e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(6); 492-498

Original Research Article

A Clinical Investigation at AIIMS Patna found A Link Between Non-Alcoholic Fatty Liver Disease and Gallstone Disease in the Hospitalized Patient Group

Mohammad Nehal Ahmad[1], Prashant Kumar[2]

[1]Senior Resident, Department of General Surgery, AIIMS, Patna, Bihar, India

[2]Senior Resident, Department of General Surgery, AIIMS, Patna, Bihar, India

Received: 22-03-2023 / Revised: 23-04-2023 / Accepted: 30-05-2023

Corresponding author: Dr. Mohammad Nehal Ahmad

Conflict of interest: Nil

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) risk factors include gallstones and cholecystectomy. This may be due to the fact that NAFLD and gallstones both share a number of risk factors for development. There isn't enough data available yet to conclusively link these clinical disorders together.

Aim: to ascertain whether there is a significant relationship between cholecystectomy and NAFLD and gallstones.

Methods: To identify hospitalizations with a diagnosis of gallstone disease (GSD), which includes calculus of the gallbladder without cholecystitis without obstruction and acquired absence of the gallbladder, as well as NAFLD, which includes simple fatty liver and non-alcoholic steatohepatitis, we studied from March 2020 to November 2021. Using logistic regression and correcting for confounding factors, odds ratios (ORs) evaluating the connection between GSD (which includes gallstones and cholecystectomy) and NAFLD were determined.

Results: In individuals with GSD, the prevalence of NAFLD was 3.3%, compared to 1% in patients without GSD. NAFLD was more common in 64.3% of GSD-afflicted women than in 35.7% of GSD-afflicted men. Multivariate-adjusted research revealed a relationship between NAFLD and gallstones after adjusting for numerous variables linked to NAFLD and GSD. Men were more likely than women to have NAFLD and gallstones together. In comparison to men, women had a greater correlation between NAFLD and cholecystectomy. P value for each comparison was below 0.001.

Conclusion: Women with GSD are more likely than men to have NAFLD. The correlation between cholecystectomy and gallstones and NAFLD suggests that these conditions may be risk factors for NAFLD.

Keywords: Gallstones, Non-alcoholic fatty liver disease, Gastroenterology, Hepatology.

Introduction

Hepatic steatosis is a sign of non-alcoholic fatty liver disease (NAFLD) when there are no other underlying causes of secondary fatty liver deposits. Hepatic steatosis is the initial symptom of NAFLD, which then gradually progresses to liver fibrosis and, in the end, end stage liver disease. Recent studies have shown that it is one of the most common causes of liver disease in the United States (US), with a prevalence as high as 20%–30%. Along with the global obesity pandemic, the prevalence of NAFLD is also rising[1,2]. Despite being a disease that is thought to advance gradually, it is currently the third most prevalent cause of liver transplant in the US[3].

Visceral obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and the metabolic syndrome are just a few of the co-morbidities that have been linked to NAFLD. It is unclear how other potential risk factors, including as gallstone disease (GSD), cholecystectomy, sleep deprivation, polycystic ovarian syndrome, hypertension, and pituitary problems, may affect the development of NAFLD[1]. However, it is widely known that insulin resistance and some form of metabolic dysregulation play a role in the pathophysiology that underlies the development of NAFLD. In this study, we examine the relationship between GSD, which includes cholelithiasis as a diagnosis and its sequelae, including cholecystectomy, and the emergence of NAFLD. The most prevalent type of gallstones are cholesterol stones, and the risk factors for their development are virtually the same as those linked to NAFLD[4]. Bile salt supersaturation and excessive production are linked to hepatic insulin resistance. It is unclear whether gallstones simply reflect the existence of metabolic syndrome risk factors, which hasten the course of NAFLD, or whether NAFLD itself causes gallstone formation[5]. On the other side, cholecystectomy is thought to change how bile acids are metabolized in the enterohepatic circulation, increasing the risk of NAFLD. In 2013, Ruhl et al[6] reported that having undergone a cholecystectomy may be a risk factor for developing NAFLD using data from the US National Health and Nutrition Examination Survey (NHANES) from 1988 to 1994. More recently, Kakati et al[7] discovered that NAFLD patients had a higher prevalence of cholecystectomy than non-NAFLD patients at a tertiary care facility in the US. However, this trial only included 379 patients, and it was limited to one centre. Therefore, a connection between cholecystectomy and NAFLD has not yet been established.

Regarding large-scale, multicenter retrospective research looking at a connection between GSD and NAFLD, there is a dearth of literature and data. Our study aims to identify the prevalence of various co-morbidities associated with NAFLD, ascertain whether there is an association between GSD and NAFLD, and discuss risk factor modification for the prevention of NAFLD development in addition to halting its progression to end stage liver disease.

Materials and Methods

Study design

ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification) diagnosis codes are being used retrospectively. The codes K80.20 (calculus of the gallbladder without cholecystitis without blockage) and Z90.49 (acquired absence of the gallbladder) were used to identify GSD. Then, using the codes K76.0 (simple fatty liver) and K75.81 (non-alcoholic steatohepatitis, NASH), the NAFLD cohort was created. Using the ICD-10 codes, co-morbidities and known risk factors were located.

Statistical analysis

Data analysis was performed using SPSS 21. A biomedical statistician reviewed the statistics. To generate nationally representative estimates of illness prevalence and demographic differences, we employed NIS specified weights. Statistical significance was defined as a two-tailed P value less than 0.05. The standardized prevalence of NAFLD and GSD by age and sex was created.

Results

There were 256 hospitalizations overall with GSD as the primary diagnosis.

NAFLD was 3.3% prevalent in GSD hospitalizations and 1.0% prevalent in non-GSD hospitalizations. GSD and NAFLD patients tended to be older and more likely to be female (Table 1). GSD hospitalizations were more frequent in white patients than non-GSD hospitalizations. The proportion of non-GSD hospitalizations was higher for other racial groups than for GSD hospitalizations. Compared to 40% of hospitalizations without GSD, 60% of GSD hospitalizations were covered by Medicare as the primary payer. In comparison to non-GSD hospitalizations, a larger percentage of GSD hospitalizations showed signs of alcohol misuse, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, and nicotine dependence. In contrast, hospitalizations for conditions other than GSD were more likely to result in obesity (Table 1). At P 0.001, each difference between the two groups was considered significant.

Table 1: Age- and sex-standardized characteristics of hospitalizations

	No gallstone disease	**All gallstone disease**	***P* value**
NAFLD (%)	1	3	< 0.001
Age, yr (mean ± SD)	47	61	< 0.001
Gender (%)			
Male	41	30	< 0.001
Female	59	70	< 0.001
Co-morbidities (%)			
Alcohol abuse	1	2	< 0.001
Diabetes mellitus	10	20	< 0.001
Dyslipidemia	20	30	< 0.001
Hypertension	30	40	< 0.001
Metabolic syndrome	0	0	< 0.001
Nicotine dependence	30	2	< 0.001
Obesity	9	6	< 0.001

After adjusting for age (Table 2), patients with gallstones were 6 times more likely to have NAFLD whereas those with cholecystectomy were 2 times more likely to have NAFLD. In addition, after adjusting for age, men with gallstones were more likely to have NAFLD than women, whereas women with cholecystectomy were more likely to have NAFLD than men.

Table 2: Logistic regression odds ratios for the association of non-alcoholic fatty liver disease with gallstone disease

All	**Age-adjusted**			**Multivariate-adjusted**		
	OR	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
Gallstone disease	3.3	2-4	< 0.001	2.5	2.1-3	< 0.001
Gallstones	6.5	6-8	< 0.001	6.	6.1-6.5	< 0.001
Cholecystectomy	2.2	2-2.5	< 0.001	2	2-2.5	< 0.001
Men						
Gallstone disease	3.1	3-3.5	< 0.001	3	2.7-3.5	< 0.001
Gallstones	7.2	7-7.5	< 0.001	6.5	6.0-7	< 0.001
Cholecystectomy	2.1	1.5-2.5	< 0.001	2.1	1.5-2.5	< 0.001
Women						
Gallstone disease	3	2.8-3.5	< 0.001	2.5	2.1-2.7	< 0.001
Gallstones	6.2	6.2-6.9	< 0.001	6.2	5.8-6.7	< 0.001
Cholecystectomy	2.2	2.2-2.5	< 0.001	2.1	1.8-2.4	< 0.001

According to a multivariate-adjusted research, patients with gallstones had a 6 times higher likelihood of developing NALFD, while those who had cholecystectomy had a 2 times higher likelihood of developing NAFLD. Additionally, the sex-adjusted study revealed that men had a greater link between NAFLD and gallstones than women did. In comparison to men, women were found to have a greater relationship between NAFLD and cholecystectomy.

Discussion

After adjusting for metabolic risk variables, it has been demonstrated that gallstones and cholecystectomy are separately linked to NAFLD, notably in Asian populations[11,12]. According to our study, people with GSD—which includes both the presence of gallstones and a history of cholecystectomy—have a prevalence of NAFLD of 3.3%, compared to 1% in patients without GSD. A multivariate-adjusted research that took into account the many variables connected to NAFLD and GSD revealed that there was a substantial relationship between NAFLD and both gallstones and cholecystectomy. However, given that the risk for gallstones is high in patients with central obesity, type 2 diabetes, and insulin resistance, the association between gallstones and NAFLD may result from the common pathogenic factors shared by both gallstone formation and NAFLD[13]. The exact pathophysiology behind the presence of gallstones leading to NAFLD is not well understood. The initiation and course of NAFLD are metabolically affected by gallbladder removal. After the gallbladder is removed, the small intestine still receives bile as a secretion. As a result, bile acids circulate through the enterohepatic system more quickly, which increases their entry into the liver[6]. Additionally, the enterohepatobiliary system's primary site of fibroblast growth factor 19 (FGF19) expression is the gallbladder[14]. Insulin's capacity to stimulate the production of hepatic fatty acids is suppressed by FGF19[15]. According to Barrera et al.'s research[16], cholecystectomy increases bile acid production while decreasing serum FGF19 levels. Studies on animals have demonstrated that cholecystectomy increases serum triglycerides and very low-density lipoprotein, which may eventually lead to NAFLD and increased triglyceride buildup in the liver. We therefore hypothesize that cholecystectomy may contribute to the beginning or development of NAFLD.

Although there is ongoing discussion about gender differences in NAFLD, it is well acknowledged that this disorder is sexually dysmorphic[17]. The majority of research found that men were more likely than women to have NAFLD after the NHANES data were analyzed[18]. However, Younossi et al.'s study[19], which categorizes people into lean or obese-overweight subgroups, found that the lean NAFLD cohort tended to be more female. We also focused on these gender distinctions in our study. According to our findings, 64.3% of women with GSD and 35.7% of males with GSD had NAFLD. Men were shown to have a stronger link between NAFLD and gallstones than women did, while women were found to have a stronger association between NAFLD and cholecystectomy. The pathophysiology underlying this disparity is attributed to typical changes in female physiology, particularly in the post-menopausal years, such as elevated rates of insulin resistance, central obesity, and changes in adipose tissue distribution as a result of estrogen level fluctuations[20]. In addition, it has been highlighted that early menarche may raise a woman's risk of NAFLD in adulthood due to the link between obesity and an early menstrual cycle[17]. Studies on animals utilizing overfed zebrafish models have demonstrated that the development of hepatic steatosis and the fibrotic progression of liver disease are facilitated by ovarian senescence, which results in hypoestrogenemia[21]. The ability to target particular populations for improved primary prevention and health promotion, as well as to provide treatment strategies that may help reduce morbidity and mortality related to NAFLD and its associated diseases, depends on our ability to comprehend gender differences in NAFLD.

Regarding the incidence of NAFLD, there are considerable racial disparities. According to our study, the prevalence of NAFLD with GSD was 72.1% in the Caucasian population, 11.8% in the African American population, 11.2% in the Hispanic population, and 4.9% in the population of other races (P 0.001). The intricate connections between environmental, behavioural, and genetic factors are most likely to blame for this[3,18]. The difference in visceral adiposity and average BMI between Caucasians and African Americans may be one reason for the racial disparity. The East Asian Indian population may have the highest risk of NAFLD, according to the most recent research[22–28].

Conclusion

We draw the conclusion that women with GSD are more likely than males to have NAFLD. Cholecystectomy and GSD may be risk factors for NAFLD based on the correlation between the two conditions and NAFLD. Gallstone formation and the associated need for cholecystectomy can be avoided with dietary changes, exercise, and weight loss. We are aware that cholecystectomy is a frequently carried out treatment and that gallstones are a prevalent disease condition. They should be further investigated in randomized clinical trials and prospective studies to determine their effect on NAFLD.

References

1. Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. World J Gastroenterol. 2017;23(47):8263-76.
2. Le MH, Devaki P, Ha NB, Jun DW, Te HS, Cheung RC et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. PLOS ONE. 2017;12(3):e0173499.
3. Machado MV, Cortez-Pinto H. Non-alcoholic fatty liver disease: what the clinician needs to know. World J Gastroenterol. 2014;20(36):12956-80. doi: 10.3748/wjg.v20.i36.12956, PMID 25278691.
4. Shabanzadeh DM. Incidence of gallstone disease and complications. Curr Opin Gastroenterol. 2018; 34(2): 81-9.
5. Ahmed MH, Ali A. Nonalcoholic fatty liver disease and cholesterol gallstones: which comes first? Scand J Gastroenterol. 2014;49(5):521-7.
6. Ruhl CE, Everhart JE. Relationship of non-alcoholic fatty liver disease with cholecystectomy in the US population. Am J Gastroenterol. 2013; 108(6):952-8.
7. Kakati D, Kumar U, Russ K, Shoreibah M, Kuo YF, Jackson B et al. Cholecystectomy does not worsen progression or outcomes in non-alcoholic fatty liver disease. Transl Gastroenterol Hepatol. 2020; 5:3
8. Healthcare cost and utilization Project. NIS database documentation [cited Mar 31, 2022]. Available from: https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp.
9. Healthcare Cost and Utilization Project. Overview of the national (nationwide) inpatient sample (NIS) [cited Mar 31, 2022]. Available from: https://www.hcup-us.ahrq.gov/nisoverview.jsp.
10. Healthcare Cost and Utilization Project. Healthcare Cost and Utilization Project Data Use

Agreement Course [cited Mar 25 2020]. Available from: https://www.hcup-us.ahrq.gov/DUA/dua_508/DUA508version.jsp.
11. Amigo L, Husche C, Zanlungo S, Lütjohann D, Arrese M, Miquel JF et al. Cholecystectomy increases hepatic triglyceride content and very-low-density lipoproteins production in mice. Liver Int. 2011;31(1):52-64.
12. Liu J, Lin H, Zhang C, Wang L, Wu S, Zhang D et al. Non-alcoholic fatty liver disease associated with gallstones in females rather than males: a longitudinal cohort study in Chinese urban population. BMC Gastroenterol. 2014; 14:213.
13. Fracanzani AL, Valenti L, Russello M, Miele L, Bertelli C, Bellia A et al. Gallstone disease is associated with more severe liver damage in patients with non-alcoholic fatty liver disease. PLOS ONE. 2012;7(7): e41183.
14. Zweers SJ, Booij KA, Komuta M, Roskams T, Gouma DJ, Jansen PL et al. The human gallbladder secretes fibroblast growth factor 19 into bile: towards defining the role of fibroblast growth factor 19 in the enter biliary tract. Hepatology. 2012;55(2):575-83.
15. Bhatnagar S, Damron HA, Hillgartner FB. Fibroblast growth factor-19, a novel factor that inhibits hepatic fatty acid synthesis. J Biol Chem. 2009;284(15):10023-33.
16. Barrera F, Azócar L, Molina H, Schalper KA, Ocares M, Liberona J et al. Effect of cholecystectomy on bile acid synthesis and circulating levels of fibroblast growth factor 19. Ann Hepatol. 2015;14(5):710-21.
17. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a sexual dimorphic disease: role of gender and reproductive status in the development and progression of nonalcoholic fatty liver disease and inherent cardiovascular risk. Adv Ther. 2017;34(6):1291-326.
18. Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. World J Hepatol. 2014;6(5): 274-83.
19. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Med (Baltim). 2012;91(6):319-27.
20. Summart U, Thinkhamrop B, Chamadol N, Khuntikeo N, Songthamwat M, Kim CS. Gender differences in the prevalence of nonalcoholic fatty liver disease in the Northeast of Thailand: A population-based cross-sectional study. F1000 Res. 2017;6:1630.
21. Turola E, Petta S, Vanni E, Milosa F, Valenti L, Critelli R et al. Ovarian senescence increases liver fibrosis in humans and zebrafish with steatosis. Dis Model Mech. 2015;8(9):1037-46.
22. Singh S, Kuftinec GN, Sarkar S. Non-alcoholic fatty liver disease in South Asians: a review of the literature. J Clin Transl Hepatol. 2017;5(1):76-81.
23. Dharmalingam M, Yamasandhi PG. Nonalcoholic fatty liver disease and type 2 diabetes mellitus. Indian J Endocrinol Metab. 2018;22(3):421-8.
24. Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2(11):901-10.
25. Mendez-Sanchez N, Cruz-Ramon VC, Ramirez-Perez OL, Hwang JP, Barranco-Fragoso B, Cordova-Gallardo J. New aspects of lipotoxicity in nonalcoholic steatohepatitis. Int J Mol Sci. 2018;19(7).
26. Speliotes EK, Massaro JM, Hoffmann U, Vasan RS, Meigs JB, Sahani DV et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart

Study. Hepatology. 2010;51(6):1979-87.
27. Wong RJ, Ahmed A. Obesity and non-alcoholic fatty liver disease: disparate associations among Asian populations. World J Hepatol. 2014; 6(5):263-73.
28. Oikonomou D, Georgiopoulos G, Katsi V, Kourek C, Tsioufis C, Alexopoulou A et al. Non-alcoholic fatty liver disease and hypertension: co prevalent or correlated? Eur J Gastroenterol Hepatol. 2018;30(9):979-85.
29. Akhavan Rezayat A, Dadgar Moghadam M, Ghasemi Nour M, Shirazinia M, Ghodsi H, Rouhbakhsh Zahmatkesh MR et al. Association between smoking and non-alcoholic fatty liver disease: A systematic review and meta-analysis. SAGE Open Med. 2018; 6: 2050312117745223.
30. Byrne CD, Targher G. G. Nafld: a multisystem disease. J Hepatol. 2015; 62(1); Suppl: S47-64.
31. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57.
32. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010;51(1): 121-9.
33. Marventano S, Salomone F, Godos J, Pluchinotta F, Del Rio D, Mistretta A et al. Coffee and tea consumption in relation with non-alcoholic fatty liver and metabolic syndrome: A systematic review and meta-analysis of observational studies. Clin Nutr. 2016;35(6):1269-81.
34. Bower G, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A et al. Bariatric surgery and non-alcoholic fatty liver disease: a systematic review of liver biochemistry and histology. Obes Surg. 2015;25(12):2280-9.