Examining the Relationship Between Atherogenic Indices and the Non-Invasive Fibrosis Biomarker FIB4

S. Paglialunga PhD
Celerion, Tempe, AZ USA

celerion
Translating Science to Medicine

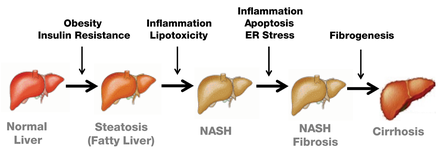
INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are the hepatic manifestation of metabolic syndrome. NASH is the most common form of chronic liver disease today and can lead to cirrhosis and end-stage liver disease (Figure 1).
- The FIB4 index is a non-invasive biomarker used to identify NASH patients at risk of advanced fibrosis. The index was developed to stage liver disease in subjects with HIV-hepatitis C virus co-infection [1], and more recently has been applied as a marker of fibrosis in NASH [2].
- NAFLD/NASH is also an independent risk for cardiovascular disease (CVD) [3]. However, the role of dyslipidemia in NASH subjects is not well understood, especially in patients with advanced fibrosis;
  - A recent large cross-sectional study of approximately 12,000 adults revealed that advanced hepatic fibrosis was associated with reduced TG levels [4].
  - Pharmacological reversal of steatohepatitis improved TG and HDL cholesterol levels but not LDL cholesterol [5].
  - Atherogenic indices are markedly higher in NASH children with advanced hepatic fibrosis compared to pediatric subjects with no or mild fibrosis [6].
- Atherogenic indices such as LDL/HDL and TG/HDL are simple lab tests that are predictive of CVD risk [7,8].

OBJECTIVE

- To examine the relationship between the non-invasive fibrosis biomarker, FIB4 index, and atherogenic indices as a clinical tool to identify CVD risk factors in overweight and obese adult men.

Figure 1. The natural history of NAFLD/NASH.



METHODS

- The dataset for this exploratory analysis was created using screening clinical laboratory results from ClinQuick®, Celerion's proprietary electronic data acquisition system.
- Male subjects, 30-70 years old, with a BMI >25 kg/m^2 were identified from a pool of 57 participants that screened over a 2-month period in 2015.
- A FIB4 cutoff value of 1.3 was applied to identify potential NASH subjects [2]. A recent meta-analysis study demonstrated that FIB4 > 1.3 reported good diagnostic accuracy compared to liver biopsy for advanced fibrosis (AUROC = 85%; sensitivity = 84%; specificity = 69%) [9].

$$\text{FIB4 index} = (\text{Age [years]} \times \text{AST [U/L]}) / (\text{Platelet count [10}^9\text{/L]} \times \sqrt{\text{ALT [U/L]}})$$

- Results are expressed as mean±SD and were analyzed by Student's t-test. Associations among variable were determined by Person correlation coefficient (R). Significance was set at p<0.05, where NS indicates not significant.

RESULTS

Figure 2. For this pilot study, 30 overweight and obese men were categorized according to their FIB4 index value; below (control) or above (>1.3) the cutoff point.

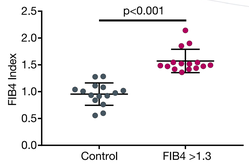


Table 1. The two groups were matched for age, BMI and HbA1c.

Parameter	Control	FIB4 >1.3	p-value
Age (years)	50.9 ± 9.6	53.1 ± 9.5	NS
BMI (kg/m^2)	32.8 ± 2.8	32.2 ± 4.3	NS
HbA1c (%)	7.6 ± 1.4	6.7 ± 1.8	NS
AST (U/L)	24.3 ± 7.8	32.0 ± 12.4	0.05
ALT (U/L)	37.1 ± 18.8	37.0 ± 25.8	NS
Platelet count (10^9/L)	219.5 ± 33.5	187.3 ± 29.1	0.009

Data represented at mean±SD. NS = not significant.

All subjects had a negative or non-reactive hepatitis B antibody test result.

Figure 3. Fasting (A) LDL cholesterol, (B) HDL cholesterol, (C) total cholesterol and (D) triglyceride levels were similar between the two groups.

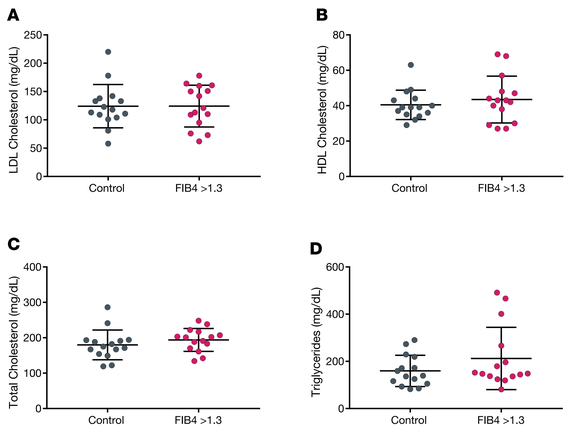


Figure 4. The atherogenic indices (A) LDL/HDL and (B) TG/HDL were not statistically different from control subjects.

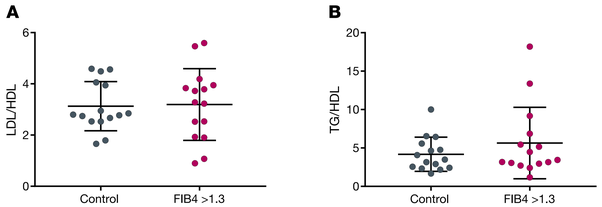
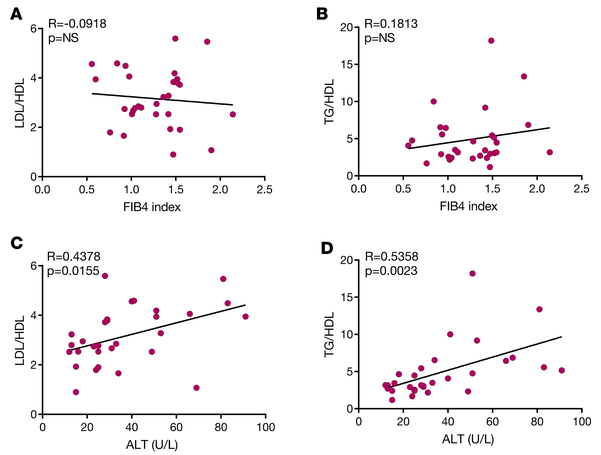


Figure 5. (A) LDL/HDL and (B) TG/HDL were not significantly associated with the FIB4 index. There was a statistically significant correlation between ALT levels and (C) LDL/HDL as well as (D) TG/HDL.



AST also significantly correlated with TG/HDL (R=0.5279, p=0.0027) but not LDL/HDL (R=0.1858, p=NS). Platelet count did not correlate with either of the atherogenic indices.

DISCUSSION & CONCLUSION

- The FIB4 index did not correlate with the atherogenic markers however, a significant association between ALT levels and LDL/HDL and TG/HDL was observed. This finding is consistent with results from Siddiqui et. al. demonstrating ALT positively correlated with CVD risk factors such a percent small dense LDL (sdLDL) and VLDL size [10].
- While this was an exploratory investigation, a number of study limitations must be addressed:
  - Fibrosis was not established by liver biopsy or imaging modalities such magnetic resonance elastography (MRE) or FibroScan®.
  - Results should be confirmed in a larger population with inclusion of both genders.
  - Subjects were generally healthy and the majority had liver function tests within 1.5x ULN.
- Although NASH subjects with advanced fibrosis are at greater risk of CVD [3], simple atherogenic indices may not reflect this prospect in an adult NAFLD cohort.
- Early clinical NAFLD/NASH studies with small cohort size may benefit from the incorporation of more sensitive biomarkers, such as percent sdLDL [10] or endothelial dysfunction (flow mediated dilation) and arterial stiffness (peripheral arterial tonometry) [11], to monitor CVD risk factors.

REFERENCES

1. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, M SS, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006; 43: 1317–25.
2. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009; 7: 1104-12.
3. Ruhl CE, Everhart JE. Epidemiology of nonalcoholic fatty liver. Clin Liver Dis. 2004; 8: 501–19.
4. Jiang ZG, Tsugawa Y, Tapper EB, Lai M, Afdhal N, Robson SC, Mukamal KJ. Low-fasting triglyceride levels are associated with non-invasive markers of advanced liver fibrosis among adults in the United States. Aliment Pharmacol Ther. 2015; 42: 106-16.
5. Corey KE, Vuppalanchi R, Wilson LA, Cummings OW, Chalasani N; NASH CRN. NASH resolution is associated with improvements in HDL and triglyceride levels but not improvement in LDL or non-HDL-C levels. Aliment Pharmacol Ther. 2015; 41: 301-9.
6. Nobili V, Alkhouri N, Bartuli A, Manco M, Lopez R, Alisi A, Feldstein AE. Severity of liver injury and atherogenic lipid profile in children with nonalcoholic fatty liver disease. Pediatr Res. 2010; 67: 665-70.
7. Assmann G, Schulte H. The importance of triglycerides: results from the prospective cardiovascular Münster (PROCAM) study. Eur J Epidemiol. 1992; 8: 99–103.
8. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 1997; 96: 2520–5.
9. Sun W, Cui H, Li N, Wei Y, Lai S, Yang Y, Yin X, Chen DF. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: A meta-analysis study. Hepatol Res. 2016; 46: 862-70.
10. Siddiqui MS, Sterling RK, Luketic VA, Puri P, Stravitz RT, Bouneva I, Boyett S, Fuchs M, Sargeant C, Warnick GR, Grami S, Sanyal AJ. Association between high–normal levels of alanine aminotransferase andrisk factors for atherogenesis. Gastroenterology. 2013; 145: 1271-9.
11. Long MT, Wang N, Larson MG, Mitchell GF, Palmisano J, Vasan RS, Hoffmann U, Speliotes EK, Vita JA, Benjamin EJ, Fox CS, Hamburg NM. Nonalcoholic fatty liver disease and vascular function: cross-sectional analysis in the Framingham heart study. Arterioscler Thromb Vasc Biol. 2015; 35: 1284-91.

CONTACT INFORMATION

Sabina Paglialunga PhD
Metabolic and Pharmacodynamic Specialist, Celerion
sabina.paglialunga@celerion.com

www.celerion.com