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Diabetes Mellitus, Insulin, Sulfonylurea and Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease

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Abstract

Background & aims: Diabetes mellitus is a risk factor for advanced fibrosis in non-alcoholic fatty liver disease. However, not all non-alcoholic fatty liver disease patients with diabetes develop advanced fibrosis. We hypothesised that prescription medications used by these patients influence the development of advanced fibrosis. We investigated the association of commonly used medications and advanced fibrosis in non-alcoholic fatty liver disease patients with diabetes.

Methods: Clinical information including demographics, medical history, medication history, biochemical and histologic variables were ascertained in 459 patients with biopsy proven non-alcoholic fatty liver disease. We compared characteristics of patients with and without diabetes and explored potential associations between classes of drugs as risk factors and advanced fibrosis among the diabetic patients with NAFLD.

Results: Presence of diabetes was an independent risk factor for advanced fibrosis. In diabetic patients, age (OR 1.09; 95%CI 1.04-1.15, p=0.000) and grade of ballooning (OR 5.59; 95%CI 2.69-11.61, p=0.000) had a positive relationship with advanced fibrosis. The use of insulin (OR 4.95; 95%CI 1.65-14.88, p=0.004) and sulfonylurea (OR 5.07; 95%CI 1.87-13.75, p=0.001) were positively associated while statin use (OR 0.31; 95%CI 0.12-0.78, p=0.013) was negatively associated with advanced fibrosis.

Conclusion: Among non-alcoholic fatty liver disease patients with diabetes, the prevalence of advanced fibrosis was higher in patients treated with insulin and sulfonylurea, but lower in patients on statins. These findings provide support for a greater role of statin use in non-alcoholic fatty liver disease patients with diabetes while limiting the use of insulin and sulfonylurea.

Keywords: NAFLD; Fibrosis; Diabetes; Insulin; Sulfonylureas; Statins

Abbreviations: NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic SteatoHepatitis; ACE-I: type 2 diabetes mellitus (DM), Angiotensinogen Converting Enzyme Inhibitor; ADA: American Diabetes Association; JNC: Joint National Committee; BMI: Body Mass Index; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International Normalised Ratio; Chol: Total Cholesterol; TG: Triglycerides; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; ARB: Angiotensin II receptor blocker; SD: Standard deviations; ORs: Odds ratios; CI: Confidence Intervals; NAS: NAFLD activity score; IGF-1: Insulin-like growth factor; HSC: Hepatic Stellate Cells; PI3K: Phosphatidyl inositol 3 kinase; ERK: Extracellular sSignal Related Kinase; CTGF: Connective Tissue Growth Factor; HCC: HepatoCellular Carcinoma

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) represents a spectrum of histologic abnormalities ranging from steatosis alone to Non-Alcoholic Steatohepatitis (NASH), to advanced fibrosis and cirrhosis [1]. Patients with type 2 Diabetes Mellitus (DM) have an increased the risk of developing NAFLD while significantly increasing the risk of NASH and hepatic fibrosis/cirrhosis [2,3]. NAFLD patients with DM have twice the mortality compared to non-diabetic NAFLD patients [4]. Multiple studies have examined anti-diabetic, lipid lowering and anti-hypertensive medications for treating NAFLD, but these studies did not identify a clear or consistent benefit on hepatic fibrosis [5]. However, not all subjects with diabetes develop advanced fibrosis or cirrhosis. We hypothesised that certain medications used by these patients may have influenced the development of advanced fibrosis in NAFLD patients with DM, as has been observed in other chronic liver disease. The use of Angiotensinogen Converting Enzyme Inhibitor (ACE-I) was observed to reduce the risk of advanced fibrosis in chronic hepatitis C patients [6]. Similarly, the use of metformin was associated with a decrease in risk of hepatocellular carcinoma while insulin/sulfonylurea therapy was reported to increase this risk [7]. The present study sought to evaluate

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the relationship between DM and advanced fibrosis in NAFLD patients and explore the association of commonly used medications and advanced fibrosis in NAFLD.

Methods

Study population

The study ascertained data from patients aged 18 years and over with histologically proven NAFLD from two hepatology clinics in Cleveland, Ohio (Cleveland Clinic Foundation and MetroHealth Medical Centre). Patients with prior therapies that may be beneficial for NAFLD such as vitamin E, pentoxifylline, pioglitazone, prescribed diet and exercise weight loss programs were excluded. Patients with other potential contributory causes of liver disease (alcohol consumption [>21 drinks and >14 drinks per week for males and females respectively], hepatotoxic drug history, chronic viral hepatitis, hemochromatosis, autoimmune hepatitis, Wilson's disease or alpha-1 antitrypsin disease) were excluded [8].

Study design

Demographic and clinical information was gathered from an electronic medical record system that is common to both hospitals. Diabetes mellitus was diagnosed by American Diabetes Association (ADA) criteria with or without the use of antidiabetic medications [9]. Hypertension was diagnosed by the Joint National Committee (JNC) 7 criteria [10]. All diagnoses were also verified based on documentation in the electronic medical records by one of the investigators (AJM or SD). Anthropometric measurements including height, weight and Body Mass Index (BMI) were recorded. Laboratory data including liver function tests [serum albumin, bilirubin, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST)], platelet count, International Normalised Ratio (INR) and markers of the metabolic syndrome (total Cholesterol (Chol), Triglycerides (TG), High Density Lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol, HbA1C) were collated. Liver biopsies were evaluated using the Non-alcoholic Steatohepatitis Clinical Research Network criteria [11]. In brief, the biopsy was scored for steatosis, lobular inflammation, ballooning and fibrosis. Stage 3 (bridging fibrosis) and 4 (cirrhosis) were classified as advanced fibrosis. Only clinical data obtained within 6 months of the corresponding liver biopsy were included. A careful medication history focused on the use of insulin, metformin, sulfonylurea, hydroxyl-methylglutaryl-coenzyme A reductase inhibitors (statins) and angiotensin converting enzyme inhibitor (ACE-I)/Angiotensin II Receptor Blocker (ARB) because these agents have been shown to affect insulin resistance, hepatic lipid metabolism or fibrosis. Approval of the study protocol was obtained from the Institutional Review Board in accordance with the ethical guidelines of the declaration of Helsinki.

Statistical analysis

Descriptive statistics were computed for all variables; means with Standard Deviations (SD) and frequencies with percentages for continuous and categorical variables respectively. Differences between patients with and without DM were analysed using the Students T test and the Pearson's Chi-square test for continuous and categorical variables respectively. In addition, similar analysis for differences between patients with and without advanced fibrosis (fibrosis stage 0-2 vs. stage 3-4) in diabetic subjects was also performed. Independent factors associated with advanced fibrosis were assessed using binary logistic regression multivariate analysis in both total cohort and in the subgroup of DM patients. Factors thought to be associated with advanced fibrosis in NAFLD including age, BMI, gender, presence of hypertension/DM, lipid profile and liver histology (grade of steatosis, inflammation and ballooning) were included in the model. The magnitude of the associations was assessed by Odds Ratios (ORs) and corresponding 95% Confidence Intervals (CI). This multivariate analysis of the cohort was internally validated using the cross-validation technique (80:20 cross validation). SPSS version 21 (Chicago, Illinois, USA) statistical software package was used to conduct the statistical computing. All P values quoted were two-sided with $P<0.05$ considered statistically significant.

Results

Available data from 459 patients with biopsy proven NAFLD were reported. As shown in Table 1, the mean age was 49 ± 12 years and 60.7% were female. The majority of patients were obese with hypertension and DM present in 56.4% and 47.9% respectively. Advanced fibrosis was present in 132 patients (28.8%). Abnormal AST and ALT were present in 54 and 58% of the patients, respectively. A relatively large proportion of the cohort had abnormal TG, HDL cholesterol, and HbA1C values.

Variable	Total cohort; n=459	DM patients; n=220	Non-DM patients; n=239	P value
Age (years)	49 ± 12	52 ± 11	46 ± 12	0.00
Proportion Female	278 (60.7%)	152 (69.1%)	126 (52.9%)	0.00
BMI (kg/m^2)	35.9 ± 8.5	37.0 ± 7.9	35.0 ± 9.0	0.01
Presence of HTN	259 (56.4%)	156 (70.9%)	103 (43.1%)	0.00
Presence of DM	220 (47.9%)	NA	NA	-
Use of Insulin	52 (11.3%)	52 (23.7%)	NA	-
Use of Metformin	94 (20.5%)	94 (42.7%)	NA	-
Use of Sulfonylurea	67 (14.6%)	67 (30.6%)	NA	-
Use of Statin	123 (26.9%)	88 (40.2%)	35 (14.6%)	0.00
Use of ACE-I/ARB	175 (38.1%)	107 (48.6%)	68 (28.5%)	0.00
Serum Bilirubin (mg/dL)	0.68 ± 0.40	0.69 ± 0.43	0.67 ± 0.38	0.61
AST (U/L)	56.8 ± 65.6	54.3 ± 35.9	59.1 ± 84.1	0.44
ALT (U/L)	72.4 ± 56.4	65.3 ± 50.1	78.9 ± 60.9	0.01
Albumin (g/dL)	4.2 ± 0.5	4.1 ± 0.5	4.3 ± 0.4	0.01
INR	1.03 ± 0.17	1.04 ± 0.18	1.02 ± 0.16	0.36
Platelet count (k/uL)	238.0 ± 77.3	231.6 ± 79.1	243.7 ± 75.3	0.10
Creatinine (mg/dL)	0.89 ± 0.38	0.85 ± 0.51	0.92 ± 0.19	0.08
Total cholesterol (mg/dL)	198.5 ± 51.7	193.9 ± 54.9	202.5 ± 48.5	0.09
TG (mg/dL)	207.1 ± 186.5	232.7 ± 231.0	184.5 ± 132.4	0.01
HDL (mg/dL)	42.6 ± 10.4	41.5 ± 10.3	43.6 ± 10.0	0.05
LDL (mg/dL)	123.6 ± 43.2	116.4 ± 45.2	130.0 ± 40.3	0.00
HbA1C%	6.5 ± 1.4	7.40 ± 1.51	5.60 ± 0.57	0.00
Ferritin (ng/mL)	231.2 ± 233.6	206.4 ± 233.9	253.9 ± 231.6	0.05
Grade of steatosis	1.9 ± 0.8	1.9 ± 0.8	1.9 ± 0.8	0.96
Grade of lobular inflammation	1.4 ± 0.7	1.5 ± 0.6	1.4 ± 0.7	0.02
Grade of ballooning	1.1 ± 0.7	1.2 ± 0.7	0.9 ± 0.7	0.00
NAS	4.5 ± 1.6	4.7 ± 1.6	4.3 ± 1.6	0.01
Stage of fibrosis	1.6 ± 1.3	2.0 ± 1.3	1.1 ± 1.2	0.00
Presence of advanced fibrosis	132 (28.8%)	91 (41.6%)	41 (17.2%)	0.00

Data expressed as mean ± SD or number and percentages (%).
SD: Standard Deviation; BMI: Body Mass Index; HTN: Hypertension; DM: Diabetes; ACE-I: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin II Receptor Blocker; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International Normalised Ratio; TG: Triglyceride; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; NAS: NAFLD activity score; NA: Not applicable

Table 1: Characteristics of NAFLD patients with and without DM.

Differences in patients with and without DM are shown in Table 1. Compared to non-DM patients, DM patients were older, a greater proportion were female, had a higher BMI and a higher prevalence of hypertension. They were also more likely to be on a statin or ACE-I/ARBs. Biochemical parameters including ALT, Albumin, TG, HDL, LDL and HbA1C were also significantly different in the 2 groups. On liver histology, while there were no differences in steatosis, DM patients had more lobular inflammation and ballooning, as well as a higher NAFLD Activity Score (NAS). Advanced fibrosis was also increased in DM patients.

Variable	Whole cohort		Cross validation 80:20.	
	OR; 95% CI	P value	OR; 95% CI	P value
Age	1.05; 1.02-1.08	0.002	1.07; 1.03-1.11	0.000
DM	2.36; 1.27-4.38	0.007	2.33; 1.15-4.73	0.019
Total Cholesterol	0.97; 0.95-0.99	0.011	0.97; 0.94-0.99	0.003
LDL Cholesterol	1.02; 1.00-1.04	0.034	1.03; 1.01-1.05	0.011
Ballooning	5.59; 3.35-9.34	0.000	7.77; 4.14-14.58	0.000

Covariates included were age, BMI, gender, presence of hypertension, presence of DM, lipids and histology.
OR: Odds ratio; CI: Confidence interval; DM: Diabetes mellitus.

Table 2: Independent risk factors of advanced fibrosis in whole cohort.

Variable	Presence of advanced fibrosis n=91	Absence of advanced fibrosis n=128	P value
Age (years)	55 ± 11	50 ± 11	0.00
Proportion Female (%)	63 (69.2%)	88 (68.8%)	0.94
BMI (kg/m^2)	36.3 ± 7.8	37.4 ± 8.05	0.32
Presence of HTN (%)	71 (78%)	84 (65.6%)	0.05
Duration of DM (years)	4.9 ± 6.3	4.6 ± 5.1	0.77
Use of Insulin (%)	26 (20.3%)	26 (28.9%)	0.14
Use of Metformin (%)	39 (42.9%)	54 (42.2%)	0.92
Use of Sulfonylurea (%)	35 (38.9%)	32 (25.0%)	0.03
Use of Statin (%)	31 (34.1%)	56 (44.1%)	0.14
Use of Ace-I/ARB (%)	41 (45.1%)	65 (50.8%)	0.40
Serum Bilirubin (mg/dL)	0.75 ± 0.49	0.65 ± 0.38	0.10
AST (U/L)	61.6 ± 37.6	48.9 ± 33.9	0.01
ALT (U/L)	65.2 ± 55.9	64.9 ± 45.7	0.96
Albumin (g/dL)	4.0 ± 0.6	4.2 ± 0.4	0.00
INR	1.06 ± 0.14	1.02 ± 0.20	0.10
Platelet count (k/uL)	202.0 ± 87.8	252.0 ± 65.2	0.00
Creatinine (mg/dL)	0.84 ± 0.29	0.87 ± 0.63	0.62
Total cholesterol (mg/dL)	178.8 ± 51.4	203.3 ± 55.3	0.00
TG (mg/dL)	204.6 ± 118.7	251.5 ± 279.5	0.18
HDL (mg/dL)	39.9 ± 11.5	42.6 ± 9.3	0.08
LDL (mg/dL)	108.0 ± 41.3	121.3 ± 47.1	0.06
HbA1C (%)	7.4 ± 1.4	7.3 ± 1.5	0.51
Ferritin (ng/mL)	213.3 ± 236.3	201.2 ± 234.2	0.74
Grade of steatosis	1.9± 0.9	1.9 ± 0.8	0.85
Grade of lobular inflammation	1.5 ± 0.6	1.5 ± 0.6	0.66
Grade of ballooning	1.5 ± 0.5	1.0 ± 0.7	0.00
NAS	5.0 ± 1.4	4.5 ± 1.7	0.02

Data expressed as mean ± SD or number and percentages (%).
SD: Standard Deviation; BMI: Body Mass Index; HTN: Hypertension; ACE-I: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin II Receptor Blocker; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International Normalised Ratio; TG: Triglyceride, HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; NAS: NAFLD activity score; NA: Not applicable.

Table 3: Baseline characteristics of DM subjects by presence of advanced fibrosis.

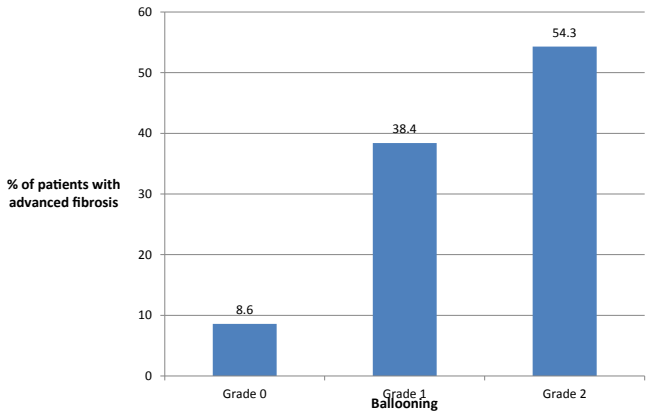

Figure 1: Relationship of grade of ballooning to advanced fibrosis in NAFLD patients with DM.

Variable	DM cohort		Cross validation 80:20.	
	OR; 95% CI	P value	OR; 95% CI	P value
Age	1.09; 1.04-1.15	0.000	1.12; 1.06-1.19	0.000
Ballooning	5.59; 2.69-11.61	0.000	7.01; 3.01-16.33	0.000
Use of Insulin	4.95; 1.65-14.88	0.004	4.64; 1.35-15.95	0.015
Use of Sulfonylurea	5.07; 1.87-13.75	0.001	4.63; 1.43-15.00	0.011
Use of Statins	0.31; 0.12-0.78	0.013	0.30; 0.10-0.86	0.025

Covariates included were age, BMI, gender, presence of hypertension, lipids, histology, use of insulin, metformin, sulfonylurea, statin and ACE-I/ARB.

OR: Odds ratio, CI: Confidence interval.

Table 4: Independent risk factors of advanced fibrosis in DM subjects.

The independent risk factors for advanced fibrosis in the entire cohort are shown in Table 2 and included the presence of DM, age, ballooning, plasma cholesterol levels which held true during the 80% : 20% cross validation.

DM patients with and without advanced fibrosis are compared in Table 3. Compared to patients without advanced fibrosis, patients with advanced fibrosis were older and had a higher incidence of hypertension. There were no significant differences in gender, BMI or duration of DM. On univariate analysis, patients with advanced fibrosis were more likely to be on sulfonylureas while there were no differences in the use of insulin, metformin, statin or ACE-I/ARB. Patients with advanced fibrosis had significantly higher AST levels, while serum albumin and platelet count were significantly lower (Table 3). There were no differences in creatinine, lipids, and HbA1C or ferritin levels. On liver histology, the grade of ballooning and NAS were significantly higher with advanced fibrosis. Further analysis showed higher grades of ballooning were associated with increasing fibrosis stage as shown in Figure 1 with grades of 0,1 and 2 ballooning associated with a prevalence of advanced cirrhosis of 8.6%, 38.4% and 54.3%, respectively.

Multivariate analysis of advanced fibrosis risk factors in the context of DM are shown in Table 4. Advanced fibrosis was independently affected by age, grade of ballooning, use of insulin, sulfonylurea and statin. Increasing age (OR 1.09; 95% CI 1.04-1.15, p=0.000) and grade of ballooning (OR 5.59; 95% CI 2.69-11.61, p=0.000) were positively associated with advanced fibrosis. Use of insulin (OR 4.95; 95% CI 1.65-14.88, p=0.004) and sulfonylurea (OR 5.07; 95% CI 1.87-13.75, p=0.001) were also positively associated with advanced fibrosis. In contrast, the use of statins (OR 0.31; 95% CI 0.12-0.78, p=0.013) was negatively associated with advanced fibrosis. The use of metformin and ACE-I/ARB were not associated with advanced fibrosis.

Discussion

In addition to confirming that DM is an independent risk factor for advanced fibrosis in NAFLD, the present study makes the novel observation that advanced fibrosis in NAFLD may be impacted by certain medications used to treat diabetes and dyslipidemia. Among patients with DM, use of insulin and sulfonylurea was positively associated with advanced fibrosis while statin therapy was negatively associated with advanced fibrosis. Age and ballooning were additional independent risk factors for advanced fibrosis.

Risk factors for advanced fibrosis among NAFLD patients identified in the present study are similar to those reported by others [3,12-15]. Even though DM is a recognized risk factor for advanced fibrosis in NAFLD we observed that certain prescribed medications affect the relation between fibrosis and diabetes mellitus [3,12-15].

Major therapeutic approaches in diabetes mellitus include either an increase in circulating insulin levels (exogenous insulin or sulfonylureas) or a decrease in insulin resistance (metformin, thiazolidinediones). Our novel observation that both insulin and sulfonylurea were risk factors for advanced hepatic fibrosis suggests that increasing circulating insulin levels are implicated in the development of fibrosis. Expression of insulin and Insulin-Like Growth Factor (IGF-1) receptors on the collagen producing Hepatic Stellate Cells (HSC) is increased during active fibrogenesis [16]. In addition, insulin and IGF-1 stimulate HSC proliferation in a dose dependent fashion [16]. Furthermore, insulin signalling via the Phosphatidyl Inositol 3 Kinase (PI3K) and extracellular signal related kinase (ERK) increases collagen gene expression [16]. Similarly, glucose and insulin stimulate the expression of connective tissue growth factor [CTGF], which is a peptide growth factor that plays a pivotal role in fibrogenesis [17-19].

Compatible with our findings, is the report that anti-diabetic medications also affect the risk of Hepatocellular Carcinoma [HCC] [7,20-22]. The use of insulin and sulfonylurea was associated with a 161% and 62% increased risk of HCC respectively, while the use of metformin was associated with 50% reduction in the incidence of HCC incidence [23]. While it is commonly postulated that insulin and insulin secretagogues have direct effects of carcinogenesis, it may also be possible that the risk of HCC development is due in part to the insulin/ insulin secretagogues stimulated progression of liver tissue to advanced fibrosis or cirrhosis, especially since HCC typically develops following the sequence of chronic hepatic inflammation to fibrosis and cirrhosis [23,24].

Our study also shows that the use of statins was associated with reduced risk of advanced hepatic fibrosis in NAFLD patients with DM. In the context of NAFLD and hyperinsulinemia, the hepatic accumulation of lipid molecules leads to inflammation and lipotoxicity [25]. Lipotoxicity plays a crucial role in the pathogenesis of hepatic steatosis, steatohepatitis and fibrosis. Similar mechanisms of lipotoxicity injury can also be seen in atherosclerosis and pancreatic β cell destruction in DM [25]. Not surprisingly, atherosclerosis and coronary artery disease are closely linked to NAFLD and represent the most frequent cause of death in these patients [26]. On the other hand, statins, being the mainstay of lipid-lowering therapy, may improve liver outcomes by lowering lipids and lipotoxicity [27]. Cholesterol lowering with statins has been reported to reduce cardiovascular risks and mortality in patients with NAFLD [28]. Cholesterol lowering by both statin and statin/ezetimibe combinations has also been shown to improve necroinflammation and reverse hepatic fibrosis in diabetic mice models [29]. However, human studies have not shown clear or consistent beneficial effect of statins in NAFLD [5,27]. 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]. Our data in a large cohort of well characterized patients with NAFLD suggests that statin use is accompanied by lower hepatic fibrosis. These data reiterate both the safety and benefit of statins in NAFLD.

This is the first study to demonstrate a direct relation between the use of insulin/sulfonylurea and risk of advanced fibrosis among NAFLD patients with DM. The recommended standard treatment strategy for DM would generally include oral hypoglycaemic agents such as metformin or sulfonylurea initially and only add insulin therapy when oral combination therapy is no longer effective or required with the progressive β cell dysfunction seen in later stages of DM [30]. Both sulfonylureas and insulin use have similar associations with advanced fibrosis. This suggests that it is the stimulation of insulin secretion or insulin per se, rather than treatment choices dictated by the severity of DM, that influences advance fibrosis. This is further supported by comparable HbA1c levels between patients with and without advanced fibrosis. In addition, the duration of DM was not significantly different between patients with and without advanced fibrosis. Furthermore, since medication history reconciliation occurred at every clinic visit and recorded automatically in the electronic medical records of each patient as per standard clinic protocol, records of medication history were robust and accurate. This information was retrieved for each patient to ascertain the use of the various medications of interest.

The potential limitations of our study include the cross sectional nature of the study which allows evaluation of associations only, rather than causal inference. Secondly, the exact duration and dose of drug use were not available. However, the duration of diabetes did not differ between DM patients with and without advanced fibrosis. In addition, all patients were on the minimal effective therapeutic dose and it is difficult to assess the median dose since antidiabetic and antihypertensive medication doses are adjusted during clinical care. Despite these potential limitations, the large number of subjects and careful review of clinical data of patients followed prospectively provides support for our hypothesis that therapies to control diabetes and dyslipidemia may have an effect on hepatic fibrosis in NAFLD. These data lay the foundation for future multicenter network based studies on the impact of medications on liver histology and progression of disease in NAFLD.

Conclusion

Our study shows that NAFLD patients with DM on insulin and sulfonylurea were more likely to have advanced hepatic fibrosis, while those on statins were less likely to have advanced hepatitis fibrosis. These data have significant clinical implications and provide novel insights into the pathogenesis of fibrosis in these patients. In addition, these findings provide additional support for statin use in NAFLD patients with DM while limiting the use of insulin and sulfonylurea. Prospective studies to evaluate concurrent medication use are warranted to explore this association in greater detail.

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