($P = 0.17$). Reduced CIMT progression in the entire cohort was independently associated with decreased liver fat (standardized β-coefficient 0.32, $P = 0.005$), reduced CK-18 levels (standardized β-coefficient 0.22, $P = 0.04$), and antihypertensive usage (standardized β-coefficient-0.31, $P = 0.009$) in multivariable regression analysis after adjusting for all potential confounders. The authors concluded that the improvement in two markers of NAFLD severity is independently associated with reduced CIMT progression.

Conclusion

NAFLD has a significant association with carotid atherosclerosis and hence with coronary atherosclerosis. All patients with NAFLD should be screened for CIMT. Lifestyle measures should be encouraged in all patients and pharmacological treatments reserved for advanced cases.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Brunt EM. Nonalcoholic steatohepatitis: Pathologic features and differential diagnosis. Semin Diagn Pathol 2005;22:330-8.
2. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;346:1221-31.
3. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: A spectrum

of clinical and pathological severity. Gastroenterology 1999;116:1413-9.
4. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, *et al.* Liver fibrosis in overweight patients. Gastroenterology 2000;118:1117-23.
5. 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.
6. Propst A, Propst T, Judmaier G, Vogel W. Prognosis in nonalcoholic steatohepatitis. Gastroenterology 1995;108:1607.
7. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, *et al.* Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007;23:75-80.
8. O'Leary DH, Bots ML. Imaging of atherosclerosis: Carotid intima-media thickness. Eur Heart J 2010;31:1682-9.
9. Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: The Atherosclerosis Risk in Young Adults (ARYA) Study. Arch Intern Med 2003;163:1787-92.
10. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: The Rotterdam Study. Circulation 1997;96:1432-7.
11. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, *et al.* The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 1998;128:262-9.
12. Brea A, Mosquera D, Martín E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: A case-control study. Arterioscler Thromb Vasc Biol 2005;25:1045-50.
13. Cai J, Zhang S, Huang W. Association between nonalcoholic fatty liver disease and carotid atherosclerosis: A meta-analysis. Int J Clin Exp Med 2015;8:7673-8.
14. Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, *et al.* Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006;29:1325-30.
15. Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Anania C, *et al.* Nonalcoholic fatty liver disease and carotid atherosclerosis in children. Pediatr Res 2008;63:423-7.
16. Loffroy R, Terriat B, Jooste V, Robin I, Brindisi MC, Hillon P, *et al.* Liver fat content is negatively associated with atherosclerotic carotid plaque in type 2 diabetic patients. Quant Imaging Med Surg 2015;5:792-8.
17. Rizzo M, Chandalia M, Patti AM, Di Bartolo V, Rizvi AA, Montalto G, *et al.* Liraglutide decreases carotid intima-media thickness in patients with type 2 diabetes: 8-month prospective pilot study. Cardiovasc Diabetol 2014;13:49.
18. Bhatia L, Scorletti E, Curzen N, Clough GF, Calder PC, Byrne CD. Improvement in non-alcoholic fatty liver disease severity is associated with a reduction in carotid intima-media thickness progression. Atherosclerosis 2016;246:13-20.