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NAFLD Patients have Limited Access to GLP1 Agonists and SGLT2 Inhibitors: NHANES-Transient Elastography 2017-2018

Truong E[1,2], Cook-Wiens G[2], Yang JD[3], Setiawan VW[4], Harrison SA[5], Alkhouri N[6], and Noureddin M[7,8,*]

[1]Department of Medicine, California

[2]Cedars-Sinai Medical Center, Los Angeles, California

[3]Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, California

[4]USC Research Center for Liver Diseases, University of Southern California School of Medicine, California

[5]Radcliffe Department of Medicine, University of Oxford, California

[6]Arizona Liver Health, Phoenix, Arizona, California

[7]Houston Liver Institute, Houston, Texas, United States

[8]Houston Research Institute, Houston, Texas, United States

***Corresponding author:**

Mazen Noureddin,
Director Houston Research Institute, Director Houston Liver Institute, 1155 Dairy Ashford, Houston, Texas 77079, United States, Tel: 310-423-6000;
E-mail: noureddinmd@gmail.com

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1. Abstract

1.1. Background and Aims: This study analyzed medications among NAFLD (controlled attenuation parameter ≥302 dB/m) ± diabetes or advanced fibrosis (AF, stiffness ≥9.7 kPa).

1.2. Method: 2017-2018 NHANES data were analyzed. Exclusion criteria were age<18, high alcohol consumption (≥7/14 drinks/week for females/males, respectively), or viral hepatitis.

1.3. Results: Of 3,899, 26.3% had NAFLD, 4.8% AF, 16.7% diabetes. Increased medications and classes were associated with NAFLD and AF. Diabetics had low usage of GLP1 agonists and SGLT2 inhibitors regardless of NAFLD status.

1.4. Conclusion: Individuals with NAFLD or AF had higher risk of polypharmacy, but decreased usage of potentially beneficial medications including GLP1 agonists and SGLT2 inhibitors.

2. Introduction

Affecting approximately 25% of the general population, non-alcoholic liver disease (NAFLD) is the leading cause of chronic liver disease worldwide and one of the leading indications for liver transplantation in the United States and Europe [1-5].

In this study, we analyzed medication use among those with NAFLD (defined as control attenuation parameter (CAP) via vibration-controlled transient elastography (VCTE or FibroScan®) ≥302 dB/m based on Youden's index by Eddowe's et al) with or without diabetes or advanced fibrosis (AF, defined as Liver Stiffness Measurement (LSM) via VCTE ≥9.7 kPa based on Youden's index) in the National Health and Nutrition Examination Surveys (NHANES) from 2017 to 2018 [6]. We aimed to determine associations between disease presence and number of medications and medication classes. We hypothesized that number of medications and medication classes increased among NAFLD with diabetes or advanced fibrosis compared to those among NAFLD without diabetes or advanced fibrosis.

3. Methods

Conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention, NHANES is a multistage, cross-sectional study of the noninstitutionalized and nonmilitary U.S. population that incorporates interviews and physical examinations including laboratory blood testing and VCTE.

We analyzed data from the NHANES cycle conducted from 2017 to 2018. Respondents included in analysis were ≥18 years and under-

went VCTE examination. Respondents were excluded for viral hepatitis B, C, D, or E, or excessive alcohol consumption (≥7/14 drinks/week for females/males, respectively). Steatosis was determined based on VCTE CAP score of ≥302 dB/m based on Youden's index per Eddowe's et al.6 Fibrosis cutoffs were determined using the same reference.

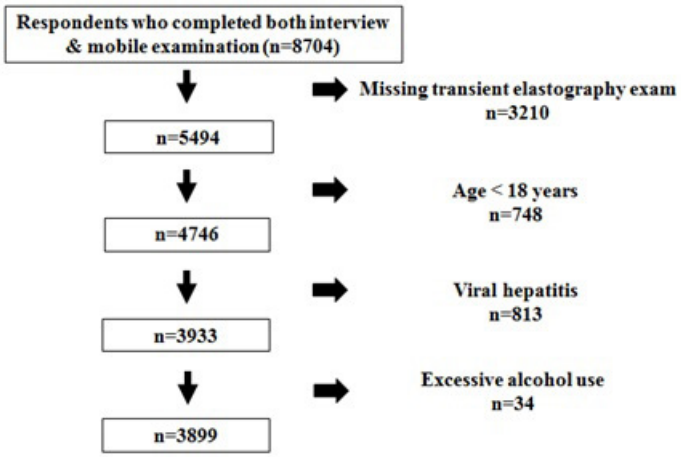
Population estimated were computed from the 2017-2018 NHANES survey weights. Descriptive statistics were reported as mean (± standard deviation) for continuous variables and proportion (95% confidence interval) for categorical variables. To compare two categories, weighted Student's t tests and Rao-Scott Chi-squared tests were used for continuous and categorical variables, respectively. Two-sided P value with 0.05 significance level was used. Analyses were performed by utilizing survey procedures and testing in R and SAS version 9.4 (SAS Institute, Cary, NC). Microsoft Excel was used to generate figures.

4. Results

A total of 3,899 subjects who underwent both interview and examination were included for analysis after exclusion for lack of VCTE exam (3210), age < 18 years (n=748), viral hepatitis (n=813), and excessive alcohol consumption (n=34) (Supplementary Figure 1).

Of 3899 subjects, 1025 (26.3%) had NAFLD, 225 (4.8%) had AF, and 651 (16.7%) had diabetes. Among 2,176 subjects with data on medication use, increased medications and medication classes were significantly associated with NAFLD (odds ratio (OR) for an increase of 1 medication=1.16 (95% CI: 1.10, 1.21; p<0.001) and AF (OR=1.11 (95% CI: 1.05, 1.19; p=0.0023).

Table 1 illustrates number of medications and medication classes amongst all subjects with and without NAFLD and AF, as well as amongst diabetics only with and without AF. Mean number of medications were 4.2/3.0 for NAFLD/non-NAFLD (95% CI 4.0-4.4/2.8-3.2) and 4.3/3.0 for AF/non-AF (95% CI 3.6-5.1/3.1-3.5). Compared to non-NAFLD respondents, those with NAFLD reported significantly higher use of metabolically beneficial medications such as statins, metformin, angiotensin converting enzyme(ACE)-inhibitors/angiotensin II receptor blockers (ARBs) ± thiazides, diuretics, antiplatelets, β-blockers, Ca2+ channel blockers, dipeptidyl peptidase 4 (DPP4) inhibitors ± metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors ± metformin, fibrates, glucagon-like peptide-1 (GLP1) agonists, insulin, sulfonylureas, and aspirin. Among diabetics with NAFLD, those with AF had a significantly lower average number of prescription medications than those without AF (AF 4.8 vs non-AF 5.4, p=0.0117). Nevertheless, among diabetics, usage of GLP1 agonists and SGLT2 inhibitors was low regardless of NAFLD status (GLP1 agonists: 1.7% [95% CI 0.64-3.51] NAFLD vs. 0.6% [95% CI 0.04-2.33] non-NAFLD, SGLT2 inhibitors: 4.7% [95% CI 1.68-9.9] NAFLD vs. 0.6% [95% CI 0.14-1.54] non-NAFLD).



Supplementary Figure: Flowsheet for Study Inclusion

Table 1: Number of Medications and Medication Classes among NHANES Respondents

	Disease Presence	Variable	Mean	Standard Error of Mean	95% CL for Mean	
Among all subjects (regardless of diabetes presence)	**NAFLD**	Number of medications	4.208*	0.105	3.984	4.431
		Number of medication classes	1.312*	0.093	1.112	1.511
	Non-NAFLD	Number of medications	3.009*	0.111	2.771	3.246
		Number of medication classes	0.519*	0.035	0.445	0.593
	AF	Number of medications	4.338*	0.349	3.594	5.083
		Number of medication classes	1.677*	0.173	1.309	2.045
	Non-AF	Number of medications	3.304*	0.092	3.109	3.499
		Number of medication classes	0.680*	0.038	0.6	0.76
Among diabetics only	**AF**	Number of medications	4.834*	0.547	3.668	6
	Non-AF	Number of medications	5.403*	0.236	4.9	5.906

AF=advanced fibrosis. CL=confidence limits. NAFLD=non-alcoholic liver disease.

*Denotes p<0.05

5. Discussion

Individuals with NAFLD or AF had increased polypharmacy in terms of overall medications and medication classes. Such medications are generally associated with cardiovascular disease and metabolic syndrome, both of which are well-known risk factors associated with NAFLD. As this study is cross-sectional, no conclusions regarding causality can be drawn; nevertheless, these medications are associated with beneficial cardiometabolic effects. Given the study's nationally representative nature, it possesses high clinical generatability and applicability. Conducted on the largest, nationally representative cohort to date with VCTE-proven NAFLD, this study encompassed accurate staging of steatosis and fibrosis via CAP and LSM, respectively.

Interestingly, diabetics with NAFLD and AF had significantly lower average number of prescription medications than those without AF. This may in part be attributable to the natural disease course of NAFLD progression, as those with cirrhosis may experience arterial hypotension that render hypertensive medications unnecessary [7]. In addition, usage of GLP1 agonists and SGLT2 inhibitors were rather low amongst diabetics, though the prevalence of metformin and other diabetic medication use remained similar to prior data [8]. Underutilization of GLP1 agonists and SGLT2 inhibitors may in part be driven by current treatment recommendations for diabetes with metformin, rather than GLP1 agonists or SGLT2 inhibitors, remaining the first-line pharmacologic therapy.9 Furthermore, both GLP1 agonists and SGLT2 inhibitors possess numerous side effects and remain costly, thereby limiting access [9-12].

6. Conclusion

In conclusion, those with NAFLD or AF are at significantly higher risk of polypharmacy, though causality between cardiometabolic comorbidities and NAFLD remains unclear. Although GLP1 agonists and SGLT2 inhibitors have been shown to be mutually beneficial in both NAFLD and diabetes, these medications are underutilized. This study highlights important considerations in selecting medications for diabetics with NAFLD, especially regarding future combination therapies.

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