

Non-aspirin NSAIDs use is associated with lowering of liver fibrosis scores in patients with fatty liver disease

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Abstract

Only a few studies are available with appropriate data on the effects of non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) use in patients with fatty liver disease. We performed a retrospective study of 1347 patients with imaging studies that showed fatty liver disease from 2016 through 2019. We then determined the change in validated indices using Fibrosis-4 (FIB4) and NAFLD fibrosis score (NFS). Patient clinical information, including NSAIDs use, was collected at baseline and then yearly. Using generalized linear models, we estimated the association between non-aspirin NSAIDs use and change in baseline indices. Non-aspirin NSAIDs use was found to be associated with significant lowering of FIB-4 score (0.596 units lower, p-value <0.0001) and NFS (0.431 units lower, p-value 0.0027) every year.

In this retrospective study of patients with fatty liver disease found on imaging, non-aspirin NSAID use was associated with lowering of fibrosis scores, suggesting that NSAID use might be associated with a lower risk for advanced fibrosis in fatty liver disease.

Keywords: Fatty liver disease; NSAIDs; Aspirin; Ibuprofen; liver fibrosis; Advance liver disease, Cirrhosis, liver fibrosis indices, NAFLD score, Fibrosis-4 score

1. Introduction

Fatty liver disease is the presence of fatty infiltration of the liver. Over time, about 10-25% of patients with fatty liver disease will progress to advanced fibrosis, cirrhosis, hepatocellular carcinoma, and death [1]. The gold standard to diagnose fatty liver disease and fibrosis is by liver biopsy. However, because the method is invasive, some validated scoring systems are often used to predict the stage of liver fibrosis that could be seen if biopsy was performed. An example of such scoring systems includes Aspartate aminotransferase (AST) to Platelet Ratio (APRI), Fibrosis-4 (FIB4) and NAFLD fibrosis score (NFS) [2].

Hepatic steatosis is usually seen in imaging studies with liver ultrasound, abdominal computed tomography or Proton-Magnetic resonance spectroscopy. When available, magnetic resonance elastography, or vibration controlled elastography can also be used to determine the severity (stage) of fibrosis [3].

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In one prospective cohort study of 361 biopsy-proven Nonalcoholic fatty liver disease (NAFLD) patients, daily aspirin use was associated with less risk of progression to fibrosis when compared with non-daily use [4]. In the same study, the use of non-aspirin NSAIDs was not associated with risk for advanced fibrosis, although this was not the primary objective in that study. Another cross-sectional study of 1856 US adult patients with the suspected chronic liver disease showed that aspirin users had lower indices (FIB4, APRI, and NFS) of liver fibrosis among them [5]. Finally, in a murine model study, the result suggested that antiplatelets inhibit the platelet-derived growth factor- β , which activates the hepatic stellate cells responsible for hepatic fibrosis [6]. It is known that aspirin has an irreversible antiplatelet effect, while other NSAIDs like ibuprofen have a reversible antiplatelet effect.

Despite the growing incidence and burden of fatty liver disease in the USA -25% in general population and 56% in patients with Diabetes Mellitus type 2 and non-alcoholic steatohepatitis (NASH) with Cirrhosis being the second most common cause of liver transplantation in USA, there are no FDA approved medication to prevent the progression of fatty liver disease or reverse the steatosis, fibrosis and inflammation in these patient populations. The data supporting the potential hepatoprotective effect of NSAIDs in liver disease are limited. Therefore, we investigated the association between non-aspirin NSAIDs use and risk of fatty liver progression to advanced fibrosis.

2. Material and methods

2.1. Study Population

Patients 18 years of age or older in the HCA Healthcare databank system (180 hospitals) with imaging studies that showed fatty liver from January 2016 to January 2019. Imaging studies suggesting fatty liver includes Computed tomography (CT), ultrasonography (US), and magnetic resonance imaging (MRI). Sunrise Hospital-Mountainview Institutional Review Board approved this study with a waiver of documented informed consent.

All patients were de-identified, and the following variables were collected at their baseline and subsequent visits: demographic (age, gender, and race), Medication [aspirin, non-aspirin NSAIDs (ibuprofen, naproxen, ketoprofen, diclofenac, and indomethacin), Statins (atorvastatin, simvastatin, and rosuvastatin)], comorbidities [coronary artery disease (CAD), congestive heart failure (CHF), diabetes mellitus (DM)], and laboratory parameters required for the calculation of the validated non-invasive indices of liver fibrosis FIB4 and NFS [7-8]. We did not use magnetic resonance elastography or vibration controlled elastography to determine the magnitude of the stage of liver fibrosis.

We included only patients who had the needed data and variables to calculate the validated indices every year. We also excluded patients with the following history: unclear or heavy alcohol use history, documented history of alcoholic hepatitis, cirrhosis, hemochromatosis, Wilson's disease, polycystic ovary syndrome, sleep apnea, hypothyroidism, viral hepatitis, autoimmune hepatitis, drug-associated hepatitis, and hepatocellular carcinoma. Based on these criteria, we identified 1347 patients with fatty liver disease.

2.2. NSAIDs use

Aspirin and non-aspirin use (ibuprofen, naproxen, ketoprofen, diclofenac, indomethacin) were confirmed by medical record review at every subsequent hospitalization. Only patients who continued to report use at all hospitalization from the year 2016 to 2019 were included. In our cohort, the cited reasons and associated diagnoses for NSAID use included CHF (0.15%), CAD (0%), and others (99.85%).

Radiologic diagnosis of fatty liver disease

US: hyperechoic texture, fatty infiltration, increased echogenicity, hepatomegaly, intra-hepatic vascular blurring (sensitivity 85%, specificity 94%, decrease sensitivity in morbid obesity) [9-10-11].

CT: reduced attenuation in the liver parenchyma, intrahepatic fat accumulation (Sensitivity 82%, Specificity 100%, non-contrast is more specific)

MRI: hepatic steatosis (Sensitivity 76%, Specificity 87%) [11-12].

2.3. Fibrosis score

Advanced fibrosis is a known prognostic factor of poor outcomes, but determining fibrosis with biopsy is limited because of the invasive nature. Thus, non-invasive screening indices that only require clinical parameters are often used

for risk stratification. Using a lower cutoff value of 1.45, a FIB4 score of less or equal to 1.45 correlates with a negative predictive value of 90%, while a FIB4 cutoff value of greater or equal to 3.25 have 97% specificity. NFS cutoff value of less than or equal to -1.455 has a negative predictive value of 88% while cutoff value that is greater or equal to 0.676 has a positive predictive value for advanced fibrosis of 82% [11].

2.4. Outcomes

All included patients had sufficient laboratory testing and clinical data needed to calculate NFS or FIB-4 scores each study year. Patients who had missing clinical or laboratory data were excluded from the cohort. Patients were excluded from analysis if their baseline FIB-4 score was greater or equal to 1.45 or if baseline NFS score was equal or greater than > 0.67. The primary outcomes were defined as an increase or decrease from baseline fibrosis scores. A secondary analysis was performed in different race, gender, and with diabetes type 2 patients.

2.5. Statistical analysis

Data are expressed as means or numbers (N) with percentages. To test for normality for age between non-aspirin NSAID use, we used Shapiro-Wilk Test and the Kruskal-Wallis test. A generalized linear model was used to determine the mean indices score at baseline and each subsequent year.

3. Results

3.1. Baseline Characteristics

Table 1 Describes the Baseline characteristics of patients in the study (n=1347).

Table 1 Baseline clinical and demographic characteristics.

| Characteristics | N = 1347 (100%) |
|--------------------------------------|-----------------|
| Mean Age | 40 |
| Gender | |
| Male | 504 (37%) |
| Female | 843 (63%) |
| Mean BMI | 34 |
| Ethnicities | |
| Black | 114 (9%) |
| White | 788 (58%) |
| Other | 445 (33%) |
| NSAIDs Use | |
| Aspirin | 138 (10%) |
| Non-Aspirin | 1209 (90%) |
| Medical Conditions | |
| Non DM | 1123 (83%) |
| DM | 224 (17%) |
| CHF | 2 (<1%) |
| CAD | 0 (0%) |
| HLD | 0 (0%) |
| Mean Baseline score of Cohort | |
| NFS | -1.94 |
| FIB-4 | 1.10 |

Abbreviations: NFS, NAFLD Fibrosis Score; fib-4, Fibrosis-4; BMI, Body Mass Index; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; DM, diabetes mellitus; CHF, Congestive Heart Failure; CAD, Coronary Artery Disease; HLD, Hyperlipidemia.

3.2. Model Analysis of different Parameters

Table 2 Describes the change in validated scores based on different parameters. NSAIDs use was associated with lowering of validated indices (p-value <0.05).

Table 2 Model Analysis of different Parameters.

| Parameters | Model Analysis | p-Value |
|-----------------------|-------------------------------|---------|
| NSAIDs Use (N) | | 0.039 |
| Non-DM | 1123 | |
| DM | 224 | |
| FIB-4 | Change in Mean Baseline Score | |
| Gender | -0.051 | 0.57 |
| NSAIDs use | -0.596 | <0.0001 |
| Black | -0.433 | 0.42 |
| Other | -0.054 | 0.62 |
| Hispanics | -0.277 | 0.0099 |
| NFS | Change in Mean Baseline Score | |
| Gender | -0.068 | 0.44 |
| NSAIDs use | -0.431 | 0.0027 |
| Black | 0.194 | 0.23 |
| Other | -0.234 | 0.03 |
| Hispanics | -0.231 | 0.03 |

Abbreviations: NFS, NAFLD Fibrosis Score; fib-4, Fibrosis-4; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; DM, diabetes mellitus.

Table 3 compares histological staging with corresponding noninvasive scores.

Table 3 Fibrosis Severity Scale and corresponding noninvasive staging Cohort Mean indices at baseline (FIB-4: 1.10; NFS: -1.94).

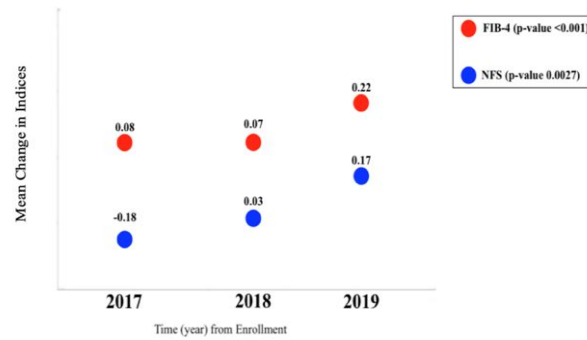
| Histologic Stage | FIB4-Index | NAFLD Score |
|-------------------------------------|------------|----------------------------------|
| F0-F1 No Fibrosis or Mild Fibrosis | <1.45 | < -1.455 |
| F1-F2 Moderate Fibrosis | 1.45-3.25 | -1.455-0.675 indeterminate score |
| F3-F4- Severe Fibrosis or Cirrhosis | >3.25 | >0.675 |

Noninvasive tests of hepatic fibrosis are used to predict the stage of liver fibrosis that could be seen if biopsy was performed.

The cohort in this study had a Baseline mean FIB4 of 1.10 and mean NFS of -1.94 which corresponds with no fibrosis or mild fibrosis at baseline.

Figure 1 Generalized Linear model analysis.

Non-aspirin NSAIDs use was associated with reduction in mean indices score during each study year (p-value <0.05).



Abbreviations: FIB-4, Fibrosis-4; NFS, NAFLD Fibrosis Score.

Figure 1 Change in validated scores with non-aspirin NSAID use.

4. Discussion

In our retrospective study of patients with fatty liver disease seen on imaging studies, non-aspirin NSAIDs use was associated with lowering of FIB-4 and NFS scores every year. Majority of the patients in the study were taking non-aspirin NSAIDs for non-cardiac reasons, which suggest that any observed changes was mostly due to non-aspirin effect. In another prospective study, similar findings were reported in biopsy-proven NAFLD patients who were taking aspirin daily [5]. The clinical data needed to fully support the hepato-protective effect of aspirin or other non-aspirin NSAIDs is still limited. The current study adds a piece of retrospective evidence to support the potential benefit of NSAIDs in fatty liver disease.

The observed benefit could be due to mechanisms previously described in murine models, which suggest that platelets stimulate the stellate cells to initiate fibrosis via platelet-derived growth factor (PDGF). NSAIDs with reversible or irreversible antiplatelet effect could potentially prevent such hepatic fibrosis by inhibition of PDGF [6].

Given the prevalence of fatty liver disease in the United States and worldwide (10-46%), NSAIDs potential benefit could be profound in these patient population. Thus, further research is needed to better understand the potential benefit and bleeding risk of NSAIDs.

We would like to mention that there have being studies in the literature with Pioglitazone in patients with NAFL/NASH confirmed on liver biopsy in patients with or without Diabetes mellitus type 2 which showed complete resolution of NASH in 51% of the patients with placebo subtracted difference of 32% [3]. This improvement correlated with improvement of adipose tissue insulin resistance and increased adiponectin level. Similar resolution of NAFL/NASH was observed in patients with Diabetes Mellitus type 2 treated with Liraglutide. 39% of patients had resolution of NASH. This effects were related to improving the body weight and, glycemic control and insulin sensitivity with Liraglutide [3].

We acknowledge that there might be limitations to this study, which are not limited to the following:

- Fatty liver diagnosis was based on imaging reports of different modalities, which could add variability in the observed results.
- Because we did not use magnetic resonance elastography or vibration controlled elastography to determine the severity of liver fibrosis, some patients in the cohort could potentially have different degree of fibrosis at baseline
- Differences in medication dose and duration of use was not accounted for in this study.
- The length of the study is not sufficient to fully determine the clinical significance of lowered fibrosis scores.
- Recall bias and exposure misclassification was not accounted for in this study. However, we tried to minimize this risk by careful examination of medical records.
- The presence of other conditions not accounted for or not yet diagnosed may also cause confounding in the observed study results.
- Non-invasive indices are not the gold standard for evaluating hepatic fibrosis; however, they have demonstrated utility for this purpose.

5. Conclusion

Non-aspirin NSAIDs use is associated with lowering of hepatic fibrosis scores. In a group of patients with fatty liver disease on imaging, non-aspirin NSAIDs use was associated with significant change in validated fibrosis indices.

Compliance with ethical standards

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Disclosure of conflict of interest

None to be disclosed for any of the authors.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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