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Anti-Reflux Medications for Gastroesophageal Reflux Disease and Hepatic Steatosis in Subjects with History of Cholelithiasis and Cholecystectomy

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Anti-Reflux Medications for Gastroesophageal Reflux Disease and Hepatic Steatosis in Subjects with History of Cholelithiasis and Cholecystectomy

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Abstract: Aim: The interplay between gastroesophageal reflux disease (GERD) and hepatic steatosis, particularly in patients with a history of cholelithiasis and cholecystectomy, remains poorly understood. This study examined correlation between the presence of GERD determined by anti-reflux medications and hepatic steatosis in this population. **Methods**: The study sample was obtained from the National Health and Nutrition Examination Survey (NHANES) 2017-2020 database. Using transient elastography, hepatic steatosis was quantified via the controlled attenuation parameter (CAP), and fibrosis was assessed through liver stiffness measurement (LSM) and non-invasive biomarkers such as FIB-4 and acMASH. Subjects were categorized into two groups: subjects with GERD (Group 1) and without GERD (Group 2). **Results**: We analyzed data from 564 subjects, including 432 females and 132 males (mean age 58.37 ± 15.52 years). The mean CAP score was 283.12 ± 62.29 dB/m, while the mean LSM was 7.49 ± 7.84 kPa. No significant differences in CAP ($p=0.4880$) or LSM ($p=0.4495$) were observed between groups. FIB-4 showed a weak correlation with anti-reflux use ($\varrho=0.12$, $p<0.01$), while CAP and acMASH scores did not significantly correlate with medication use ($p=0.3748$ and $p=0.5326$, respectively). Logistic regression indicated no independent effect of anti-reflux medications on hepatic steatosis or fibrosis. **Conclusion**: Anti-reflux medications, which manage GERD, had no correlation with hepatic steatosis, underscoring the need for holistic care approaches in post-cholecystectomy patients.

Keywords: MASLD; NAFLD; Proton Pump Inhibitors; FIB-4; acMASH; controlled attenuation parameter; GERD

Background

Gastroesophageal reflux disease (GERD) and hepatic steatosis, including metabolic dysfunction-associated steatotic liver disease (MASLD), represent major global health concerns due to their rising prevalence and substantial impact on morbidity and healthcare costs [1]. GERD affects 5/1000 person-years, reducing quality of life and increasing healthcare utilization. It is associated with conditions such as Barrett's esophagus and is exacerbated by obesity, dietary factors, and psychological stressors such as anxiety and depression [2]. Hepatic steatosis, encompassing simple steatosis and metabolic dysfunction-associated steatohepatitis (MASH), affects 17–51% of the global population, with higher prevalence in Western countries, obese individuals, and patients with diabetes [3].

In patients with a history of cholelithiasis and cholecystectomy, the interplay between these conditions becomes even more complex. Cholelithiasis, often associated with metabolic syndrome, disrupts bile acid metabolism, a critical regulator of lipid homeostasis and gastrointestinal motility [4]. Post-cholecystectomy alterations, such as changes in bile flow and gut microbiota, may exacerbate GERD symptoms and potentially contribute to hepatic steatosis progression [5–7]. Cholecystectomy causes ultrasound evidence of increased hepatic steatosis [7]. Despite these associations, the exact prevalence of GERD and MASLD in this specific subgroup is not well established.

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Several studies have demonstrated an intricate relationship between GERD and hepatic steatosis. Meta-analyses by Wijarnpreecha et al. [8] and Xue et al. [9] found that GERD is significantly associated with MASLD, with odds ratios of 2.07 and 1.28, respectively, suggesting a bidirectional risk due to shared pathophysiological pathways like obesity-induced systemic inflammation and increased intra-abdominal pressure. Leng et al. [10] confirmed a causal relationship between GERD and MALSD using Mendelian randomization, emphasizing genetic predisposition and metabolic interlinkages.

Anti-reflux drugs, particularly proton pump inhibitors (PPIs), have been a cornerstone in GERD management, but refractory cases remain challenging [11]. Interestingly, some evidence suggests that the metabolic benefits of certain pharmacologic agents may also modulate hepatic steatosis [12]. It had been showed that PPIs use is associated with increased liver steatosis [13].

This study aims to explore the relationship between anti-reflux medications, GERD, and hepatic steatosis in patients with a history of cholelithiasis and cholecystectomy. Understanding these interactions may provide insights into optimizing treatment strategies for this complex patient population.

Materials and Methods

Data Source and Study Population

The sample for this study was drawn from the National Health and Nutrition Examination Survey (NHANES) database for the years 2017-2020, which is managed by the National Center for Health Statistics at the Centers for Disease Control and Prevention. NHANES is a continuous cross-sectional study designed to assess the health and nutritional status of individuals in the United States, providing a wealth of information on demographics, dietary practices, physical assessments, laboratory results, and survey data.

Data Collection from Subjects

Data were gathered through a combination of questionnaires, laboratory analyses, and physical examinations to evaluate various factors, including age, sex, waist circumference (WC), body mass index (BMI), and levels of alanine aminotransferase (ALT), high-density lipoprotein (HDL), aspartate aminotransferase (AST), platelet count (PLT), serum glucose, hemoglobin A1c (HbA1c), along with results from liver ultrasound transient elastography.

Transient Elastography

Participants underwent assessments of hepatic fibrosis and steatosis using transient elastography devices from Echosens™, USA. Liver stiffness measurements (LSM) were recorded in kilopascals (kPa), while hepatic steatosis was evaluated in decibels per meter (dB/m) via the controlled attenuation parameter (CAP). The severity of steatosis was categorized according to median CAP values: S1 was defined as ≥274 dB/m, S2 as ≥290 dB/m, and S3 as ≥302 dB/m. Median LSM values of ≥9.7 kPa and ≥13.6 kPa indicated significant advanced fibrosis (F3) and cirrhosis (F4), respectively.

Non-Invasive Biomarkers

FIB-4 is a non-invasive tool used to evaluate liver fibrosis. It incorporates age, AST, ALT, and platelet count. The formula for FIB-4 is: FIB-4 = (Age [years] × AST [U/L]) / (Platelet count [10^9/L] × √ALT [U/L]). Where AST is aspartate aminotransferase, ALT is alanine aminotransferase, and the platelet count is expressed in 10^9/L. The acMASH were calculated for all subjects with the following formula: acMASH = AST (U/L)/Serum Cr (μmol/L)*10.

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Statistical Analysis

Qualitative variables were expressed in terms of frequencies, while continuous variables were summarized as mean ± standard deviation (SD) or median (range), depending on the context. To compare group means, independent samples t-tests, unpaired t-tests with Welch's correction, and Mann-Whitney tests were employed. Pearson and Spearman correlation coefficients were used as appropriate. To investigate the relationship between GERD and hepatic steatosis, logistic regression analysis was performed. All statistical analyses were carried out using GraphPad Prism 8, with a significance level set at $p < 0.05$ for all tests.

Results

Demographic Characteristics of Study Participants

The study population included subjects with a history of cholelithiasis and cholecystectomy, categorized into two groups: subjects with GERD using anti-reflux medications (Group 1) and individuals without GERD (Group 2). A summary of demographic data for the entire cohort, as well as for each group, is presented in **Table 1**.

Table 1. Baseline Characteristics of Study Participants.

Variable	*All Subjects (N=564)*	*Group 1: GERD (N=77)*	*Group 2: without GERD (N=487)*	*p-value*
Age (mean ± SD)	58.37 ± 15.52	63.62 ± 12.87	57.54 ± 15.76	0.0003**
Female (N)	432	48	384	0.0023**
Diabetes (N)*	145	51	259	0.0841
Hypertension (N)	310	26	119	0.0362**
Smoke (N)	256	39	217	0.99
Advanced Fibrosis (based on LSM, N)	81	12	69	0.8614
LSM	7.49 ± 7.84	8.13 ± 8.04	7.39 ± 7.81	0.4495
CAP	283.12 ± 62.29	278.45 ± 63.41	283.85 ± 62.15	0.4880
Weight*	90.54 ± 25.58	90.38 ± 19.53	90.57 ± 26.43	0.9419
Height*	162.92 ± 8.98	163.68 ± 8.49	162.80 ± 9.06	0.4063
Waist Circumference*	109.45 ± 17.32	111.33 ± 12.25	109.17 ± 17.97	0.2002
BMI (kg/m²)*	34.00 ± 8.83	33.69 ± 6.69	34.05 ± 9.13	0.6806
Hip Circumference *	116.03 ± 17.78	115.73 ± 14.63	116.08 ± 18.24	0.8571
HDL (mmol/L)	1.35 ± 0.38	1.33 ± 0.36	1.36 ± 0.38	0.5410
Cholesterol (mmol/L)	4.70 ± 1.05	4.57 ± 0.97	4.72 ± 1.06	0.2136
PLT	253.75 ± 74.12	242.55 ± 65.02	255.52 ± 75.36	0.1145
ALT	21.34 ± 13.68	21.47 ± 13.25	21.31 ± 13.76	0.9254
AST	20.77 ± 9.38	21.26 ± 8.41	20.69 ± 9.53	0.5914
ALB (g/L)	39.36 ± 3.48	39.65 ± 3.56	39.31 ± 3.46	0.4369
ALP	84.92 ± 34.37	88.32 ± 25.01	84.38 ± 35.61	0.2309
Total Bilirubin (umol/L)	7.80 ± 4.93	9.15 ± 6.60	7.59 ± 4.58	0.0489**
BUN (mmol/L)	5.70 ± 2.24	6.55 ± 2.63	5.56 ± 2.14	0.0023
Cr (umol/L)	76.82 ± 28.18	88.62 ± 43.33	74.95 ± 24.50	0.0084
Globulin (g/L)	31.01 ± 4.42	30.57 ± 4.26	31.07 ± 4.44	0.3415
Glucose (mmol/L)	6.01 ± 2.15	6.16 ± 2.38	5.99 ± 2.11	0.5499
GGT (IU/L)	34.10 ± 62.38	41.83 ± 49.27	32.88 ± 64.17	0.1595
HbA1c *	6.08 ± 1.23	6.23 ± 1.24	6.06 ± 1.23	0.2679
acMASH	2.96 ± 1.63	2.69 ± 1.26	3.00 ± 1.68	0.0557
FIB-4	1.24 ± 0.79	1.40 ± 0.74	1.21 ± 0.80	0.0382**

*had missing in the dataset. ** Statistically significant.

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Our study cohort consisted of 564 participants who had a history of cholelithiasis and cholecystectomy, including 432 females (76.60%) and 132 males (23.40%). The mean age was 58.37 ± 15.52 years. Anthropometric measurements revealed an average BMI of 33.999 ± 8.83 kg/m², a mean waist circumference of 109.45 ± 17.32 cm, and an average hip circumference of 116.03 ± 17.78 cm.

Comorbidities were prevalent among the participants, with 54.96% reporting a history of hypertension, 25.71% having diabetes mellitus, and 12% classified as pre-diabetic. Additionally, 45.39% of the cohort were either current smokers or had a history of smoking.

Laboratory findings showed a mean total cholesterol level of 4.70 ± 1.05 mmol/L and a mean HDL cholesterol level of 1.35 ± 0.38 mmol/L. The average HbA1c was 6.08 ± 1.23%, indicating that a substantial proportion of the participants had abnormal glucose metabolism.

Moreover, 81 subjects identified with advanced liver fibrosis based on LSM, and the mean LSM in all subjects was 7.49 ± 7.84 kPa. This subgroup demonstrated a mean CAP score of 283.12 ± 62.29 dB/m, consistent with significant hepatic steatosis.

Notably, there were significant missing values for BMI and waist circumference across both groups, limiting the ability to compute hepatic steatosis index (e.g., HSI).

Comparisons Between Groups

Liver function tests among subjects without GERD (Group 2) revealed a mean ALT level of 21.31 ± 13.76 IU/L, an AST level of 20.69 ± 9.53 IU/L, and a GGT level of 32.88 ± 64.17 IU/L. Assessments in this group showed a mean platelet count of 255.52 ± 75.36 × 10^9/L and a mean albumin level of 39.31 ± 3.46 g/L, reflecting generally preserved liver synthetic function.

Using an independent samples t-test, we compared key variables between Group 1 and Group 2. There were statistically significant differences in demographic factors, including age, female gender, and presence of hypertension (**Table 1**).

Correlation Analyses

Spearman correlation analyses were performed to evaluate relationships between CAP, FIB-4, and acMASH scores with using anti-reflux medications. CAP and GERD: CAP score was not correlated with using anti-reflux medications (Spearman's $\varrho = -0.025$, $p = 0.56$), suggesting that greater hepatic steatosis was not associated with GERD symptoms. FIB-4 and GERD: FIB-4 scores showed a weak but significant correlation with using anti-reflux medications (Spearman's $\varrho = 0.12$, $p < 0.01$). GERD and acMASH: acMASH score, representing histological features of metabolic steatohepatitis, was not associated with using anti-reflux medications (Spearman's $\varrho = -0.060$, $p = 0.16$). **Table 2** summarizes the key findings of correlation analysis.

Table 2. Correlation and Regression Analyses Results.

Variable	*Correlation with using anti-reflux medications (ρ)*	*Regression Odds Ratio (95% CI)*	*p-value*
CAP	-0.025	0.9981 (0.9939 to 1.002)	0.3748
FIB-4	0.12	0.9594 (0.6126 to0 1.426	0.8461
acMASH	-0.060	0.9382 (0.7571 to 1.131)	0.5326

Regression Analysis

To explore the predictors of GERD among these patients, we recommend a logistic regression analysis. Using anti-reflux medications for GERD as a dichotomous variable (present/absent) can be used as the dependent variable. Independent variables could include CAP, FIB-4, acMASH scores, age, sex, and diabetes and hypertension. A multivariable logistic regression model will allow adjustment for potential confounders and enable estimation of the odds ratios for each independent variable.

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The findings highlight associations between GERD and markers of hepatic steatosis and fibrosis, suggesting overlapping pathophysiological pathways. **Table 2** summarizes the key findings of correlation and regression analyses.

Discussion

The intersection of GERD, hepatic steatosis, and prior cholelithiasis presents a uniquely challenging domain in gastroenterology and hepatology. This study evaluated this intricate relationship, examining the potential correlation between GERD determined by anti-reflux medication usage and hepatic steatosis in patients with a history of gallstones and cholecystectomy. The results provide a perspective, offering both clarity and questions for future investigation.

GERD and hepatic steatosis share overlapping etiologies, driven by common risk factors such as obesity, insulin resistance, and metabolic syndrome [14,15]. Obesity, in particular, exacerbates GERD through increased intra-abdominal pressure while fueling hepatic fat accumulation via systemic inflammation and altered lipid metabolism [16]. Meta-analyses by Wijarnpreecha et al. [8] and Xue et al. [9] underscore the heightened risk of MASLD in GERD patients, with pooled odds ratios suggesting a significant association between these conditions. However, our study did not find a significant correlation between anti-reflux medication use and hepatic steatosis, as indicated by similar CAP values across groups. This finding aligns with the hypothesis that while GERD and hepatic steatosis are interrelated, their interaction is mediated by shared risk factors rather than direct pharmacological influences of anti-reflux medications.

The weak correlation observed between FIB-4 scores and anti-reflux medication use warrants attention. While the correlation is not definitive, it raises pertinent questions about the long-term impact of these medications, particularly in patients at risk for advanced fibrosis. Anti-reflux medications have been implicated in altering gut microbiota and systemic inflammation—factors that could influence hepatic fibrogenesis [17–19]. However, the absence of significant associations in CAP and acMASH scores reinforces the need for further longitudinal studies to clarify these interactions.

Patients with a history of cholelithiasis and cholecystectomy represent a unique population with disrupted bile acid metabolism and altered gut microbiota [20]. These changes could independently modulate GERD and hepatic steatosis progression [21,22]. Gallstones, linked to metabolic syndrome, underscore the metabolic interdependence of GERD and hepatic steatosis [23]. Understanding how bile acid dynamics interact with anti-reflux treatments is critical, as such insights could guide therapeutic strategies in this high-risk group.

PPIs and other anti-reflux therapies are pivotal in managing GERD [11]. Yet, concerns about their long-term safety, including potential metabolic side effects, remain. While this study did not find significant correlations between anti-reflux medications and hepatic steatosis, the weak association with fibrosis indicators like FIB-4 suggests that vigilance is required. Future research should consider stratifying patients by duration and intensity of anti-reflux medication use to explore dose-dependent effects on hepatic outcomes.

Moreover, limitations in missing BMI and waist circumference data restricted the calculation of hepatic steatosis indices like HSI, which could have enriched the analysis. Future studies should aim to address these gaps to enhance diagnostic precision.

This study highlights the importance of a multifaceted approach to managing GERD and hepatic steatosis, particularly in post-cholecystectomy patients. Lifestyle interventions, including weight management, dietary modifications, and physical activity, should remain central to therapy, complemented by pharmacological treatments. Anti-reflux medications, while effective in alleviating GERD symptoms, should be prescribed with awareness of their potential metabolic implications.

Future research should prioritize longitudinal designs to elucidate the temporal relationship between GERD, hepatic steatosis, and fibrosis. Additionally, studies investigating the interaction between bile acid metabolism, gut microbiota, and anti-reflux therapies could yield transformative insights. Exploring novel therapeutic agents targeting shared pathways in GERD and hepatic steatosis, as well as refining non-invasive diagnostic tools, will further enhance patient care.

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Conclusion

This cross-sectional study highlights no significant differences in hepatic steatosis or fibrosis between GERD subjects who are anti-reflux medication users and subjects without GERD among patients with prior cholelithiasis and cholecystectomy. While FIB-4 showed a weak correlation with GERD, CAP and acMASH scores were not significantly associated.

Authors' Contributions: MS: Reviewing the literature, Methodology, Investigation, Conceptualization, Data curation, Formal analysis, Writing—the original draft, review & and editing

Institutional Review Board Statement: The studies involving human participants were reviewed and approved by the Centers for Disease Control and Prevention. The participants provided their written informed consent to participate in this study. The NHANES database was approved by the Ethics Review Committee of the National Center for Health Statistics (Protocol #2018-01 (Effective beginning October 26, 2017), Continuation of Protocol #2011-17 (Effective through October 26, 2017)).

Data Availability: Data is available at the official website of NHANES (https://www.cdc.gov/nchs/nhanes/index.htm).

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Conflict of Interest: The author declare that they have no conflict of interest.

Animal Studies: Not applicable.

Research Involving Recombinant DNA: Not applicable.

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