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Prescribing of evidence-based diabetes pharmacotherapy in patients with metabolic dysfunction-associated steatohepatitis

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ABSTRACT

Introduction Metabolic dysfunction-associated steatohepatitis (MASH) is highly prevalent in type 2 diabetes (T2D). Pioglitazone and glucagon-like peptide-1 receptor agonists (GLP-1RA) are medications used in T2D that can resolve MASH and should be considered in all patients with T2D and MASH. We assessed prescription rates of evidence-based T2D pharmacotherapy (EBP) in MASH, and ascertained racial/ethnic disparities in prescribing.

Research design and methods We conducted a cross-sectional study on patients in Duke University Health System with diagnosis codes for T2D and MASH between January 2019 and January 2021. Only patients with ≥1 primary care or endocrinology encounter were included. The primary outcome was EBP, defined as ≥1 prescription for pioglitazone and/or a GLP-1RA during the study period. A multivariable logistic regression model was used to examine the primary outcome.

Results A total of 847 patients with T2D and MASH were identified; mean age was 59.7 (SD 12) years, 61.9% (n=524) were female, and 11.9% (n=101) and 4.6% (n=39) were of Black race and Latino/a/x ethnicity, respectively. EBP was prescribed in 34.8% (n=295). No significant differences were noted in the rates of EBP use across racial/ethnic groups (Latino/a/x vs White patients: adjusted OR (aOR) 1.82, 95% CI 0.78 to 4.28; Black vs White patients: aOR 0.76, 95% CI 0.44 to 1.33, p=0.20).

Conclusions EBP prescriptions, especially pioglitazone, are low in patients with T2D and MASH, regardless of race/ethnicity. These data underscore the need for interventions to close the gap between current and evidence-based care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ US guidelines for primary care physicians and endocrinologists recommend evidence-based type 2 diabetes pharmacotherapy (EBP)—pioglitazone and glucagon-like peptide-1 receptor agonists—for patients with diabetes who have metabolic dysfunction-associated steatohepatitis (MASH).

WHAT THIS STUDY ADDS

⇒ EBP prescription rates for MASH, especially pioglitazone prescription rates, are low.

⇒ We found no racial/ethnic disparities in EBP prescribing.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical interventions are needed to better align current and evidence-based prescribing practices for patients with diabetes and MASH.

⇒ Racial/ethnic disparities exist in MASH outcomes, and these data highlight the need for future research to identify where such disparities may exist in the MASH care pathway.

INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH),[1] previously known as non-alcoholic steatohepatitis (NASH), is a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD) that is present in up to 40% of patients with type 2 diabetes (T2D).[2] Patients with T2D, particularly those of historically marginalized groups, are at uniquely high risk of MASH progression to cirrhosis, hepatocellular carcinoma, and liver mortality.[3] Compared with non-Latino/a/x (NL) White patients, Latino/a/x patients have a higher risk of MASLD development and progression, and Black patients may experience higher mortality from MASLD than White patients.[3]

A growing body of evidence indicates that certain T2D medications can halt, and even reverse, MASH progression.[4] Pioglitazone, a thiazolidinedione, is a peroxisome proliferator-activated receptor-γ agonist that primarily targets adipose tissue; it enhances lipid storage and redistribution, as well as glucose utilization.[4] Pioglitazone has been in use since the early 2000s, and it was the first T2D medication to show efficacy in reversing biopsy-proven MASH.[5] Multiple studies have since demonstrated its efficacy in reversal of

Table 1 Demographic and clinical characteristics

Characteristics	All patients (n=847)
Age, mean (SD)	59.7 (11.9)
Female sex, n (%)	524 (61.9)
Race-ethnicity (combined), n (%)*	
NL black	101 (11.9)
NL white	627 (74.0)
NL Other or multiple races	46 (5.4)
Latino/a/x	39 (4.6)
Not reported/declined	34 (4.0)
First race Indicated, n (%)	
Black	111 (13.1)
White	655 (77.3)
Asian	29 (3.4)
Native Hawaiian or other Pacific Islander	5 (0.6)
American Indian or Alaskan Native	11 (1.3)
Other	21 (2.5)
Not reported	15 (1.8)
Multiracial indicated, n (%)	6 (0.7)
Latino/a/x ethnicity, n (%)	39 (4.6)
Insurance status, n (%)	
Government	465 (55.0)
Managed care	162 (19.2)
Private	188 (22.3)
Self-Pay	26 (3.1)
Other	4 (0.5)
Comorbidities, n (%)	
Hypertension	390 (46.0)
Hyperlipidemia	352 (41.6)
Chronic kidney disease	121 (14.3)
Congestive heart failure	58 (6.9)
Coronary artery disease	106 (12.5)
Cerebrovascular disease	46 (5.4)
Peripheral vascular disease	21 (2.5)
ASCVD†	157 (18.5)
Chronic lung disease	107 (12.6)
Any malignancy	131 (15.5)
Metastatic solid tumor	18 (2.1)
Dementia	10 (1.2)
Depression	136 (16.1)
Bladder cancer	0 (0.0)
Fractures	87 (10.3)
Mean BMI, mean (SD)‡	34.5 (7.1)
Smoking status, n (%)	
Current smoker	59 (7.0)
Former smoker	330 (39.0)
Never smoker	458 (54.1)
Diabetes medication use, n (%)	
Metformin	529 (62.5)
Sulfonylureas	260 (30.7)
DPP4 inhibitors	125 (14.8)
SGLT2 inhibitors	150 (17.7)
Insulin	528 (62.3)
EBP	295 (34.8)
GLP-1RA alone	240 (28.3)
Pioglitazone alone	30 (3.5)
Both Pioglitazone and GLP-1RA	25 (3.0)
Clinical care, n (%)	
Any PCP encounter	685 (80.9)
Type of provider listed as PCP	
MD	590 (69.7)
DO	73 (8.6)
NP	77 (9.1)
PA	52 (6.1)
Unknown	55 (6.5)
Any endocrinology encounter	496 (58.6)
Hepatology consult	31 (3.7)
Hepatology follow-up visit	192 (22.7)
Number of outpatient encounters, mean (SD)	10.25 (7.7)
Average laboratory values, mean (SD)[c]	
HbA1c (%)	7.5 (1.5)
LDL, mg/dL	88.7 (36.5)
HDL, mg/dL	46.6 (40.7)
Triglycerides, mg/dL	193 (158.6)
ALT, IU/L	46.0 (37.5)
AST, IU/L	48.0 (55.6)
GGT IU/L	114.7 (159.3)
Albumin, g/L	3.8 (0.8)
Platelet count, × 10^9/L	193.6 (92.7)
eGFR, mL/min/1.73 m^2	73.6 (24.6)
FIB-4 Score, mean (SD)	3.8 (5.2)
FIB-4 Score, categories, n (%)	
Low risk	294 (34.7)
Indeterminate risk	176 (20.8)
High risk	265 (31.3)
Missing	112 (13.2)
Liver imaging and biopsy, n (%)	
Liver ultrasound	360 (42.5)
Transient elastography	53 (6.3)
CT abdomen	156 (18.4)

Continued

Table 1 Continued

Characteristics	All patients (n=847)
MRI abdomen	166 (19.6)
Liver biopsy	52 (6.1)

*Combined race-ethnicity variable that was used for analyses.
†ASCVD is defined as a diagnosis code for any of the following conditions: coronary artery disease, cerebrovascular disease, peripheral arterial disease, generalized and aortic atherosclerosis.
‡Missing data: BMI (n=2), HbA1c (n=38), LDL (n=128), HDL (n=113), triglycerides (n=104), ALT (n=36), AST (n=36), GGT (n=799), albumin (n=36), platelet count (n=79), eGFR (n=41).
ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; DO, doctor of osteopathic medicine; DPP4, dipeptidyl peptidase-4; EBP, evidence-based type 2 diabetes pharmacotherapy (ie, prescription for pioglitazone and/or GLP-1RA); eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4; GGT, gamma glutamyltransferase; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; MD, medical doctor; NL, non-Latino/a/x; NP, nurse practitioner; PA, physician assistant; PCP, primary care physician; SGLT2, sodium-glucose cotransporter-2.

MASH and liver fibrosis.[5–8] More recently, glucagon-like peptide-1 receptor agonists (GLP-1RA) have emerged as a T2D medication class with substantial A1c-lowering and weight loss capabilities, and the ability to reverse MASH; GLP-1RAs shown to improve MASH in trials include liraglutide[9] and semaglutide.[10] Sodium-glucose cotransporter-2 inhibitors may also promote reduction of liver fat and liver enzymes in patients with T2D and MASLD.[11] Based on existing data, guidelines now recommend consideration of both pioglitazone and GLP-1RA in patients with T2D with known MASH, or in whom there is an elevated suspicion for MASH.[4 12]

Given the clear liver benefits of pioglitazone and GLP-1RA, T2D providers have a new opportunity to intervene on liver-related morbidity and mortality through prescribing of evidence-based medications. Currently, there are limited data as to the prescribing practices of T2D providers caring for patients with T2D and MASH, and whether racial/ethnic disparities exist in the use of evidence-based T2D pharmacotherapy (EBP) in MASH.

The primary objective of this study was to explore the use of pioglitazone and GLP-1RA in patients with T2D and known MASH. We also aimed to assess whether racial or ethnic disparities exist in the prescribing of pioglitazone and GLP-1RA in MASH. While this analysis was conducted prior to the release of recent guidelines promoting the use of pioglitazone and GLP-1RA in those with suspicion for MASH, these data provide a helpful benchmark on which to monitor practice changes over time, and to understand whether providers were considering the known liver benefits of these medications when managing T2D with comorbid MASH.

RESEARCH DESIGN AND METHODS

Data source and sample

We conducted a cross-sectional study of adult patients with diagnosed T2D (ICD-10 code E11.xx) and NASH (ICD-10 code K75.81) in the Duke University Health System (DUHS) between January 1, 2019 and January 1, 2021. The nomenclature for NASH changed to MASH in June 2023,[1] so while ICD codes in this study correspond to the previous nomenclature of NASH, we use the updated nomenclature throughout this manuscript. To increase the likelihood that T2D was being managed in DUHS, we only included patients with ≥1 clinic encounter with a Duke primary care physician (PCP) or Duke endocrinologist during the study period.

Data collection and fibrosis-4 calculation

Given concerns as to the impact of healthcare disparities on liver outcomes, our primary independent variables of interest were race and ethnicity. In the descriptive table (table 1), race and ethnicity are presented as individual variables. Due to small counts, race and ethnicity were combined as a single variable for statistical analysis, with the following categories: Latino/a/x, NL Black, NL White, NL Asian, Other or multiple races, and not reported/unknown.

We collected additional data on demographic and clinical characteristics, including age, biological sex, insurance status, comorbidities, medication use, type and frequency of outpatient care, body mass index (BMI) and laboratory data, including the fibrosis-4 (FIB-4) Score. Of the non-invasive tests (NITs) for liver fibrosis in MASLD, FIB-4 is the most validated and widely available. Currently it is recommended as the first line NIT for risk-stratifying MASLD in patients with T2D.[4 13 14] FIB-4 was calculated using age and mean alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet counts during the study period. The following equation was used to calculate FIB-4: (age × AST)/(platelets × √(ALT)).[15] Patients who did not have ALT, AST, and platelets checked were categorized as having missing FIB-4 Scores. Because FIB-4 is only validated for individuals ≥35 years of age, FIB-4 was not calculated for patients <35 years of age, and these patients were likewise marked as having missing FIB-4 Scores (table 1). FIB-4 was additionally categorized into the following established groups based on risk of advanced liver fibrosis: low risk (FIB-4 <1.3), indeterminate risk (FIB-4 1.3–2.67) and high risk (FIB-4 >2.67).[15] For patients ≥65 years of age, we used an upper limit of 2.0 (instead of 1.3) for low risk, since this cut-off leads to lower false-positive rates for advanced fibrosis in this age group.[16]

Outcomes

The primary outcome was EBP for MASH, defined as ≥1 prescription for pioglitazone and/or a GLP-1RA at any time during the study period. Pioglitazone is the only medication of its pharmaceutical class in routine clinical use. Included GLP-1RAs were: exenatide, liraglutide, dulaglutide, lixisenatide, and semaglutide. Pioglitazone and GLP-1RA prescribing were examined individually as secondary outcomes.

In order to identify the rationale for prescribing of EBP (ie, whether EBP was prescribed specifically to improve liver outcomes in T2D vs strictly for another indication such as glycemia lowering, weight reduction, or cardiovascular benefit), manual chart review of primary care and endocrinology notes in the electronic health record was conducted on the subset of patients who received EBP (n=295). Chart review was conducted by one author (A-SA) who is a board-certified endocrinologist.

Statistical analysis

Primary and secondary outcomes were first assessed in a univariable logistic regression model, where the single predictor was the race-ethnicity analysis variable, that is, Latino/a/x, NL Black, NL White. Patients identified as NL Asian, Other or multiple races, and not reported/unknown race were excluded from the models due to small counts. Patients with missing insurance status, or "other" insurance status were also excluded (online supplemental figure 1). Unadjusted results are included in online supplemental table 1. A multivariable logistic regression model with race-ethnicity was subsequently assessed for the primary outcome of EBP. The model was adjusted for the following covariates: age, sex, insurance status, FIB-4 category (high risk, indeterminate risk, low risk, and missing score), BMI, hemoglobin A1c (HbA1c), ALT, estimated glomerular filtration rate, comorbidities (coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, dementia, chronic lung disease, malignancy, depression), any encounter in different PCP clinic types (family medicine, internal medicine, urgent care), provider type of assigned PCP (medical doctor, doctor of osteopathic medicine, nurse practitioner and physician assistant) and whether patients had any endocrinology encounter during the study period (yes/no). Age and BMI were non-linear and required a spline term in the model, split at the median value for each. The ORs and 95% CIs for each model covariate were calculated. Statistical analyses were conducted using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA). A value of p<0.05 was considered statistically significant.

RESULTS

Our cohort included 847 patients with a diagnosis of both T2D and MASH in DUHS. The mean age was 59.7 years (SD 12), 61.9% (n=524) were female, and 11.9% (n=101) and 4.6% (n=39) were of NL Black race and Latino/a/x ethnicity, respectively. Mean HbA1c was 7.5% (SD 1.5) and most patients were prescribed metformin (62.5%, n=529) and insulin (62.3%, n=528) for their T2D. Mean ALT and AST were 46.0 (SD 37.5) and 48.0 (SD 55.6), respectively, and mean FIB-4 was 3.8 (SD 5.2). Table 1 summarizes patient and clinical characteristics.

Of the 847 patients, 34.8% (n=295) were prescribed EBP; GLP-1RA alone, pioglitazone alone and both pioglitazone and GLP-1RA were prescribed in 28.3% (n=240), 3.5% (n=30), and 3.0% (n=25) of patients, respectively. The rate of EBP prescribing was 43.6% (n=17) in Latino/a/x patients, 34.7% (n=35) in NL Black patients, and 34.1% (n=214) in NL White patients (table 2).

A total of 703 patients were included in the adjusted model (online supplemental figure 1). No significant differences were noted in the odds of being prescribed EBP across racial/ethnic groups (Latino/a/x vs NL White patients: adjusted OR (aOR) 1.82, 95% CI 0.78 to 4.28; NL Black vs NL White patients: aOR 0.76, 95% CI 0.44 to 1.33, p=0.20) after controlling for other factors (table 3). While most covariates in the logistic regression model were not associated with odds of being prescribed EBP, at least one endocrinology encounter during the study period was associated with threefold higher odds of EBP (aOR 3.1, 95% CI 2.1 to 4.8). Additionally, increases in HbA1c and BMI values were likewise associated with higher odds of EBP prescription (table 3).

Details of EBP prescribing

Of pioglitazone prescriptions (n=55), 32.7% (n=18) were written by PCPs and 67.3% (n=37) were written by endocrinologists. Of GLP-1RA prescriptions, 31.7% (n=84)

Table 2 Rate of evidence-based T2D pharmacotherapy in MASH across race and ethnicities (n=767)

Outcome	Latino/a/x n=39	NL Black n=101	NL White n=627
EBP	17 (43.6%)	35 (34.7%)	214 (34.1%)
GLP-1RA alone	13 (33.3%)	32 (31.7%)	176 (28.1%)
Pioglitazone alone	1 (2.6%)	2 (2.0%)	21 (3.3%)
Both GLP-1RA and pioglitazone	3 (7.7%)	1 (1.0%)	17 (2.7%)

EBP, evidence-based T2D pharmacotherapy (prescription for pioglitazone and/or GLP-1RA; GLP-1RA, glucagon-like peptide-1 receptor agonist; MASH, metabolic dysfunction-associated steatohepatitis; NL, non-Latino/a/x; T2D, type 2 diabetes.

Table 3 Odds of EBP for MASH (n=703)

Covariate	aOR for EBP (95% CI)	P value
Race/ethnicity*		
Latino/a/x versus NL White	1.82 (0.78 to 4.28)	0.20
NL Black versus NL White	0.76 (0.44 to 1.33)	
Age		
<59 years, 1 year increase	1.00 (0.98 to 1.04)	0.17
>59 years, 1 year increase	0.96 (0.92 to 1.00)	
Female sex versus male	1.08 (0.74 to 1.59)	0.69
Insurance group		
Managed care versus government	1.63 (0.94 to 2.80)	0.05
Private versus government	1.25 (0.75 to 2.09)	
Self-pay versus government	0.28 (0.08 to 1.04)	
Comorbidities (yes versus no)		
Congestive heart failure	0.63 (0.31 to 1.29)	0.21
Coronary artery disease	0.71 (0.40 to 1.27)	0.25
Cerebrovascular disease	0.70 (0.31 to 1.57)	0.39
Peripheral vascular disease	1.07 (0.35 to 3.29)	0.91
Chronic lung disease	0.93 (0.55 to 1.58)	0.79
Any malignancy	0.97 (0.56 to 1.67)	0.91
Metastatic solid tumor	0.31 (0.07 to 1.31)	0.11
Dementia	1.90 (0.39 to 9.35)	0.43
Depression	1.07 (0.66 to 1.73)	0.79
BMI		
Mean BMI <34, 1 unit increase	1.12 (1.04 to 1.21)	<0.01
Mean BMI >34, 1 unit increase	1.01 (0.98 to 1.06)	
Clinical care (yes versus no)		
Endocrinology visit	3.14 (2.08 to 4.75)	<0.01
Family medicine visit	1.11 (0.73 to 1.68)	0.62
Internal medicine visit	1.32 (0.84 to 2.09)	0.23
Urgent care visit	1.04 (0.69 to 1.57)	0.86
PCP title		
DO versus MD	0.84 (0.43 to 1.63)	0.11
NP versus MD	0.40 (0.20 to 0.81)	
PA versus MD	0.86 (0.42 to 1.76)	
Unspecified versus MD	1.35 (0.63 to 2.92)	
# of outpatient visits, 1 unit increase	1.03 (1.00 to 1.06)	0.03
Laboratory values		
Mean HbA1c (%), 1 unit increase	1.30 (1.13 to 1.48)	<0.01
Mean ALT (IU/L), 5 units increase	0.99 (0.96 to 1.02)	0.53
Mean eGFR (mL/min/1.73 m^2), 5 unit increase	0.99 (0.95 to 1.04)	0.73
Mean FIB-4 Score		
High risk versus low risk	0.56 (0.35 to 0.90)	0.05
Indeterminate versus low risk	0.57 (0.35 to 0.93)	
Missing versus low risk	0.70 (0.35 to 1.43)	

Model was adjusted for: age, sex, insurance status, FIB-4 category, BMI, HbA1c ALT, eGFR, comorbidities (coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, dementia, chronic lung disease, malignancy, depression), whether patients had any encounter in a family medicine, internal medicine, urgent care, or endocrinology clinic (yes/no for each), and provider type of assigned PCP (medical doctor, doctor of osteopathic medicine, nurse practitioner and physician assistant).
*Primary covariate of interest. Results from multivariable logistic regression model.
ALT, alanine aminotransferase; aOR, adjusted OR; BMI, body mass index; DO, doctor of osteopathic medicine; EBP, evidence-based T2D pharmacotherapy (prescription for pioglitazone and/or glucagon-like peptide-1 receptor agonist); eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; MASH, metabolic dysfunction-associated steatohepatitis; MD, medical doctor; NL, non-Latino/a/x; NP, nurse practitioner; PA, physician assistant; PCP, primary care physician; T2D, type 2 diabetes.

were written by PCPs and 68.3% (n=181) were written by endocrinologists. Of the 295 patients prescribed EBP, 41.7% (n=123) had MASLD/MASH documented in either PCP and/or endocrinology notes, yet only 7.8% (n=23) mentioned the prescription of EBP for its benefit in MASLD/MASH.

DISCUSSION

Because of their known benefit in halting, or even reversing, MASH progression, pioglitazone and GLP-1RA should be considered in all patients with T2D who have MASH.[4 12] In this study conducted at a large academic health center we demonstrated low prescription (<40%) of EBP in patients with T2D and MASH, and the majority of chart notes (>90%) did not mention MASH as a reason for prescribing EBP in patients with T2D and MASH. Unlike T2D medications used for cardiorenal benefit,[17] we did not find racial/ethnic disparities in EBP for MASH.

We found pioglitazone prescriptions to be particularly low (6.5%), despite its known benefits in MASH[4 18 19] and its wide availability and affordability relative to other T2D medications. While the reasons for pioglitazone underuse are unclear, concerns related to long-term safety may have contributed. For instance, a cross-sectional analysis of the National Health and Nutrition Examination

Survey cohort identified a steep decline in pioglitazone prescriptions between 2005 and 2006 (20%) and 2013 and 2014 (4%).[20] This timing coincides with the Food and Drug Administration black box warning for ischemic cardiovascular disease risk with rosiglitazone in 2007, the black box warning for bladder cancer risk with pioglitazone in 2011, and the approval of generic pioglitazone the same year; these events may have led to less promotion of pioglitazone for T2D care. Notably, data on the association between pioglitazone and bladder cancer are mixed,[21] yet the benefits of pioglitazone on MASH and cardiovascular disease[4 12 22] likely outweigh the marginal risk of bladder cancer in many cases. Furthermore, while pioglitazone can contribute to weight gain—which can raise concern in patients with T2D and MASH—this effect is dose-dependent (1% with pioglitazone 15 mg/day, 3%–5% with 45 mg/day)[4] and can be offset by lifestyle interventions and/or other T2D medications that promote weight loss, such as GLP-1RA or sodium-glucose cotransporter-2 inhibitors.

In addition to concerns related to safety and side effects, lack of clinician awareness about the benefits of pioglitazone in MASH may contribute to its low prescription rates. In a survey of >750 clinicians, including hepatologists, endocrinologists and PCPs, 47% were unaware of the appropriateness of using pioglitazone to treat MASH.[23] PCPs—who conduct the majority of outpatient T2D care—were less likely than other clinicians to be aware of pioglitazone's role in the treatment of MASH (42%, in comparison to 77% for endocrinology).[23]

Prescriptions for GLP-1RA (31.3%) were substantially higher than for pioglitazone (6.5%) in our study. As most GLP-1RA prescriptions were placed by endocrinologists in this study (68.3%), greater clinician familiarity and comfort with prescribing GLP-1RA for the purpose of T2D and weight management may have accounted for this finding. We noted that only 7.8% of all EBP prescriptions (n=23/295) were accompanied by clinical documentation that MASLD/MASH diagnosis influenced T2D medication decision making. Overall, these data suggest that clinicians may be basing their T2D medication decisions on T2D and other comorbidities (eg, obesity, cardiovascular disease), without considering the benefits of GLP-1RA (and pioglitazone) in MASH. This possibility is further supported by the fact that higher HbA1c and BMI values were associated with higher odds of EBP, whereas ALT and FIB-4 (ie, liver-specific measures) values did not appear to influence the odds of EBP prescription (table 3).

To the best of our knowledge, this is the first study to explore racial/ethnic disparities in the use of evidence-based T2D medications for MASH. Additional strengths of this study include: (1) The large sample of patients with a diagnosis code for MASH who were engaged in T2D care in DUHS, and (2) Inclusion of a T2D cohort with suboptimal glycemic control (mean HbA1c >7%) in whom T2D medication management was likely merited.

Our study has some limitations. First, the largest trial demonstrating benefit of GLP-1RA therapy (ie, semaglutide) in MASH was published online in November 2020, and subsequently in print March 2021;[10] because our data were collected between 2019 and 2021, they do not capture changes in GLP-1RA prescribing that may have occurred after this study. These data were also collected prior to the release of primary care and endocrinology guidelines (2022) that recommend the use of GLP-1RA in MASLD/MASH.[4] However, as a result, this study serves as a helpful baseline on which to measure improvements in EBP that may occur over time. Another limitation is that our study included the first year of the COVID-19 pandemic (2020–2021), so the frequency of PCP and specialist visits, as well as prescriptions placed, may not reflect usual T2D and MASH practice. Given the known under-recognition of MASLD/MASH in practice,[23 24] it is also important to acknowledge that our reliance on diagnosis codes may have resulted in many missed cases of MASH that were not included in this study. We decided to focus this study on the treatment of MASH in cases where a diagnosis had already been made, however future studies assessing for rates of (and disparities in) MASH detection would also be invaluable for understanding how to tailor interventions and care approaches to improving liver outcomes in all patients with T2D. Finally, while one in four patients in this study were of non-White race, greater diversity would have allowed for more robust comparison between under-represented racial/ethnic groups, particularly those of Latino/a/x ethnicity.

CONCLUSIONS

In summary, prescription rates for EBP in patients with MASH and T2D are low and do not align with current guidelines and best practices. We identified no racial/ethnic disparities in EBP. Further study is needed to understand whether disparities exist further upstream in the care pathway, including in evidence-based testing and diagnosis of MASLD/MASH. Our findings suggest that interventions are needed to promote evidence-based prescribing for MASH in T2D; future studies should examine whether gaps between current and guideline-based care narrow over time.

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Contributors A-SA, AP and MO were involved in the conception, design and conduct of the study, as well as the interpretation of results. A-SA, AP and MO

had full access to all the data in the study and AP performed data analyses. A-SA and AP drafted the manuscript. BCB, CM and MJC were involved in study design, interpretation of results, and they edited, reviewed and approved the final version of the manuscript. A-SA (the guarantor) accepts full responsibility for the study's work and conduct, had access to the data, and controlled the decision to publish.

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Competing interests CM has consulted for NovoNordisk and has served on the advisory board for Boehringer Ingelheim, Inc. CM has also received grants from GlaxoSmithKline, Exact Sciences and Madrigal to conduct research at Duke University. All other authors declare no competing interests with this work.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and is based on data collected retrospectively from the Duke University Healthcare System. The Duke Health Institutional Review Board approved the study under protocol number Pro00110434. Only deidentified data were used.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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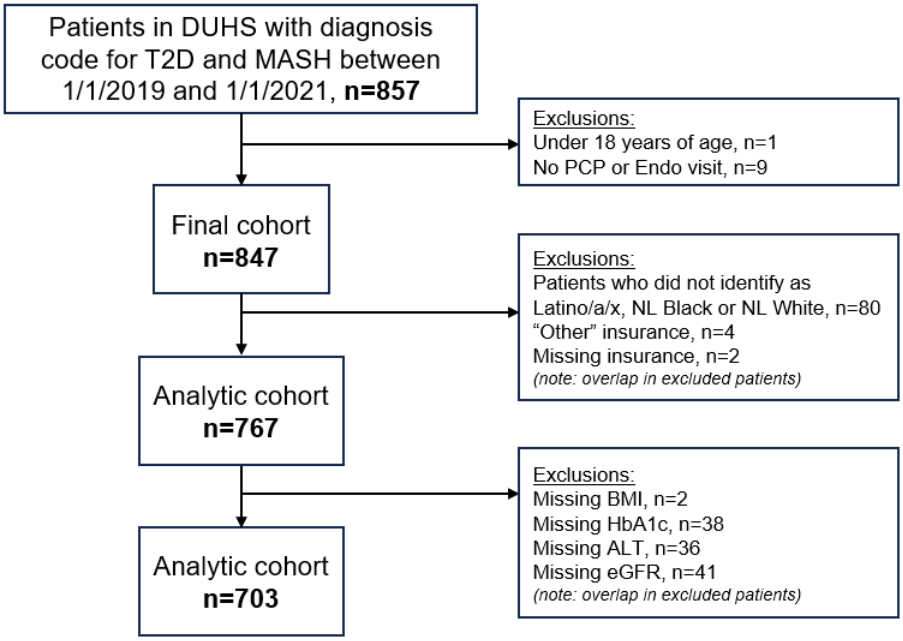
REFERENCES

1 Rinella ME, Lazarus JV, Ratziu V, *et al*. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78:1966–86.
2 Younossi ZM, Golabi P, de Avila L, *et al*. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;71:793–801.
3 Samji NS, Snell PD, Singal AK, *et al*. Racial disparities in diagnosis and prognosis of nonalcoholic fatty liver disease. *Clin Liver Dis (Hoboken)* 2020;16:66–72.
4 Cusi K, Isaacs S, Barb D, *et al*. American association of clinical endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American association for the study of liver diseases (AASLD). *Endocr Pract* 2022;28:528–62.
5 Belfort R, Harrison SA, Brown K, *et al*. A placebo-controlled trial of Pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297–307.
6 Sanyal AJ, Chalasani N, Kowdley KV, *et al*. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362:1675–85.
7 Cusi K, Orsak B, Bril F, *et al*. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305–15.
8 Aithal GP, Thomas JA, Kaye PV, *et al*. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008;135:1176–84.
9 Armstrong MJ, Gaunt P, Aithal GP, *et al*. Liraglutide safety and efficacy in patients with non-alcoholic Steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679–90.
10 Newsome PN, Buchholtz K, Cusi K, *et al*. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021;384:1113–24.
11 Wei Q, Xu X, Guo L, *et al*. Effect of SGLT2 inhibitors on type 2 diabetes mellitus with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)* 2021;12:635556.
12 ElSayed NA, Aleppo G, Aroda VR, *et al*. 4. comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2023. *Diabetes Care* 2023;46:S49–67.
13 Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, *et al*. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797–835.
14 Kanwal F, Shubrook JH, Adams LA, *et al*. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2021;161:1657–69.
15 Sterling RK, Lissen E, Clumeck N, *et al*. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43:1317–25.
16 McPherson S, Hardy T, Dufour J-F, *et al*. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol* 2017;112:740–51.
17 McCoy RG, Van Houten HK, Deng Y, *et al*. Comparison of diabetes medications used by adults with commercial insurance vs medicare advantage, 2016 to 2019. *JAMA Netw Open* 2021;4:e2035792.
18 Chalasani N, Younossi Z, Lavine JE, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the study of liver diseases. *Hepatology* 2018;67:328–57.
19 Musso G, Cassader M, Paschetta E, *et al*. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017;177:633–40.
20 Le P, Chaitoff A, Rothberg MB, *et al*. Trends in pioglitazone use among U.S. adults with type 2 diabetes and suspected nonalcoholic fatty liver disease. *Expert Opin Investig Drugs* 2020;29:205–8.
21 Filipova E, Uzunova K, Kalinov K, *et al*. Pioglitazone and the risk of bladder cancer: a meta-analysis. *Diabetes Ther* 2017;8:705–26.
22 ElSayed NA, Aleppo G, Aroda VR, *et al*. 3. Prevention or delay of type 2 diabetes and associated comorbidities: standards of care in diabetes-2023. *Diabetes Care* 2023;46:S41–8.
23 Kanwal F, Shubrook JH, Younossi Z, *et al*. Preparing for the NASH epidemic: a call to action. *Gastroenterology* 2021;161:1030–42.
24 Alexopoulos A-S, Duffy R, Kobe EA, *et al*. Underrecognition of nonalcoholic fatty liver disease in poorly controlled diabetes: a call to action in diabetes care. *J Endocr Soc* 2021;5:bvab155.

Supplemental Material

Supplementary Figure 1:



Abbreviations: DUHS=Duke University Healthcare System; T2D=type 2 diabetes; MASH=metabolic dysfunction-associated steatohepatitis; PCP=Primary Care Physician; BMI=body mass index; HbA1c=hemoglobin A1c; ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate.

Supplementary Table 1: Unadjusted model results

Outcome	Latino/a/x	NL Black	NL White	Latino/a/x vs. NL White, OR (95% CI)	NL Black vs. NL White , OR (95% CI)	p-value
EBP	17 (43.59%)	35 (34.65%)	214 (34.13%)	1.77 (0.60, 5.24)	0.47 (0.14, 1.57)	0.488
GLP-1 RA	16 (41.03%)	33 (32.67%)	193 (30.78%)	1.56 (0.81, 3.03)	1.09 (0.70, 1.71)	0.401
Pioglitazone	4 (10.26%)	3 (2.97%)	38 (6.06%)	1.49 (0.78, 2.87)	1.02 (0.66, 1.59)	0.248

Supplementary Table 2: Sensitivity analysis- odds of evidence-based T2D pharmacotherapy for MASH, with addition of fractures as a covariate (n=703)

Covariate	aOR for EBP (95% CI)	p-value
Race/ethnicity*		
Latino/a/x vs. NL White	1.85 (0.79, 4.34)	0.21
NL Black vs. NL White	0.78 (0.45, 1.37)	
Age		
< 59 years, 1 year increase	1.01 (0.98, 1.04)	0.15
> 59 years, 1 year increase	0.96 (0.91, 1.00)	
Female sex vs. male	1.05 (0.71, 1.55)	0.81
Insurance group		
Managed care vs. Government	1.60 (0.93, 2.76)	0.06
Private vs. Government	1.23 (0.74, 2.06)	
Self-pay vs. Government	0.28 (0.08, 1.05)	
Comorbidities (yes vs. no)		
Congestive heart failure	0.57 (0.27, 1.18)	0.13
Coronary artery disease	0.73 (0.41, 1.30)	0.29
Cerebrovascular disease	0.66 (0.29, 1.51)	0.33
Peripheral vascular disease	1.00 (0.32, 3.09)	1.00
Chronic lung disease	0.93 (0.54, 1.58)	0.78
Any malignancy	0.92 (0.53, 1.60)	0.76
Metastatic solid tumor	0.33 (0.08, 1.39)	0.13
Dementia	1.81 (0.37, 8.97)	0.47
Depression	1.04 (0.64, 1.68)	0.88
Fractures	1.54 (0.85, 2.77)	0.15
BMI		
Mean BMI <34, 1 unit increase	1.13 (1.05, 1.21)	<0.01
Mean BMI >34, 1 unit increase	1.02 (0.98, 1.06)	
Clinical care (yes vs. no)		
Endocrinology visit	3.11 (2.06, 4.71)	<0.01
Family medicine visit	1.12 (0.74, 1.70)	0.59
Internal medicine visit	1.37 (0.86, 2.17)	0.18
Urgent care visit	1.00 (0.66, 1.52)	1.00
PCP title		
DO vs. MD	0.83 (0.43, 1.62)	0.12
NP vs. MD	0.40 (0.20, 0.82)	
PA vs. MD	0.90 (0.44, 1.85)	
Unspecified vs. MD	1.32 (0.61, 2.85)	
# of outpatient visits, 1 unit increase	1.03 (1.00, 1.06)	0.03
Laboratory values		
Mean Hemoglobin A1c (%), 1 unit increase	1.30 (1.14, 1.49)	<0.01
Mean ALT (IU/L), 5 units increase	0.99 (0.96, 1.02)	0.53
Mean eGFR ($mL/min/1.73m^2$), 5 unit increase	0.99 (0.95, 1.04)	0.72
Mean FIB-4 score		
High risk vs. low risk	0.56 (0.35, 0.91)	0.05
Indeterminate vs. low risk	0.57 (0.34, 0.92)	
Missing vs. low risk	0.71 (0.35, 1.45)	

*Primary covariate of interest. Results from multivariable logistic regression model. Abbreviations: aOR=adjusted OR; EBP=evidence-based T2D pharmacotherapy (prescription for pioglitazone and/or glucagon-like peptide-1 receptor agonist); NL=non-Latino/a/x; BMI=body mass index; PCP=primary care physician; DO=doctor of osteopathic medicine; MD=Medical doctor; NP= nurse practitioner; PA=physician assistant; ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate; FIB-4=fibrosis-4. Model was adjusted for: age, sex, insurance status, FIB-4 category, BMI,

hemoglobin A1c ALT, eGFR, comorbidities (coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, dementia, chronic lung disease, malignancy, depression), and whether patients had any encounter in a family medicine, internal medicine, urgent care or endocrinology clinics (yes/no for each).