World Journal of
Gastroenterology

World Journal of Gastroenterology

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AIMS AND SCOPE

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RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Cohort Study

Medications in type-2 diabetics and their association with liver fibrosis

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Author contributions: Siddiqui MT, Amin H, Al-Yaman W and Singh A were involved in conceptualization, data curation, and project administration; Siddiqui MT, Amin H, Al-Yaman W, Singh A, Chadalvada P and Garg R were involved in writing; Lopez R performed the statistical analysis; all authors were involved in interpretation of the results, reviewing and editing of the draft.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer.

Informed consent statement: This was a retrospective study which involved the chart review. Requirement for individual patient consent was waived by the IRB.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at singha4@ccf.org.

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Abstract

BACKGROUND
The prevalence of nonalcoholic fatty liver disease (NAFLD) is significantly rising worldwide. Type-2 diabetes (T2D) is a major risk factor for NAFLD progression.

AIM
To assess the association of commonly used medications to advanced fibrosis (AF) in patients with biopsy-proven NAFLD and T2D.

METHODS
We used the International Classification of Disease 9th Revision Clinical Modification coding system to identify patients with T2D and included patients who underwent liver biopsy for suspected NAFLD between January 1, 2000 to December 31, 2015. We compared demographics, clinical characteristics, and differences in pattern of medication use in patients who had biopsy-proven AF to those without it. A univariate and multivariate analysis was performed to assess the association of different classes of medication with the presence of AF.

RESULTS
A total of 1183 patients were included in the final analysis, out of which 32% (*n* = 381) had AF on liver biopsy. Mean age of entire cohort was 52 years and majority were females (65%) and Caucasians (85%). Among patients with AF, 51% were on oral hypoglycemics, 30% were on insulin, 66% were on antihypertensives and 27% were on lipid lowering agents for the median duration of 19 mo, 10 mo, 26

mo, and 24 mo respectively. Medications associated with decreased risk of AF included metformin, liraglutide, lisinopril, hydrochlorothiazide, atorvastatin and simvastatin while the use of furosemide and spironolactone were associated with higher prevalence of AF.

CONCLUSION
In our cohort of T2D with biopsy proven NAFLD, the patients who were receiving metformin, liraglutide, lisinopril, hydrochlorothiazide, atorvastatin and simvastatin were less likely to have AF on biopsy, while patients who were receiving furosemide and spironolactone had a higher likelihood of having AF when they underwent liver biopsy. Future studies are needed to confirm these findings and to establish measures for prevention of NAFLD progression in patients with T2D.

Key words: Diabetes medications; Anti-lipid medications; Antihypertensive medication; Fatty liver; Advanced fibrosis

Core tip: Prevalence of non-alcoholic fatty liver disease is increasing worldwide. Certain medications such as HMG-CoA reductase inhibitors (statins) and Angiotensin converting enzyme inhibitors have been shown to be associated with reduction in advanced fibrosis in patients with viral hepatitis. Patients with T2D are at a higher risk of developing advanced fibrosis. Given that these patients require lifelong medications to treat type 2 diabetes, we sought to analyze their association with biopsy proven liver fibrosis. We hope that our findings will help researchers in the future explore and design prospective studies to further enhance our understanding of this association.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been emerging as one of the most important cause of liver disease worldwide, and it is likely to become a leading cause of end-stage liver disease (ESLD) in the near future[1]. The global prevalence of NAFLD has been estimated to be around 25%, affecting nearly 1.8 billion individuals worldwide[2,3], of which 51.6 million are in the United States alone, representing 21.9% of adult United States population[4]. The pathological spectrum of NAFLD can range from benign hepatic steatosis to more severe forms such as non-alcoholic steatohepatitis (NASH), advanced fibrosis (AF), cirrhosis, and ESLD[5]. The subtype of NAFLD characterized by NASH is a potentially progressive liver disease that can lead to cirrhosis, hepatocellular carcinoma, liver transplantation, and death, and result in significant health-care and economic burden[6].

As the epidemics of obesity and type 2 diabetes mellitus (T2D) increase worldwide, the prevalence of NAFLD is rising rapidly[6]. Recently T2D has been recognized as a major risk factor for progressive liver disease, with standardized mortality rates for cirrhosis greater than that for cardiovascular disease[7]. A study by Williamson *et al*[8] showed that 56.9% patients with T2D had steatosis on ultrasonography. After excluding patients with secondary cause of steatosis, prevalence of NAFLD was 42.6% in their population[8]. Independent predictors for NAFLD in their patient population were body mass index (BMI), duration of diabetes, Hemoglobin A1c, triglyceride levels, and metformin use[8]. A meta-analysis of 17 studies involving 10897 patients concluded that the overall prevalence of NAFLD among patients with T2D is significantly higher and optimal management of T2D may play a role in preventing NAFLD[9]. Patients with T2D are usually on a number of prescription medications. These include oral hypoglycemics, insulin, anti-lipid and anti-hypertensive medications. It is known that diabetes mellitus is a risk factor for AF in NAFLD,

however, not all NAFLD patients with diabetes develop AF. This may be due to effects of certain medications used to treat diabetes and dyslipidemia[10]. In one study the use of angiotensin converting enzyme (ACE) inhibitor was observed to reduce the risk of AF in chronic Hepatitis C patients[11]. There is paucity of data on the association of various medications with AF in patients with T2D, which is a well-known risk factor for advanced liver disease. The aim of this study was to assess the association of commonly used medications (anti-lipid, anti-diabetic and anti-hypertensive medications) with AF in patients with T2D and NAFLD.

MATERIALS AND METHODS

Study design
This is a retrospective cohort study.

Data source and patient selection criteria
Our study protocol was approved by Institutional Review Board of the Cleveland Clinic. We used the International Classification of Disease 9th Revision Clinical Modification (ICD-9 CM) coding system and identified the patients with T2D (ICD 9 code: 250.xx) and suspected NAFLD (ICD 9 code: 571.8 and 571.9) from the Cleveland Clinic Electronic Medical Record System. We included patients who were 18 years or older and who underwent liver biopsy between January 1, 2000 to December 31, 2015. The decision to do liver biopsy was based on the clinical judgment of treating physician. Biopsies were reviewed by a group of expert gastroenterology and hepatology pathologists to detect fibrosis. Liver biopsies were classified according to NASH-CRN classification. Fibrosis was staged on a 5-point scale: Stage 0 = no fibrosis, stage 1 = zone 3 perisinusoidal/perivenular fibrosis, stage 2 = zone 3 and periportal fibrosis, stage 3 = septal/bridging fibrosis, and stage 4 = cirrhosis. AF was defined as fibrosis stage 3-4. We excluded the patients who did not have liver biopsy within 24 mo of T2D diagnosis, as well as, those with incomplete medical records or with secondary causes of hepatic steatosis {viral hepatitis, hemochromatosis, α1-antitrypsin deficiency, Wilson disease, lipodystrophy, starvation, on parenteral nutrition, abetalipoproteinemia, and using certain medications (corticosteroids, valproate, and antivirals)} were excluded. Patients were also excluded if they consumed more than 30 g of alcohol per day for males or more than 20 g per day for females. We collected age, gender, patient demographics including race, BMI, systolic and diastolic blood pressure, existing concurrent comorbidities such as hypertension, hyperlipidemia, laboratory results, medications and their duration of use.

Statistical analysis
We used Pearson's chi-square (χ^2) tests or Fisher's Exact to analyze the differences in patient demographics. For continuous variables, we performed a one-way Analysis of Variance (ANOVA) or the non-parametric Kriskal Wallis tests. Findings are reported either as mean ± SD, median (25th, 75th percentiles) or percentage. A multinomial logistic regression analysis was performed to identify the independent clinical factors associated AF. Age, gender, race, BMI, concurrent hypertension, hyperlipidemia, chronic kidney disease, inflammatory bowel disease, deep vein thrombosis, use of oral hypoglycemic medications, insulin, antihypertensive medications, antilipidemic medications, and aspirin were considered for inclusion in the logistic regression model and a stepwise variable selection method was used to choose the final model; variables with $P < 0.10$ were included in the final model. We adjusted for age, gender, race and BMI. SAS (Version 9.4, The SAS Institute, Cary, NC, United States) was used for all analyses and a two-sided P value of less than 0.05 was considered to be statistically significant.

RESULTS

After applying inclusion and exclusion criteria, a total of 1183 subjects were identified and included in the final analysis. Out of these patients, 32.2% (n = 381) had AF (fibrosis score 3-4) on their liver biopsy. The demographics and clinical characteristics of participants are shown in Table 1. The mean age at liver biopsy for our cohort was 52 ± 11 years and 65.7% patients were female. The majority of patients were Caucasians (85.1%) followed by African American (9.2%) and other races (5.7%). Overall mean systolic and diastolic blood pressures (SBP and DBP) in our cohort were 129.6 ± 17.1 mmHg and 73.7 ± 11.0 mmHg, respectively. There was no difference in the SBP between the two fibrosis groups[1] (129.5 ± 16.6 *vs* 129.9 ± 18.2, P = 0.66) but

significant difference existed between the DBP in the two groups (74.5 ± 10.5 *vs* 72.1 ± 11.7, *P* < 0.001). Hypertension and hyperlipidemia were more prevalent in Fibrosis 0-2 group (70% *vs* 57.7%, *P* < 0.001; 68.2% *vs* 49.1%, *P* < 0.001) whereas CKD was more prevalent in Fibrosis 3-4 group (4.6% *vs* 13.6%, *P* < 0.001).

In terms of medications in the AF group (*n* = 381), 51.7% were on oral hypoglycemic, 30.1% were on insulin, 65.4% were on antihypertensive and 37.3% on anti-lipidemic medications for a median duration of 17.4 mo, 8.3 mo, 18.1 mo, and 20.9 mo respectively. Table 2 presents a summary of medication use in our cohort. Figure 1 shows a visual representation of medication usage among the two groups. Unadjusted and adjusted odds ratio (OR) of clinical factors associated with AF have been listed in the Table 3. Amongst oral hypoglycemic medications, Metformin use was associated with decreased risk of AF [OR = 0.64 (0.49, 0.82), *P* < 0.001]. We did not find a statistically significant association between Glipizide (*P* = 0.75), Pioglitazone (*P* = 0.11) or Sitagliptin/Januvia (*P* = 0.79) and the presence of AF. Liraglutide use was also associated with decreased risk of AF [OR = 0.30 (0.14, 0.64), *P* = 0.002]. We did not find a statistically significant association between the use of Detemir/Levemir (*P* = 0.83), Lantus (*P* = 0.14), Humulin (*P* = 0.35) or Byetta (*P* = 0.65) and the presence of AF. Amongst anti-hypertensive medications, use of Lisinopril [OR = 0.74 (0.56, 0.97), *P* = 0.031] and Hydrochlorothiazide [OR = 0.57 (0.43, 0.76), *P* < 0.001] were associated with decreased risk of AF. In contrast, use of Furosemide [OR = 1.9 (1.4, 2.5), *P* < 0.001) and Spironolactone [OR = 3.1 (2.0, 4.6), *P* < 0.001] were associated with increased risk of AF. For other anti-hypertensive medications we did not find any statistically significant association. Amongst anti-lipidemics, use of Atorvastatin [OR = 0.62 (0.44, 0.86), *P* = 0.004] and Simvastatin [OR = 0.61 (0.44, 0.85), *P* = 0.003] were associated with decreased risk of AF. We did not find a statistically significant association for other anti-lipid agents.

DISCUSSION

This study is the first study in the literature exploring the association of different pharmacological modalities used in the treatment of T2D and AF in biopsy-proven NAFLD. Our study highlights the critical findings that certain prescription medications taken by patients with T2D are associated with decreased risk of AF. These medications might be playing a protective role by decreasing the rate of NAFLD progression. In our cohort of patients, oral hypoglycemic like metformin and liraglutide, anti-hypertensive medications like Lisinopril and Hydrochlorothiazide, and anti-lipid medication like Atorvastatin and Simvastatin are associated with decreased risk of AF, suggesting that they could perhaps have a protective effect on NAFLD.

Diabetes is a known cause of NAFLD and advanced liver disease is the most common cause of deaths in patients with T2D, showing a reciprocal relationship between the two. Treatment approaches in T2D mainly include either decreasing insulin resistance (metformin, thiazolidinediones) or increasing circulating insulin levels (exogenous insulin or sulfonylureas)[10,12,13]. A study by Hazlehurst *et al*[14]. explored the role of different classes of antidiabetic medications as a therapeutic disease modifying effect on NAFLD in patients with T2D. They specifically highlighted a promising role of metformin and GLP-1 agonists in treatment of NAFLD[14]. Our observation that Metformin is associated with a decrease in AF might suggests that insulin resistance is likely implicated in the pathophysiology of development of hepatic fibrosis. Metformin is effective as an anti-diabetic drug due to its ability to improve peripheral insulin sensitivity. Lowering blood glucose is achieved by decreasing gluconeogenesis in the liver, stimulating glucose uptake in the muscle, and increasing fatty acid oxidation in adipose tissue[15]. At the molecular level, some of the beneficial effects of metformin have been associated to the phosphorylation and nuclear export of Liver-kinase B1 which activates adenosine monophosphate-activated protein kinase, a regulator of energy metabolism, able to stimulate ATP-producing catabolic pathways (glycolysis, fatty acid oxidation, and mitochondrial biogenesis) and to inhibit ATP-consuming anabolic processes (gluconeogenesis, glycogen, fatty acid, and protein synthesis), leading to decreased glucose levels in the blood and ultimately decreased glucose mediated organ injury[16]. A meta-analysis showed a 50% reduction in Hepatocellular carcinoma (HCC) incidence with metformin use (*n* = 8 studies; OR = 0.50, 95%CI: 0.34-0.73), further strengthening our observation that Metformin likely plays a protective role in liver disease[17]. In addition to Metformin, Liraglutide also showed a decreased risk of AF. Liraglutide is a glucagon-like-peptide 1 (GLP-1) analog that binds to the same receptors as the endogenous metabolic hormone GLP-1 and improves glucose

Table 1 Demographic and clinical characteristics

Factor	Overall (*n* = 1183)		Fibrosis 0-2 (*n* = 802)		Fibrosis 3-4 (*n* = 381)		*P* value
	n	Statistics	*n*	Statistics	*n*	Statistics	
Age at biopsy (yr)	1183	52.0 ± 11.6	802	50.3 ± 11.5	381	55.5 ± 11.1	< 0.001[1]
Gender	1183		802		381		0.017[3]
Female		777 (65.7)		545 (68.0)		232 (60.9)	
Male		406 (34.3)		257 (32.0)		149 (39.1)	
Race	1183		802		381		< 0.001[3]
Caucasian		1007 (85.1)		665 (82.9)		342 (89.8)	
African American		109 (9.2)		97 (12.1)		12 (3.1)	
Other		67 (5.7)		40 (5.0)		27 (7.1)	
Smoking	1173		795		378		0.041[3]
Never		675 (57.5)		477 (60.0)		198 (52.4)	
Former		426 (36.3)		274 (34.5)		152 (40.2)	
Current		72 (6.1)		44 (5.5)		28 (7.4)	
BMI	1183	35.4 ± 8.3	802	35.4 ± 8.1	381	35.2 ± 8.8	0.57[1]
BMI group	1183		802		381		0.59[2]
Normal weight		74 (6.3)		41 (5.1)		33 (8.7)	
Overweight		233 (19.7)		161 (20.1)		72 (18.9)	
Obese		596 (50.4)		413 (51.5)		183 (48.0)	
Severely obese		280 (23.7)		187 (23.3)		93 (24.4)	
SBP	1183	129.6 ± 17.1	802	129.5 ± 16.6	381	129.9 ± 18.2	0.66[1]
DBP	1183	73.7 ± 11.0	802	74.5 ± 10.5	381	72.1 ± 11.7	< 0.001[1]
Hypertension	1183	781 (66.0)	802	561 (70.0)	381	220 (57.7)	< 0.001[3]
Hyperlipidemia	1183	734 (62.0)	802	547 (68.2)	381	187 (49.1)	< 0.001[3]
CKD	1183	89 (7.5)	802	37 (4.6)	381	52 (13.6)	< 0.001[3]
IBD type	1181		802		379		0.29[3]
CD		29 (2.5)		18 (2.2)		11 (2.9)	
UC		14 (1.2)		12 (1.5)		2 (0.53)	
None		1138 (96.4)		772 (96.3)		366 (96.6)	
IBD	1181	43 (3.6)	802	30 (3.7)	379	13 (3.4)	0.79[3]
Stricturing disease	1183	17 (1.4)	802	10 (1.2)	381	7 (1.8)	0.43[3]
DVT	1183	66 (5.6)	802	43 (5.4)	381	23 (6.0)	0.64[3]

[1]ANOVA.
[2]Kruskal-Wallis test.
[3]Pearson's χ^2 test. Statistics presented as mean ± SD or *n* (%). BMI: Body mass index; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; CKD: Chronic kidney disease; CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; DVT: Deep venous thrombosis.

homeostasis *via* its glucose-dependent stimulation of insulin secretion, inhibition of postprandial glucagon secretion and delayed gastric emptying[18]. A recent multicenter, double-blind, randomized, placebo-controlled phase 2 study published by Armstrong *et al*[19] showed that 39% of the patients who received liraglutide and underwent end-of-treatment liver biopsy had resolution of definite NASH compared with 9% of the patients in the placebo group [relative risk 4.3 (95%CI: 1.0-17.7), *P* = 0.01]. Also they noted that 9% of the patients in the liraglutide group had progression of fibrosis compared to 36% in the placebo group [0.2 (0.1-1.0), *P* = 0.04], further supporting the findings of our study.

Another observation made in our study was the protective role of Lisinopril, an angiotensin-converting enzyme, a medication commonly prescribed to lower blood pressure, in patients with T2D. A recent meta-analysis showed that renin angiotensin system inhibitors resulted in a marginally significant reduction in liver fibrosis score [MD = -0.30, 95%CI (-0.62, 0.02), *P* = 0.05] and a significant reduction in liver fibrosis area [MD = -2.36%, 95%CI (-4.22%, -0.50%), *P* = 0.01], hence concluding that these medications perhaps play a more protective role in liver disease[20]. Multiple animal studies have suggested that angiotensin II contributes to hepatic fibrosis by
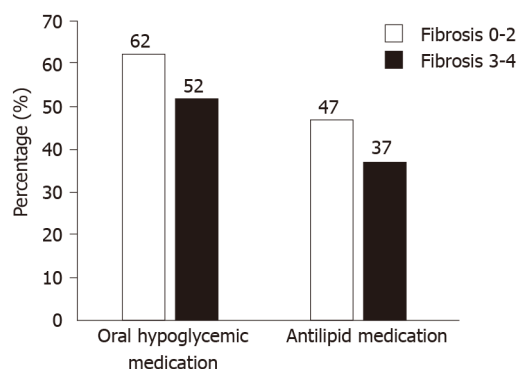
Figure 1 Graphical presentation of differences in medication usage among patients in different fibrosis groups.

interacting with the angiotensin II receptor type 1 (AT1 receptor) leading to the activation of hepatic stellate cells-the main collagen producing cells in the liver[21-23]. One animal model illustrated that inhibition of angiotensin II decreases the generation of reactive oxygen species, resulting in less collagen synthesis by hepatic stellate cells, and downregulates the vascular endothelial growth factor[24]. While another model suggested that angiotensin-receptor blockade leads to downregulation pro inflammatory/profibrotic cytokines[25], thus attenuating liver fibrosis. A study investigating the effect of Ramipril, an ACE inhibitor on the incidence of diabetes suggested that the use of ACE inhibitors may reduce the incidence of hyperglycemia in new diabetics as well as in those with insulin resistance[26]. Hence, this additional benefit that ACE inhibitors provide in diabetics may also contribute in part to the observed reduction in fibrosis in patients with NAFLD.

Our data in a large cohort of well characterized patients with NAFLD also suggests that the use of statins like Atorvastatin and Simvastatin is associated with reduced risk of advanced hepatic fibrosis in NAFLD patients with T2D. In the presence of NAFLD and hyperinsulinemia, there is accumulation of lipid molecules in the liver which further leads to inflammation and lipotoxicity[27], playing a fundamental role in the pathogenesis of hepatic steatosis, steatohepatitis and fibrosis. Statins, the mainstay of lipid-lowering therapy, improves liver outcomes by lowering lipids and lipotoxicity[28]. Apart from that, statins have also been reported to reduce cardiovascular risks and mortality in patients with NAFLD[29]. In a Swedish study that explored changes in liver histology over time among patients with NAFLD, there was less fibrosis in patients prescribed a statin[30]. However, previous studies have concluded that statin should not be used for NASH alone without the association of dyslipidemia[31]. For the simplification of the medication classification furosemide and spironolactone were considered under antihypertensive group, while these medications do lower blood pressure, they are often used primarily as diuretics. It is possible that patients were receiving these medications for advanced liver disease associated fluid overload or ascites.

The prevalence of NAFLD has progressively increased over the past 10 years, making it a significant health burden and the treatment of NAFLD is of prime concern to health care professionals and patients due to significant mortality and morbidity it implies[32]. Treatment is focused on lifestyle changes and managing the associated comorbidities. Lifestyle modification includes attention to patient's diet by promoting intake of fruits and vegetables and avoiding high fat content; and increasing physical activity[33,34]. Obesity treating drugs like Orlistat and bariatric surgery may also help in selected cases in achieving weight loss that can help in NAFLD[34,35]. Other measures include insulin sensitizers, drugs that reduce blood lipids, glucagon-mimetics, drugs that may reduce fibrosis, angiotensin receptor blockers, and medicines believed to reduce endoplasmic reticular stress such as vitamin E, ursodeoxycholic acid, and S-adenosyl methionine[30]. Several newer agents such as Obeticholic acid and GFT505 have shown promising results and various other pharmacotherapies are still being studied[32]. Treatment options such as gene based therapeutic treatment of NAFLD in diabetics are still in the experimental phases, however they could offer promising therapeutic options in the near future[36].

Our study has several limitations. It is a retrospective analysis and association does not imply causal relationship. In our multivariable analysis we adjusted for possible confounders, however, it is possible that one or more unknown confounders might be responsible for some of the results which we have observed. Since our study

Table 2 Medication use

Factor	Overall (*n* = 1183)		Fibrosis 0-2 (*n* = 802)		Fibrosis 3-4 (*n* = 381)		*P* value
	n	Statistics	*n*	Statistics	*n*	Statistics	
Oral hypoglycemic medications	1183	691 (58.4)	802	494 (61.6)	381	197 (51.7)	0.001[2]
Oral hypoglycemic duration (mo)	691	19.4 (5.0, 52.1)	494	20.6 (5.5, 54.4)	197	17.4 (3.4, 50.0)	0.098[1]
Metformin use	1183	631 (53.3)	802	461 (57.5)	381	170 (44.6)	< 0.001[2]
Metformin duration (mo)	631	20.0 (5.1, 53.3)	461	20.8 (5.4, 54.5)	170	18.3 (4.5, 52.1)	0.36[1]
Glipizide use	1183	116 (9.8)	802	82 (10.2)	381	34 (8.9)	0.48[2]
Glipizide duration (mo)	116	17.2 (5.6, 45.4)	82	19.2 (5.5, 47.7)	34	16.4 (6.0, 42.2)	0.85[1]
Pioglitazone use	1183	136 (11.5)	802	100 (12.5)	381	36 (9.4)	0.13[2]
Pioglitazone duration (mo)	136	15.5 (5.6, 44.8)	100	15.8 (6.1, 51.9)	36	12.5 (3.0, 40.8)	0.30[1]
Sitagliptin/Januvia use	1183	147 (12.4)	802	100 (12.5)	381	47 (12.3)	0.95[2]
Sitagliptin/Januvia duration (mo)	147	7.2 (1.6, 26.2)	100	7.4 (2.3, 26.6)	47	5.0 (0.30, 24.9)	0.23[1]
Saxagliptin use	1183	10 (0.85)	802	9 (1.1)	381	1 (0.26)	0.13[2]
Insulin	1183	370 (31.3)	802	253 (31.5)	381	117 (30.7)	0.77[2]
Insulin duration (mo)	370	10.9 (2.7, 34.0)	253	11.9 (3.0, 36.8)	117	8.3 (2.5, 25.3)	0.12[1]
Liraglutide use	1183	69 (5.8)	802	61 (7.6)	381	8 (2.1)	< 0.001[2]
Liraglutide duration (mo)	69	8.9 (2.6, 21.2)	61	8.6 (2.5, 17.9)	8	20.8 (5.0, 35.0)	0.13[1]
Detemir/Levemir use	1183	67 (5.7)	802	48 (6.0)	381	19 (5.0)	0.49[2]
Detemir/Levemir duration (mo)	67	5.9 (1.1, 17.7)	48	3.9 (0.85, 16.4)	19	9.0 (1.8, 17.7)	0.39[1]
Lantus use	1183	202 (17.1)	802	127 (15.8)	381	75 (19.7)	0.10[2]
Lantus duration (mo)	202	8.2 (0.80, 37.6)	127	9.2 (0.90, 42.8)	75	6.6 (0.20, 25.1)	0.17[1]
Humulin use	1183	65 (5.5)	802	49 (6.1)	381	16 (4.2)	0.18[2]
Humulin duration (mo)	65	12.0 (2.8, 34.0)	49	12.8 (2.0, 34.9)	16	8.4 (5.2, 18.7)	0.88[1]
Byetta use	1183	119 (10.1)	802	83 (10.3)	381	36 (9.4)	0.63[2]
Byetta duration (mo)	119	10.2 (3.8, 24.0)	83	11.9 (4.4, 24.0)	36	7.1 (2.5, 24.5)	0.21[1]
Antihypertensive medications	1183	787 (66.5)	802	538 (67.1)	381	249 (65.4)	0.56[2]
Antihypertensive duration (mo)	787	26.8 (4.7, 63.1)	538	31.3 (5.8, 65.8)	249	18.1 (3.1, 55.5)	0.010[1]
Lisinopril use	1183	377 (31.9)	802	274 (34.2)	381	103 (27.0)	0.014[2]
Lisinopril duration (mo)	377	16.1 (3.8, 49.0)	274	18.1 (3.6, 49.4)	103	12.4 (5.2, 48.6)	0.86[1]
Losartan use	1183	112 (9.5)	802	71 (8.9)	381	41 (10.8)	0.29[2]
Losartan duration (mo)	112	18.6 (3.2, 51.4)	71	24.1 (6.2, 54.3)	41	9.1 (2.1, 25.8)	0.077[1]
Furosemide use	1183	252 (21.3)	802	135 (16.8)	381	117 (30.7)	< 0.001[2]
Furosemide duration (mo)	252	8.7 (1.8, 39.4)	135	10.9 (2.3, 47.2)	117	7.9 (1.4, 30.0)	0.16[1]
Hydrochlorothiazide use	1183	371 (31.4)	802	279 (34.8)	381	92 (24.1)	< 0.001[2]
Hydrochlorothiazide duration (mo)	371	32.9 (7.9, 65.6)	279	34.4 (9.2, 67.1)	92	22.6 (4.8, 58.0)	0.089[1]
Spironolactone use	1183	115 (9.7)	802	47 (5.9)	381	68 (17.8)	< 0.001[2]
Spironolactone duration (mo)	115	5.4 (0.90, 29.1)	47	18.7 (3.6, 46.9)	68	3.0 (0.25, 10.4)	< 0.001[2]
Amlodipine use	1183	180 (15.2)	802	128 (16.0)	381	52 (13.6)	0.30[2]
Amlodipine duration (mo)	180	14.1 (3.0, 40.4)	128	14.7 (3.0, 40.9)	52	12.2 (3.5, 31.2)	0.45[1]
Metoprolol use	1183	273 (23.1)	802	185 (23.1)	381	88 (23.1)	0.99[2]
Metoprolol duration (mo)	273	11.4 (0.20, 45.1)	185	12.2 (0.20, 45.9)	88	10.0 (0.20, 36.1)	0.41[1]
Carvedilol use	1183	50 (4.2)	802	28 (3.5)	381	22 (5.8)	0.068[2]
Carvedilol duration (mo)	50	8.9 (2.3, 22.3)	28	11.3 (1.4, 28.7)	22	8.4 (2.9, 13.5)	0.39[1]
Antilipidemic medications	1183	522 (44.1)	802	380 (47.4)	381	142 (37.3)	0.001[2]
Antilipidemic duration (mo)	522	24.3 (5.3, 54.6)	380	24.8 (5.5, 62.4)	142	20.9 (4.4, 43.3)	0.086[1]
Rosuvastatin use	1183	84 (7.1)	802	61 (7.6)	381	23 (6.0)	0.33[2]
Rosuvastatin duration (mo)	84	10.4 (2.7, 40.8)	61	10.8 (3.0, 35.4)	23	7.7 (2.2, 41.2)	0.58[1]
Atorvastatin use	1183	243 (20.5)	802	179 (22.3)	381	64 (16.8)	0.028[2]
Atorvastatin duration (mo)	243	21.0 (5.3, 61.9)	179	23.5 (5.4, 66.7)	64	14.6 (4.4, 45.4)	0.30[1]
Simvastatin use	1183	251 (21.2)	802	187 (23.3)	381	64 (16.8)	0.010[2]
Simvastatin duration (mo)	251	15.6 (3.4, 45.8)	187	15.6 (3.6, 51.1)	64	16.5 (1.6, 36.8)	0.21[1]
Pravastatin use	1183	79 (6.7)	802	57 (7.1)	381	22 (5.8)	0.39[2]
Pravastatin duration (mo)	79	13.8 (2.4, 33.9)	57	13.8 (2.0, 30.7)	22	15.4 (4.3, 34.7)	0.81[1]

Gemfibrozil use	1183	38 (3.2)	802	27 (3.4)	381	11 (2.9)	0.66[2]
Gemfibrozil duration (mo)	38	12.3 (3.0, 50.5)	27	7.9 (2.1, 49.0)	11	33.5 (5.8, 62.3)	0.12[1]
Fenofibrate use	1183	109 (9.2)	802	78 (9.7)	381	31 (8.1)	0.38[2]
Fenofibrate duration (mo)	109	17.2 (5.7, 40.7)	78	22.0 (6.0, 44.6)	31	12.6 (3.1, 28.7)	0.27[1]
Aspirin use	1183	339 (28.7)	802	245 (30.5)	381	94 (24.7)	0.037[2]
Aspirin dose	335		241		94		0.98[2]
81 mg		328 (97.9)		236 (97.9)		92 (97.9)	
325 mg		7 (2.1)		5 (2.1)		2 (2.1)	

[1]Kruskal-Wallis test.
[2]Pearson's χ^2 test. Statistics presented as median (P25, P75) or *n* (%).

population was recruited from a single center, generalization should be avoided. In addition, despite using the strict exclusion criteria, some degree of recall bias may have been present while evaluating for alcohol consumption and medication use. On the other hand, the large sample size of biopsy proven NAFLD patients is a major strength of the current study.

In conclusion, in this large cohort of T2D with biopsy proven NAFLD, patients who were receiving Metformin, Liraglutide, Lisinopril, Hydrochlorothiazide, Atorvastatin and Simvastatin were less likely to have AF on liver biopsy while patients who were receiving Furosemide and Spironolactone had a higher likelihood of having AF on liver biopsies. Although our study does not indicate a causation it is important that physicians are aware of this key association. In the management and treatment of patients with NAFLD, clinicians should consider both liver disease and the associated metabolic co-morbidities. Along with diet and physical activity, focus should be given on specific pharmacological therapies that have been proven to be beneficial in NAFLD. Despite the consistent increase in the knowledge of therapeutic options for NAFLD, its management still remains a challenge for the scientific community and additional clinical trials are needed to evaluate the efficacy of various agents in NAFLD and T2D.

Table 3 Assessment of associations between clinical factors and advanced fibrosis

Factor	Unadjusted		Adjusted[1]	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Hypertension	0.59 (0.46, 0.76)	< 0.001	0.52 (0.39, 0.68)	< 0.001
Hyperlipidemia	0.45 (0.35, 0.58)	< 0.001	0.42 (0.32, 0.54)	< 0.001
CKD	3.3 (2.1, 5.1)	< 0.001	2.6 (1.7, 4.2)	< 0.001
IBD	0.91 (0.47, 1.8)	0.79	0.94 (0.47, 1.9)	0.85
DVT	1.1 (0.67, 1.9)	0.64	0.99 (0.58, 1.7)	0.97
Oral Hypoglycemic medications	0.67 (0.52, 0.85)	0.001	0.69 (0.53, 0.89)	0.004
Metformin use	0.60 (0.47, 0.76)	< 0.001	0.64 (0.49, 0.82)	< 0.001
Glipizide use	0.86 (0.57, 1.3)	0.48	0.93 (0.60, 1.4)	0.75
Pioglitazone use	0.73 (0.49, 1.10)	0.13	0.71 (0.47, 1.08)	0.11
Sitagliptin/Januvia use	0.99 (0.68, 1.4)	0.95	0.95 (0.65, 1.4)	0.79
Insulin	0.96 (0.74, 1.3)	0.77	1.02 (0.77, 1.3)	0.91
Liraglutide use	0.26 (0.12, 0.55)	< 0.001	0.30 (0.14, 0.64)	0.002
Detemir/Levemir use	0.82 (0.48, 1.4)	0.49	0.94 (0.53, 1.7)	0.83
Lantus use	1.3 (0.95, 1.8)	0.10	1.3 (0.92, 1.8)	0.14
Humulin use	0.67 (0.38, 1.2)	0.18	0.75 (0.41, 1.4)	0.35
Byetta use	0.90 (0.60, 1.4)	0.63	1.1 (0.72, 1.7)	0.65
Antihypertensive medications	0.93 (0.72, 1.2)	0.56	0.77 (0.59, 1.02)	0.064
Lisinopril use	0.71 (0.55, 0.93)	0.014	0.74 (0.56, 0.97)	0.031
Losartan use	1.2 (0.83, 1.9)	0.30	1.09 (0.71, 1.7)	0.70
Furosemide use	2.2 (1.6, 2.9)	< 0.001	1.9 (1.4, 2.5)	< 0.001
Hydrochlorothiazide use	0.60 (0.45, 0.79)	< 0.001	0.57 (0.43, 0.76)	< 0.001
Spironolactone use	3.5 (2.4, 5.2)	< 0.001	3.1 (2.0, 4.6)	< 0.001
Amlodipine use	0.83 (0.59, 1.2)	0.30	0.74 (0.51, 1.07)	0.11
Metoprolol use	1.00 (0.75, 1.3)	0.99	0.87 (0.64, 1.2)	0.37
Carvedilol use	1.7 (0.96, 3.0)	0.071	1.6 (0.89, 3.0)	0.12
Antilipidemic medications	0.66 (0.51, 0.85)	0.001	0.58 (0.45, 0.76)	< 0.001
Rosuvastatin use	0.78 (0.48, 1.3)	0.33	0.66 (0.40, 1.1)	0.12
Atorvastatin use	0.70 (0.51, 0.96)	0.029	0.62 (0.44, 0.86)	0.004
Simvastatin use	0.66 (0.48, 0.91)	0.011	0.61 (0.44, 0.85)	0.003
Pravastatin use	0.80 (0.48, 1.3)	0.39	0.75 (0.44, 1.3)	0.28
Gemfibrozil use	0.85 (0.42, 1.7)	0.66	0.92 (0.44, 1.9)	0.82
Fenofibrate use	0.82 (0.53, 1.3)	0.38	0.73 (0.47, 1.1)	0.18
Aspirin use	0.74 (0.56, 0.98)	0.037	0.58 (0.43, 0.78)	< 0.001

[1]Adjusted for age at time of biopsy, gender, race and body mass index. CKD: Chronic kidney disease; IBD: Inflammatory bowel disease; DVT: Deep venous thrombosis; OR: Odds ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background
The prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated around 25% of the global population and is expected to increase further in the coming years. Type-2 diabetes mellitus is a major risk factor for NAFLD with significant portion of diabetic patients develop progressive liver disease and a proportion of these patients also develop advanced fibrosis (AF). NAFLD pose significant health care burden and is associated with significant mortality and morbidity.

Research motivation
Patients with diabetes are commonly on multiple medication regimen, of which, some have a positive impact on slowing the progression of NAFLD to AF. For instance, HMG-CoA reductase inhibitors (statins) and Angiotensin converting enzyme inhibitors have been shown previously to be associated with reduction in AF in viral hepatitis patients. There is a paucity of data on the association of these medications on the progression of liver fibrosis in NAFLD patients.

Research objectives

We aimed to understand the association of the different pharmacologic modalities used in the treatment of diabetes mellitus on the progression of liver fibrosis in NAFLD patients with type-2 diabetes.

Research methods

We identified all adult patients with type-2 diabetes mellitus who underwent liver biopsy for suspected NAFLD at the Cleveland Clinic between January 1, 2000 to December 31, 2015. We retrospectively reviewed a cohort of 1183 patients with type-2 diabetes and biopsy proven NAFLD. We compared demographics, clinical characteristics, and differences in pattern of medication use in patients who had biopsy-proven NAFLD with and without advance fibrosis. A univariate and multivariate analysis was performed to assess the association of different classes of medication with and without the presence of AF.

Research results

We found that the patients who were receiving Metformin, Liraglutide, Lisinopril, Hydrochlorothiazide, Atorvastatin and Simvastatin were less likely to have AF on biopsy, while patients who were receiving furosemide and spironolactone were more likely to have AF when they underwent liver biopsy. Diabetic patients with chronic kidney disease were more likely to have AF on liver biopsy.

Research conclusions

Our study highlights the protective role of some of the commonly used medications in the treatment of type-2 diabetes mellitus. We propose that Metformin, Liraglutide, Lisinopril, Hydrochlorothiazide, Atorvastatin and Simvastatin may have a beneficial role in slowing down the progression of NAFLD.

Research perspectives

Although it is possible that some unknown confounding factors could have impacted our findings, this study lays a solid groundwork for future prospective studies to further investigate the protective role of these medications on the progression of liver fibrosis in diabetic patients with NAFLD.

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