IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2022 Vol.:26, Issue:1

Antiplatelet Therapy Associated with Lower Prevalence of Advanced Liver Fibrosis in Non-Alcoholic Fatty Liver Disease

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Sarmad Rafiq*[1], Tanveer Hamid[1], Muhammad Sarmad Rafiq[1], Saddam Hussain[1], Mohammad Armaghan Farooq Dar[1], Jawad Mahmood[2], Muhammad Asim Hamza[3]

1. *Sligo University Hospital, Ireland*
2. *Good Hope Hospital University Hospital, Birmingham N.H.S Trust UK.*
3. *Health Education England, UK Countess of Chester Hospital*

Submitted: 24 November 2022
Accepted: 30 November 2022
Published: 30 December 2022

Keywords: Antiplatelet Therapy, Advanced Liver Fibrosis, Non-Alcoholic Fatty Liver Disease

ABSTRACT

Introduction: Liver fibrosis results from an imbalance between extracellular matrix formation and degradation. **Objectives:** The main objective of the study is to find the antiplatelet therapy associated with lower prevalence of advanced liver fibrosis in non-alcoholic fatty liver disease. **Material and methods:** This cross-sectional study was conducted in Sligo University Hospital, Ireland during 2021 to 2022. All subjects were negative for viral hepatitis and they also had normal values for copper and iron. Liver fibrosis was primarily assessed by TE using a FibroScan touch device with the FibroScan M-Probe. In addition, serologic testing for liver fibrosis was performed using the FibroTest. **Results:** In this study the data was collected from 50 patients with biopsy-demonstrated NAFLD, a connection between the seriousness of the metabolic syndrome and NAFLD was watched. While proportions of adiposity correlated with hepatic steatosis, hepatic inflammation and fibrosis were related with the presence and seriousness of the metabolic syndrome. This finding has clinical ramifications, since hepatic ultrasound and serum transaminases have restricted utility in foreseeing hepatic inflammation and fibrosis and there is current dependence on liver biopsies to affirm the analysis and show anticipation. **Conclusion:** It is concluded that there is a protective association between the use of antiplatelet agents and the occurrence of liver fibrosis. Platelets play a pivotal role in the mechanisms involved in disease progression.

INTRODUCTION

Liver fibrosis results from an imbalance between extracellular matrix formation and degradation. The background of liver fibrosis is chronic inflammation and subsequent microcirculation disturbance including microthrombosis. Platelets actively participate in liver fibrosis not only as a part of the clotting system but also by releasing granules containing important mediators[1]. In fact, platelets may play a dual role in the pathophysiology of liver fibrosis as they are able to stimulate regeneration as well as aggravate the destruction of the liver[2].

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver diseases among adults in Western countries. The term NAFLD covers a wide disease spectrum from varying grades of steatosis to non-alcoholic steatohepatitis, which can progress to liver cirrhosis and hepatocellular carcinoma in a relevant proportion of affected individuals[3]. In addition to liver-related morbidity and mortality, there is a close relationship between NAFLD and cardiovascular disease (CVD) as NAFLD can be considered a hepatic manifestation of the metabolic syndrome. The presence of liver fibrosis further increases the risk of developing CVD as well as mortality from CVD. In view of these facts, international guidelines recommend screening for CVDs in patients with NAFLD[4].

Therapeutic modalities to improve NAFLD and liver fibrosis in general are insufficient. There is emerging evidence that platelets play an important role in the establishment and progression of liver disease. Platelets release factors, such as PDGF-β, chemokine (C-X-C motif) ligand 4, or serotonin, that participate in liver fibrosis progression either by direct activation of hepatic stellate cells (HSCs) or by recruiting inflammatory cells to the liver[5]. Serotonin released by platelets could also reduce blood flow in the hepatic microcirculation by activating the contraction of HSCs or liver sinusoidal endothelial cells (LSECs). Furthermore, platelets sequestrate in the liver sinusoids during liver damage where they license LSECs to express chemokine receptors; this further amplifies the hepatic influx of innate and adaptive immune cells[6].

On the contrary, prescribing statins to patients with chronic liver disease often raises the issue of hepatotoxicity among clinicians given that statins are metabolized in the liver by CYP450 isoenzymes[7]. However, one of the most common side effects of statins, asymptomatic transaminitis, is still relatively uncommon (around 3%), occurs in the first year of treatment

initiation, is dose-dependent, and is usually self-limiting. Moreover, statin use was safe even among those with NAFLD and elevated liver enzymes, meaning that statins might target both genesis or deterioration of NAFLD and risk of coronary artery disease, which is increased in NAFLD patients[8]. Lastly, a meta-analysis showed that the prevalence of transaminitis among patients using statins or other lipid lowering medication is not significantly different from that of individuals using placebo[9].

Objectives

The main objective of the study is to find the antiplatelet therapy associated with lower prevalence of advanced liver fibrosis in non-alcoholic fatty liver disease.

MATERIAL AND METHODS

This cross-sectional study was conducted in Sligo University Hospital, Ireland during 2021 to 2022.

Inclusion criteria

All the patients who done the biopsy of liver and clinically proven NAFLD were included in this study.

Exclusion criteria

All patients having any major surgery, pregnant women and any other metabolic diseases were excluded from this study.

Data collection

All subjects were negative for viral hepatitis and they also had normal values for copper and iron. Liver fibrosis was primarily assessed by TE using a FibroScan touch device with the FibroScan M-Probe. In addition, serologic testing for liver fibrosis was performed using the FibroTest. All subjects expended <14 standard drinks of alcohol every week. Nine male subjects and eight female subjects had prior sort 2 diabetes, five dealt with their diabetes with diet alone, and 12 were taking metformin. Each subject and their particular control was given a score of 1 for each element of the metabolic syndrome, for a most extreme score of 5, with a score of ≥3 being indicative of the metabolic syndrome. Baseline characteristics at the time of first anticoagulant or antiplatelet prescription in people with or without liver disease were

analysed. We considered five types of antiplatelets, aspirin, clopidogrel, dipyridamole, prasugrel and ticagrelor. For stratified analyses involving specific medications, we have only analysed drug types that had more than 100 individuals.

Biochemical analysis

A pathologist blinded to subject details scored liver biopsies, allotting a score from 0 to 4 for inflammation, steatosis, and fibrosis as previously described. For additional fibrosis assessment, all biopsies were stained with Masson's Trichrome, percent fibrosis was calculated in triplicate by microscopy and image analysis and data were expressed as mean percentages.

Statistical analysis

The data of the different baseline variable was analyzed on SPSS 19 packages. Data of 50 patients was expressed as mean and SD. Significance was set at 0.05.

RESULTS

In this study the data was collected from 50 patients with biopsy-demonstrated NAFLD, a connection between the seriousness of the metabolic syndrome and NAFLD was watched. While proportions of adiposity correlated with hepatic steatosis, hepatic inflammation and fibrosis were related with the presence and seriousness of the metabolic syndrome. This finding has clinical ramifications, since hepatic ultrasound and serum transaminases have restricted utility in foreseeing hepatic inflammation and fibrosis and there is current dependence on liver biopsies to affirm the analysis and show anticipation.

Table 01: Laboratory value differences between NAFLD participants with and without metabolic syndrome

Laboratory values	**Mean±SD**	**p Value***
Triglycerides (mg/dL)	185.1±103.6	<0.001
Cholesterol, total (mg/dL)	196.8±42.3	0.86
Cholesterol, HDL (mg/dL)	41.2±10.2	<0.001
Cholesterol, LDL (mg/dL)	121.2±35.3	0.66
Cholesterol, HDL/LDL	37.0±15.6	<0.001
Fasting glucose (mg/dL)	96.6±14.6	<0.001
Fasting insulin (µU/mL)	27.2±31.4	<0.001
Fasting C peptide (mg/dL)	4.6±1.6	<0.001
HOMA-IR (mg/dL×µU/mL/405)	6.5±7.4	<0.001
HbA1c (%)	5.6±0.5	0.04
Alanine aminotransferase (U/L)	77.6±47.9	0.47
Aspartate aminotransferase (U/L)	53.6±34.4	0.69
Alkaline phosphatase (U/L)	85.1±32.8	0.43
γ-Glutamyl transferase (U/L)	60.3±39.6	0.15
Albumin (g/dL)	4.17±0.39	0.04
Serum iron (µg/dL)	90.5±31.1	0.006
Serum ferritin (ng/mL)	236.3±265.4	0.27
Transferrin saturation (%)	25.6±10.4	0.008
Albumin (g/dL)	4.17±0.39	0.04

Table 02: Logistic Regression Analyses of Factors Associated With the Presence of Liver Fibrosis

	Univariate		Multivariate, Model 1	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Platelets (/nL)	0.99 (0.99-0.99)	0.0006	0.99 (0.99-0.10)	0.02
Antiplatelet agents, no vs. mono vs. combination therapy	0.76 (0.59-0.98)	0.036	0.70 (0.53-0.94)	0.02
Statins, use	1.05 (0.57-1.63)	0.8		
Antidiabetic drugs, use	1.64 (0.98-2.73)	0.056		

The use of antiplatelet agents was inversely associated with the presence of liver fibrosis in a dose-dependent manner, i.e., a stronger association was observed for the intake of one versus two antiplatelet agents.

DISCUSSION

Emerging data have revealed a pathogenic role of platelets in the pathogenesis of liver fibrosis and inflammation. Platelets sequestrate within hepatic sinusoids during liver injury and interact with hepatic sinusoidal epithelial cells (LSECs), which results in the release of a large number of mediators, such as chemokines, cytokines, growth factors, lipid mediators, or procoagulants[9]. By releasing these mediators, platelets recruit and activate inflammatory cells, including granulocytes, macrophages, and T cells, to the liver and thereby perpetuate liver inflammation. Furthermore, platelet-derived mediators, such as PDGF-β, are potent inducers of HSC transformation to profibrotic myofibroblasts. Additionally, platelets are fundamental regulators of plasma serotonin concentrations, and serotonin results by activation of HSCs and LSECs and the subsequent vasoconstriction to reduced hepatic microcirculation[10]. These and other data suggest that platelets could be attractive targets for antifibrotic and anti-inflammatory therapy of liver diseases[11]. Indeed, a significant number of studies in animal models, such as models of viral hepatitis or NALFD, platelet depletion, or application of the platelet activation inhibitors aspirin or clopidogrel, reduced infiltration of virus-specific T cells and ameliorated hepatic inflammation, fibrosis progression, and

hepatocellular carcinoma development. However, data on the impact of antiplatelet agents on liver disease in humans are scarce[12].

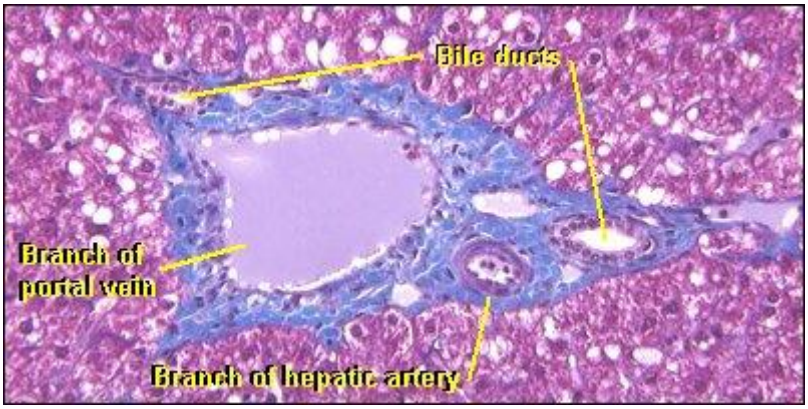

Figure 01: In the section of equine liver below (Masson's trichrome stain), the capsule and septae are stained blue, while hepatocytes are magenta. Notice how the capsule extends as a septum into the liver about one

Recent studies have pointed that NAFLD, in its whole spectrum ranging from pure fatty liver to non-alcoholic steatohepatitis (NASH), might represent another feature of MS[13]. Pathophysiologic considerations, clinical associations, and laboratory investigations support that insulin resistance and hyper-insulinaemia have a central role in pathogenesis of both MS and non-alcoholic fatty liver[14]. Studies concluded that NAFLD, in the presence of normoglycaemia and normal or moderately increased body weight, is characterized by clinical and laboratory data similar to those found in diabetes and obesity such as impaired insulin sensitivity and abnormalities in lipid metabolism[15-17]. Ninty percent of individuals with NAFLD have at least one risk factor of MS, and 33% have all the features of MS. Study concluded that liver fat content is significantly increased in subjects with the MS as compared with those without the syndrome, independently of age, gender, and body mass index[18].

CONCLUSION

It is concluded that there is a protective association between the use of antiplatelet agents and the occurrence of liver fibrosis. Platelets play a pivotal role in the mechanisms involved in disease progression. Their inhibition seems to be a promising therapeutic target. The results of previous observational studies show that ASA treatment was correlated with a decrease in liver fibrosis progression as well as HCC development.

REFERENCES

1. Pamela Czajka; Adam Przybyłkowski; Anna Nowak; Marek Postula; Marta Wolska; Dagmara Mirowska-Guzel; Anna Czlonkowska; Ceren Eyileten; (2021). *Antiplatelet drugs and liver fibrosis. Platelets, (), –* . doi:10.1080/09537104.2021.1883574
2. Lonardo A, Mantovani A, Targher G, Baffy G. Nonalcoholic Fatty Liver Disease and Chronic Kidney Disease: Epidemiology, Pathogenesis, and Clinical and Research Implications. *International Journal of Molecular Sciences*. 2022; 23(21):13320. https://doi.org/10.3390/ijms232113320
3. Qureshi K, Abrams GA. Metabolic liver disease of obesity and role of adipose tissue in the pathogenesis of nonalcoholic fatty liver disease. World J Gastroenterol. 2007;13:3540–3553.
4. Sanyal AJ, Campbell-Sargent C, Mirshahi F, et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology. 2001;120:1183–1192.
5. Paterson JM, Morton NM, Fievet C, Kenyon CJ, Holmes MC, Staels B. Metabolic syndrome without obesity: hepatic overexpression of 11-b-hydroxysteroid dehydrogenase type 1 in transgenic mice. Proc Natl Acad Sci. 2004;101:7088–7093.
6. Wei Y, Rector RS, Thyfault JP, Ibdah JA. Nonalcoholic fatty liver disease and mitochondrial dysfunction. World J Gastroenterol. 2008;14:193–199.
7. Dyson, J., Jaques, B., Chattopadyhay, D., Lochan, R., Graham, J., Das, D., et al. (2014). *Hepatocellular cancer: the Impact of Obesity, Type 2 Diabetes and a Multidisciplinary Team - PubMed*. *J. Oh Hepatol.* 60 (1), 110–117. doi:10.1016/j.jhep.2013.08.011
8. Ekstedt, M., Hagström, H., Nasr, P., Fredrikson, M., Stål, P., Kechagias, S., et al. (2015). Fibrosis Stage Is the Strongest Predictor for Disease-specific Mortality in NAFLD after up to 33 Years of Follow-Up. *Hepatology* 61 (5), 1547–1554. doi:10.1002/HEP.27368
9. Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M., et al. (2020). A New Definition for Metabolic Dysfunction-Associated Fatty Liver Disease: An International Expert Consensus Statement. *J. Hepatol.* 73 (1), 202–209. doi:10.1016/J.JHEP.2020.03.039
10. Yin H, Shi A, Wu J. Platelet-Activating Factor Promotes the Development of Non-Alcoholic Fatty Liver Disease. *Diabetes Metab Syndr Obes*. 2022;15:2003-2030 https://doi.org/10.2147/DMSO.S367483
11. Raffaello A, Mammucari C, Gherardi G, et al. Calcium at the center of cell signaling: interplay between endoplasmic reticulum, mitochondria, and lysosomes. *Trends Biochem Sci*. 2016;41(12):1035–1049. doi:10.1016/j.tibs.2016.09.001
12. Groenendyk J, Agellon LB, Michalak M. Calcium signaling and endoplasmic reticulum stress. *Int Rev Cell Mol Biol*. 2021;363:1–20. doi:10.1016/bs.ircmb.2021.03.003
13. Khamphaya T, Chukijrungroat N, Saengsirisuwan V, et al. Nonalcoholic fatty liver disease impairs expression of the type II inositol 1,4,5-trisphosphate receptor. *Hepatology*. 2018;67(2):560–574. doi:10.1002/hep.29588
14. Thillaiappan NB, Chakraborty P, Hasan G, et al. IP3 receptors and Ca2+ entry. *Biochim Biophys Acta Mol Cell Res*. 2019;1866(7):1092–1100. doi:10.1016/j.bbamcr.2018.11.007
15. Lai S, Li Y, Kuang Y, et al. PKCδ silencing alleviates saturated fatty acid induced ER stress by enhancing SERCA activity. *Biosci Rep*. 2017;37(6):BSR20170869. doi:10.1042/BSR20170869
16. Chang, Wai, et al. "Antithrombotic therapy in patients with liver disease: population-based insights on variations in prescribing trends, adherence, persistence and impact on stroke and bleeding." *The Lancet Regional Health - Europe*, vol. 10, 2021, p. 100222, https://doi.org/10.1016/j.lanepe.2021.100222. Accessed 13 Dec. 2022.
17. Schwarzkopf K, Bojunga J, Rüschenbaum S, Martinez Y, Mücke MM, Seeger F, Schoelzel F, Zeuzem S, Friedrich-Rust M, Lange CM. Use of Antiplatelet Agents Is Inversely Associated With Liver Fibrosis in Patients With Cardiovascular Disease. Hepatol Commun. 2018 Oct 5;2(12):1601-1609. doi: 10.1002/hep4.1254. PMID: 30556044; PMCID: PMC6287477.
18. Ratziu V, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L, et al. LIDO Study Group; CYTOL study group. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol* 2006;6:6.