International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 02 (D); February 2019; Page No.17386-17389
DOI: http://dx.doi.org/10.24327/ijcar.2019.17389.3296

Research Article

CAROTID ATHEROSCLEROSIS IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE – A TERTIARY CARE EXPERIENCE

Shubha Immaneni, Murali Ramamoorthy, Vivekan Manoharan, Venkateswaran Arcot Rajeshwaran, Malarvizhi Murugesan , Rajkumar Solomon and Chezhian Annasamy

Institute of Medical Gastroenterology Madras Medical College Chennai

A R T I C L E I N F O

Article History:
Received 12th November, 2018
Received in revised form 23rd December, 2018
Accepted 7th January, 2019
Published online 28th February, 2019

Key words:
Carotid intima media thickness, Nonalcoholic fatty liver disease, metabolic syndrome, cardiovascular risk factors

A B S T R A C T

Background: Non-alcoholic fatty liver disease shares many features of metabolic syndrome and its presence could signify a substantial cardiovascular risk.
Aim: This study is an attempt to investigate the association of non-alcoholic fatty liver disease with carotid intima-media thickness and plaque as surrogate measures of increased cardiovascular risk.
Methods: Carotid atherosclerosis and cardiovascular risk factors were assessed in 52 patients with an ultrasound diagnosis of NAFLD and 50 age and sex matched controls attending the MGE OPD, MMC & RGGGHS, Chennai from February 2017 to January 2018 were prospectively evaluated. Anthropometric factors like waist circumference and blood pressure was measured, fasting serum samples were analyzed for glucose, triglyceride, cholesterol and its fractions, alanine and aspartate transaminase. Liver ultrasonographic scanning was used for assessing fatty liver. Carotid atherosclerosis was assessed by B-mode ultrasonography of common carotid artery and internal carotid artery and the relation between the two was observed. The maximum CIMT (MCIMT) was measured and the average measurement was used. The metabolic syndrome and its traits 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 intima-media thickness (IMT) of 0.85±0.30 mm and 0.48±0.17 mm (P<0.0001) and plaque prevalence of 62% and 28% (P=0.020), respectively.
Results: The level of carotid intima-medial thickness was more in cases than in controls which was statistically significant.
Conclusion: Patients with NAFLD show a cluster of risk factors of the metabolic syndrome and advanced carotid atherosclerosis. NAFLD appears to be a feature of the metabolic syndrome, and its detection on abdominal ultrasound should alert to the existence of an increased cardiovascular risk.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition characterized by fatty infiltration of liver cells resembling that of alcohol-induced liver injury but occurring in patients who do not abuse alcohol.[1–3] The spectrum of NAFLD ranges from fatty liver alone to steatohepatitis, which is histologically similar to alcoholic hepatitis and may progress to end-stage liver disease.[4] NAFLD is also now believed to be an integral part of metabolic syndrome which comprises a cluster of abnormalities such as abdominal obesity, atherogenic dyslipidemia, hypertension, elevated plasma glucose, and a prothrombotic and a proinflammatory state that greatly increases individual's probability of developing atherosclerotic cardiovascular disease (CVD) and Type 2 diabetes mellitus.[5-7]

Corresponding author:* **Murali Ramamoorthy
Institute of Medical Gastroenterology Madras Medical College Chennai

Mortality associated with NAFLD, 10-15 years after its diagnosis, is about 10-12%, and is significantly higher in patients with the more advanced stages of this condition. In this same period of time, the risk of progression to cirrhosis is 5-10%, and 1-2% to hepatocellular carcinoma.[8] Increasing number of studies have shown that the higher mortality rate among NAFLD patients in comparison to the general population is chiefly due to concomitant cardiovascular disease (CVD) than does the progression of the liver disorder.[9-11]The strong association between NAFLD and Metabolic syndrome may explain the high cardiovascular mortality observed in NAFLD patients.[12] Furthermore, accumulating evidence suggests that NAFLD is by itself a risk factor for coronary artery disease independently of established risk factors.[13-15]

Increased carotid artery intima-medial thickness (CIMT) is considered a surrogate marker of early generalized atherosclerosis and subclinical CVD.[16] Targher *et al*.[17]

reported in a prospective nested case–control study that NAFLD is a strong predictor of future cardiovascular events among Type 2 diabetes mellitus. Targher *et al*. in another study also showed a correlation between higher CIMT and severity of liver disease assessed by histological grades.[18] In this case– control study, we investigated the association of NAFLD with carotid intima-media thickness (IMT) and plaque as surrogate measures of increased cardiovascular risk.[16]

MATERIALS AND METHODS

The study was conducted in the Institute of Medical Gastroenterology Rajiv Gandhi Government General Hospital. In a cross‐sectional study, all consecutive patients >18 years old with hepatomegaly detected on clinical and/or ultrasonographic examination attending as OPD between from February 2017 to January 2018 were enrolled. Exclusion criteria included pregnancy or patients who were not willing to participate. A written informed consent was taken from all the participants and study protocol was approved by the Institutional Ethics Committee. Detailed general examination including anthropometric measurements and systemic examination was done in all the cases and controls. Patients with conditions likely to alter serum aminotransferase levels like viral, autoimmune or toxic hepatic diseases, use of hepatotoxic drugs within six months, patients who had undergone gastrointestinal surgery, known patients with biliary obstruction, primary biliary cirrhosis and pregnancy were excluded from the study. Complete haemogram, erythrocyte sedimentation rate, urine routine examination, fasting blood sugar, post prandial blood sugar levels, blood urea, serum creatinine, liver function tests, lipid profile, HbsAg, Anti HCV by ELISA, HIV, ECG, Ultrasound examination of abdomen and carotid Doppler were done in all.

Ultrasonography

Ultrasonography was performed using a high‐resolution B‐mode scanner of with a 3.5 MHz convex‐array probe. NAFLD was diagnosed if atleast 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.

The diagnosis of NAFLD was based on the presence of hepatic steatosis as bright/echogenic liver on abdominal ultrasound after exclusion of alcohol consumption, smoking, positive hepatic markers of viral hepatitis, autoimmune hepatitis, Wilson's disease, hemochromatosis alpha‐1 anti‐trypsin deficiency, and medications known to cause fatty liver.

NAFLD was diagnosed according to the criteria of the American Gastroenterological Association (AGA): hepatic steatosis confirmed by US and/or liver biopsy, exclusion of other causes liver of disease (namely alcohol intake >30 g/day for men and >20 g/day for women, markers of chronic B and C hepatitis virus infections, auto-immune hepatic disorders, Wilson disease, hemochromatosis, and alpha-1-antitripsin deficiency), no history of prior gastric or jejunoileal bypass, no exposure to hepatotoxins, and no use of any drug known to cause hepatic steatosis during the last six months.[19]

Carotid Intima Medial Thickness

High resolution B mode ultrasonography of both the common and internal carotid arteries was performed using 10 MHz linear array transducer. The maximum CIMT (MCIMT) was measured and the average measurement was used.[20] The anterior and posterior walls of the common carotid arteries, internal carotid arteries, and carotid bulbs were evaluated for determination of presence of carotid plaque, defined as a focal thickening > 1.2 mm of the intima-media complex, measured from the media-adventitia interface to the intima–lumen interface. The data obtained was subjected to standard statistical analysis.

Metabolic Syndrome

The participants were assessed for metabolic syndrome (MetS) as per ATP III guidelines. Metabolic syndrome was defined by the presence of 3 or more of the following conditions: abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women), hypertriglyceridemia (≥ 150 mg/dl), and low high-density lipoprotein (HDL)-cholesterol level (<40 mg/dl in men and <50 mg/dl in females), hypertension (systolic blood pressure ≥ 130mmHg and diastolic ≥ 85 mmHg) and fasting hyperglycemia (≥ 100 mg/dl). The waist circumference was measured at the highest point of the iliaccrest at minimal respiration to the nearest 0.1 cm. Three readings of systolic and diastolic blood pressure were obtained from each participant and the average of the last two measurements was used. The current use of antihypertensive medication was also considered as an indication of high blood pressure. Fasting blood samples of subjects were collected and analyzed for sugar, triglycerides, cholesterol and its fractions

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 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

52 patients with NAFLD were compared with 50 age, sex and BMI matched controls (Table 2). The patients with NAFLD had significantly higher waist circumference, diastolic blood pressure, higher levels of fasting blood sugar levels and trigylcerides. They also had significantly higher CIMT than controls. intima-media thickness (IMT) of 0.85±0.30 mm and 0.48±0.17 mm (*P*<0.0001) and plaque prevalence of 62% and 28% (*P*=0.020), respectively (Table 1). Atheromatous carotid plaque was defined as CIMT values ≥ 1.2 mm.[21] The metabolic syndrome and its traits were significantly more frequent in NAFLD patients than in control subjects. We observed 27% prevalence of metabolic syndrome in patients with NAFLD as compared to 4% in controls.

Table 1 CIMT and Carotid plaque in patients with NAFLD and controls

Variables	Patients with NAFLD (n=52)	Controls (n=50)	p value
CIMT (mm)	0.85±0.30	0.48±0.17	<0.0001
Carotid plaque (%)	28 (54)	11 (22)	<0.02

NAFLD: Nonalcoholic fatty liver disease, CIMT: Carotid intima media thickness

Table 2 Comparison of clinical and biochemical characteristics in patients with NAFLD and controls

Variables	Patients with NAFLD (n=52)	Controls (n=50)	p value
Age (years)	46.58±7.86	47.12±8.56	0.13
Male sex n (%)	28 (54)	27 (52)	0.58
BMI (kg/m^2)	27.12±3.54	26.87±3.82	0.47
Waist circumference	95±6	87±5.1	0.04
Diastolic Blood pressure	88±14	72±8.1	0.01
Fasting blood sugar	116±21	86±16	0.01
Triglyceride	158±43.2	108±21	0.001
HDL Cholesterol	44±7.2	52.43±8.8	0.05
Metabolic syndrome	14 (27%)	2(4%)	0.001
Alanine transaminase	44±12	24±8	0.01
Aspartate transaminase	42±9.6	22±6.1	0.03

Data are expressed in mean±SD or n (%). NAFLD: Nonalcoholic fatty liver disease
HDL: High-density lipoprotein, BMI: Body mass index

DISCUSSION

Nonalcoholic steatohepatitis emerged from an anecdotal disease which was first described by Ludwig *et al*.[22] in 1980 to the most common cause of incident chronic liver disease at the end of the current decade. Although the world-wide prevalence of NAFLD has not yet been determined, it is 10-24% in common population and 57.5% in obese individuals. The prevalence of NAFLD in the general population has been reported by Mohan *et al*.[23] as 22% in normal glucose tolerance to 55% in patients with Type 2 diabetes. Increasing recognition of the importance of NAFLD and its strong relationship with the metabolic syndrome has stimulated an interest in the possible role of NAFLD in the development of CVD.[24]

Mean age of NAFLD patients in a study by Bacon *et al* was 47 years.[25] Ludwig *et al*[22] similarly noted mean patients age of 54 years. In various other studies mean age varied between 47 and 54 years. In our study, maximum numbers of subjects were in 5th decade. The age range of patients was from 18-72 years and the mean age was 46.58±7.86 years. In a study Brea *et al*.[26] 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. Similarly Assay N *et al*, concluded that patients with NAFLD, even without metabolic syndrome were at higher risk for atherosclerosis and assessment of NAFLD may be helpful for cardiovascular risk stratification.[27]

As shown in recent reports from different populations, [28-29] adults with metabolic syndrome are at consistently increased risk for cardiovascular and all-cause mortality. Carotid plaque incidence, a measure of advanced atherosclerosis, was independently associated with patients with NAFLD in our study. Likewise, an increased incidence and progression of carotid plaque in subjects with Metabolic Syndrome has been reported recently from the prospective Bruneck Study.[30] Thus, the close association of NAFLD with Metabolic syndrome might explain the high cardiovascularmortality observed in NAFLD.[5]

CONCLUSION

NAFLD is a hepatic manifestation of metabolic syndrome. NAFLD has a significant association with carotid atherosclerosis and hence with coronary atherosclerosis. NAFLD without other cardiovascular risk factors may be associated with increased CIMT and increased risk of cardiovascular events in patients with incidentally diagnosed fatty liver on abdominal ultrasonography. Hence all patients with NAFLD should be screened for CIMT. Lifestyle measures should be encouraged in all patients and pharmacological treatments reserved for advanced cases.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional ethics committee

References

1. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002; 346:1221–1231.
2. McCullough AJ. Update on nonalcoholic fatty liver disease. *J Clin Gastroenterol*. 2002; 34:255–262.
3. Brunt EM. Nonalcoholic steatohepatitis. *Semin Liver Dis*. 2004;24:3–20.
4. Younossi Z, Diehl AM, Ong JP. Nonalcoholic fatty liver disease: an agenda for clinical research. *Hepatology*. 2002;35:746 –752.
5. Matteoni CA, Younossi ZM, Gramlich T *et al*. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology*. 1999;116:1413–1419.
6. Bellentani S, Bedogni G, Tiribelli C. Liver and heart: A new link? J Hepatol 2008;49:300‐2
7. Neuschwander Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD single topic conference. Hepatology. 2003;37:1202–19.
8. Schiff ER, Maddrey WC, Sorrell MF (2012) Schiff's diseases of the liver. (11th Edn.), John Wiley & Sons, Inc., Hoboken.
9. Ekstedt M, Franzén LE, Mathiesen *et al*. (2006) Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 44: 865-873.
10. Marchesini G, Moscatiello S, Di Domizio S *et al* (2008) Obesity-associated liver disease. J Clin Endocrinol Metab 93: 74-80.
11. Rafiq N, Bai C, Fang Y, Srishord M *et al*. (2009) Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 7: 234-238.
12. Lin YC, Lo HM, Chen JD (2005) Sonographic fatty liver, overweight and ischemic heart disease. World J Gastroenterol 11: 4838-4842.
13. Hamaguchi M, Kojima T, Takeda N *et al*. (2007) Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol 13: 1579-1584.
14. Mirbagheri SA, Rashidi A, Abdi S *et al* (2007) Liver: an alarm for the heart? Liver Int 27: 891-894.
15. Targher G, Bertolini L, Padovani R *et al*. (2010) Prevalence of non-alcoholic fatty liver disease and its association with cardiovascular disease in patients with type 1 diabetes. *J Hepatol* 53: 713-718.
16. O'Leary DH, Polak JF. Intima‐media thickness: A tool for atherosclerosis imaging and event prediction. *Am J Cardiol* 2002;90:18L‐21L.
17. Targher G, Bertolini L, Padovani R *et al* Non‐alcoholic fatty liver disease is associated with carotid artery wall

thickness in diet‐controlled type 2 diabetic patients. J Endocrinol Invest 2006;29:55‐60.
18. Targher G, Bertolini L, Padovani *et al.* Relations between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006;29:1325‐30.
19. Loria P, Adinolfi LE, Bellentani S *et al*. (2010) The NAFLD Expert Committee of the Associazione Italiana per lo studio del Fegato (AISF). Practice guidelines for the diagnosis and management of nonalcoholic fatty liver disease: A decalogue from the Italian Association for the Study of the Liver (AISF) Expert Committee. Dig Liver Dis 42: 272-282.
20. Lim TK, Lim E, Dwivedi G *et al*. Normal value of carotid intima-media thickness—a surrogate marker of atherosclerosis: quantitative assessment by B-mode carotid ultrasound. *J Am Soc Echocardiogr*. 2008;21(2):112–6.
21. Touboul PJ, Hennerici MG, Meairs S *et al*. (2007) 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 23: 75-80.
22. Ludwig J, Viggiano TR, McGill DB. Nonalcoholic steatohepatitis: Mayo clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434‐8.
23. Mohan V, Farooq S, Deepa M *et al*. Prevalence of non‐alcoholic fatty liver disease in urban South Indians in relation to different grades of glucose intolerance and metabolic syndrome. Diabetes Res Clin Pract 2009;84:84‐91
24. Targher G, Arcaro G. Non‐alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007;191:235‐40.
25. Diehl AM, Li ZP, Li HZ. Cytokines and pathogenesis of non-alcoholic steato hepatitis. Gut. 2005;54:303-6.
26. Brea A, Mosquera D, Martín E *et al*. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: A case‐control study. Arterioscler Thromb Vasc Biol 2005;25:1045‐50
27. Assy N, Djibre A, Farah R *et al*. Presence of coronary plaques in patients with nonalcoholic fatty liver disease. 2010;254(2):393-400.
28. Malik S, Wong ND, Franklin SS *et al*. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
29. Hunt KJ, Resendez RG, Williams K *et al*. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation*. 2004;110:1251–1257.
30. Bonora E, Kiechl S, Willeit J *et al*. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome. *Diabetes Care*. 2003;26:1251–1257.

How to cite this article:

Shubha Immaneni *et al* (2019) 'Carotid Atherosclerosis in Patients with non Alcoholic Fatty Liver Disease – a Tertiary care Experience', *International Journal of Current Advanced Research,* 08(02), pp.17386-17389.
DOI: http://dx.doi.org/10.24327/ijcar.2019.17389.3296

****