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Epidemiology of Metabolic Dysfunction-Associated Fatty Liver Disease in Type 2 Diabetes Mellitus and Effects of Antiglycemic Therapy on Liver Fibrosis: A Retrospective Study

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Abstract

Background: Metabolic dysfunction-associated fatty liver disease (MAFLD) is a globally prevalent and multifaceted liver disorder, closely linked to metabolic conditions such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia and hypertension. The coexistence of MAFLD and T2DM poses substantial health challenges due to their mutual impact on disease progression and prognosis, thereby augmenting the susceptibility to developing cirrhosis and hepatocellular carcinoma (HCC). Some antiglycemic therapies may improve hepatic steatosis and liver histology. The aim of the study was to elucidate MAFLD prevalence, impact of T2DM and other metabolic risk factors on liver stiffness measurement (LSM), correlation of MAFLD with chronic kidney disease (CKD) and ischemic heart disease (IHD) and the influence of antiglycemic medications on LSM, utilizing data derived from fibroscan results.

Methods: A retrospective analysis of electronic health records was conducted encompassing patients who underwent fibroscan assessments at an Australian Hospital from January 1, 2022 to March 31, 2023. The inclusion criteria for MAFLD comprised a controlled attenuation parameter (CAP) score ≥ 248 dB along with metabolic dysfunction. During the demographic analysis, patients were stratified on the basis of presence or absence of T2DM while excluding patients with type 1 diabetes mellitus (T1DM) and other potential causes of hepatic steatosis. Linear regression analysis was employed to identify factors associated with LSM scores < 8 or > 8 kPa, indicative of clinically significant fibrosis. Comprehensive medication data were retrospectively extracted from electronic charts and cross-verified with general practitioner medical records.

Results: Among 1,129 participants who underwent fibroscan evaluation, 437 (38.71%) individuals had MAFLD. Statistical evidence demonstrated a significant association between T2DM and MAFLD ($P < 0.001$), revealing a 4.81-fold increase in the odds of MAFLD, accompanied by a 31% higher LSM ($P < 0.001$). Furthermore, a robust correlation was observed between MAFLD and CKD (3.38-fold increase in odds, $P < 0.001$), as well as IHD (2.10-fold increase in odds, $P < 0.001$). Of significance, individuals with T2DM using glucagon-like peptide-1 receptor agonists (GLP-1a) and sodium-glucose cotransporter 2 inhibitors (SGLT-2i) manifested significantly lower LSM (-20.55% and -25.17%, respectively), while insulin use was associated with a 101.38% higher LSM compared to non-insulin users.

Conclusions: MAFLD exhibits a notably high prevalence in this cohort, with T2DM leading to a higher LSM. Individuals with MAFLD frequently have concurrent CKD and IHD. The observed LSM reduction among individuals using SGLT-2i or GLP-1a underscores the potential utility of clinical trials to assess their efficacy in attenuating MAFLD progression.

Keywords: MAFLD; Type 2 diabetes mellitus; Antiglycemic therapy; Liver fibrosis

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common liver disorder worldwide, affecting approximately one-quarter of the global population [1]. It is defined as the presence of excess hepatic steatosis based on biopsy or imaging in the absence of a secondary cause (e.g., heavy alcohol intake, medications such as amiodarone, methotrexate, antiretrovirals, tamoxifen, and disorders such as hepatitis C) [2]. International expert opinion recommends substituting the term NAFLD with metabolic dysfunction-associated fatty liver disease (MAFLD) and proposes a revised definition that encompasses metabolic risk factors such as obesity, type 2 diabetes

mellitus (T2DM), dyslipidemia or hypertension [3]; however, an ongoing discussion persists regarding nomenclature, and a consensus has not yet been reached at this juncture. As our study focuses on individuals with T2DM, the term MAFLD was employed for clarity and alignment with contemporary discourse.

NAFLD encompasses a continuum of disease. The subset of NAFLD that is progressive is called non-alcoholic steatohepatitis (NASH) and this diagnosis requires biopsy with fat infiltration in the liver as well as some lobular inflammation and evidence of hepatocyte ballooning. The NASH subtype can progress to cirrhosis [2]. NASH has now emerged as one of the primary contributors to hepatocellular carcinoma (HCC), ranking as the second most prevalent cause of HCC among individuals awaiting liver transplantation in the United States, superseded only by hepatitis C [4]. Experts advocating for a transition in nomenclature also recommend describing MAFLD by incorporating the grade of activity and stage of fibrosis, rather than relying on the term NASH [3]. NAFLD exhibits associations with various cardiometabolic disorders, including obesity, T2DM, hypertension, and dyslipidemia [5]. The likelihood of developing NASH is two to three times greater in individuals with obesity and/or T2DM [5].

The concurrent prevalence of MAFLD and T2DM can be explained by their shared risk factors and pathophysiological mechanisms. A prevalence study encompassing 20 countries revealed a strikingly high 55% global prevalence of MAFLD in individuals with T2DM [6]. The bidirectional association between MAFLD and T2DM involves visceral adiposity and insulin resistance (IR) as pivotal mediators within the pathophysiological pathway. Notably, visceral adipose tissue is acknowledged for its capacity to augment *de novo* gluconeogenesis, while the presence of hepatic fat is intricately linked to hepatic IR [7]. Furthermore, MAFLD accentuates IR in both hepatic and adipose tissues, thereby potentially fostering the progression towards the development of T2DM [8]. The prevalence of MAFLD in T1DM is much lower than T2DM. One study found 8.8% prevalence of steatosis in T1DM while others found no increased risk in T1DM [5].

MAFLD itself is not a benign disease; a comprehensive analysis spanning 13 to 14.5 years and six studies revealed increased mortality, particularly in cardiovascular (CV)-related deaths [9]. MAFLD is additionally correlated with microvascular complications, particularly chronic kidney disease (CKD), with a higher incidence observed in cases of NASH and cirrhosis [10].

Accurate MAFLD diagnosis poses notable challenges. While liver biopsy remains the gold standard for diagnosis, its invasiveness and potential complications make non-invasive imaging techniques such as transient elastography and magnetic resonance imaging increasingly attractive [11]. Emerging biomarkers and serum indices, such as the MAFLD fibrosis score and fibrosis-4 (FIB-4) index, offer additional diagnostic tools [12]. However, ongoing research is required to refine diagnostic algorithms for this complex interplay.

Lifestyle modifications, such as weight loss, dietary changes, and exercise, are the cornerstone of MAFLD management. Bariatric surgery has emerged as a potential option for selected patients with severe obesity [2]. Pharmacological agents, including pioglitazone, vitamin E, sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1a), have demonstrated beneficial effects on liver fibrosis and glycemic control; however, none are currently approved for MAFLD treatment [10].

Aims

In this cross-sectional study, MAFLD prevalence was examined within a cohort residing in the catchment area of Logan Hospital in Queensland, Australia. MAFLD severity in individuals with T2DM was examined in comparison to other cardiometabolic predictors such as obesity, hypertension and dyslipidemia. Additionally, the association of MAFLD with ischemic heart disease (IHD) and CKD was also explored. Furthermore, the impact of glycemic control and various diabetes treatments on liver fibrosis was examined to assess whether improvement was linked to effective glycemic control, as indicated by hemoglobin A1c (HbA1c) levels, or attributed to specific medications. Fibroscan results were utilized as a key metric for assessment.

Materials and Methods

Design settings and subjects

This study conducted a retrospective analysis of electronic health records for individuals aged > 18 years who underwent fibroscan testing at Logan Hospital Queensland, Australia from January 1, 2022 to March 31, 2023. MAFLD was defined as a controlled attenuation parameter (CAP) score of ≥ 248 dB as used in most studies [13] and the presence of at least one metabolic risk factor (obesity, T2DM, dyslipidemia or hypertension). The dataset included consecutive fibroscans performed for various indications but largely due to abnormal liver function tests (LFTs). All alternative diagnoses such as alcoholic liver disease (alcohol intake > 20 g/day for women and > 30 g/day for men over at least a 2-year period), active or past history of hepatitis C, other viral hepatitis (e.g., hepatitis B, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV)), malnutrition, pregnancy, Wilson's disease, parenteral nutrition, angiolipoproteinemia, medications, Reye's syndrome, inborn errors of metabolism, ischemic hepatitis, biliary obstruction and liver metastasis were excluded from the study [2]. Individuals with T1DM were also excluded from the study. Steatosis grades were determined based on liver stiffness measurement (LSM) scores, categorized as low risk (< 8 kPa), moderate risk (8 - 12 kPa), and high risk (> 12 kPa). These cut-off values were applied in accordance with the Baveno VI classification employed by the American Association for the Study of Liver Diseases (AASLD) [10, 14]. Patient body mass index (BMI) data were adjusted for ethnicity for patients from South Asia (BMI 23 - 27.4 kg/m^2 classified as overweight, BMI 27.5 - 30.0 kg/m^2 as class 1 obese) [15]. As international experts define MAFLD using "positive criteria", which involve cardiometabolic risk factors such as obesity, T2DM, hypertension and hyperlipidemia [3], patients with these characteristics were included in our study. These cardiometabolic risk factors and

history of CKD and IHD were recorded from medical notes. To cross-verify covariates, patients' BMI values for obesity were recorded from electronic medical charts, HbA1c values were obtained from both internal and external pathology laboratories, information on antiglycemic therapy for T2DM was collected from medical notes, the use of anti-hypertensive therapy for hypertension was examined from medical notes and prescriptions, and lipid profiles and anti-hyperlipidemic therapy for hyperlipidemia were reviewed. HbA1c values were considered within a 3-month window relative to the fibroscan. Medication history including total daily dose of insulin was extracted from medical records and cross-verified with general practitioner prescriptions to enhance the integrity and accuracy of the dataset. Confirmation from pharmacy records ensured that medication scripts were dispensed within at least 6 months of the fibroscan, allowing for a reasonable timeframe to assess the effects of medications on LSM. To validate CKD history, estimated glomerular filtration rate (eGFR) and proteinuria of patients were recorded, corresponding to their CKD stages, within a 3-month timeframe before or after the fibroscan procedure, as extracted from laboratory records. CKD stages were defined as: stage 1 - eGFR > 90 with albuminuria; stage 2 - eGFR 60 - 89 with albuminuria; stage 3a - eGFR 45 - 59, stage 3b - eGFR 30 - 44; stage 4 - eGFR 15 - 29; stage 5 - eGFR < 15) [16]. Additionally, coronary angiograms or other functional studies related to IHD were also examined.

Statistical analysis

Summary statistics are reported depending on the type of the variable. The mean and standard deviation (SD) are reported for continuous variables, except in the case of variables with highly skewed distributions, where the median and interquartile range (IQR) are instead reported. Counts and corresponding percentages are reported for each level of a categorical variable.

Fisher's exact test was used to test the associations of MAFLD with sex, T2DM, CKD, and IHD in the full study cohort, and the associations of T2DM with CKD and IHD in patients with MAFLD.

The effects of LSM, BMI and HbA1c % (all continuous) on total daily insulin dose in MAFLD patients using insulin were tested using a multiple linear regression model. Predictors of LSM were identified using two multiple linear regression models. The first model tested for the effects of general patient variables on LSM in patients with MAFLD: age (continuous), sex (binary), T2DM (binary), obesity (binary), hypertension (binary) and dyslipidemia (binary). The second model tested for the effects of T2DM-specific patient variables on LSM in patients with MAFLD and T2DM: HbA1c % (continuous), and the use of six diabetic treatments (metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitors (DPP4i), GLP-1a, SGLT-2i and insulin; all binary). Due to significant deviations away from the assumptions of linear regression (linearity, normality of residuals and homoskedasticity of residuals) when fitting the models with LSM as the outcome, the model was fit using natural-log transformed LSM values, which sufficiently corrected these deviations. Due to the log transformation of the outcome, the interpretation of the coefficient estimates is: for a binary predictor, a coefficient value of β corresponds to a $100 \times (\exp(\beta) - 1)$ percent change in the outcome relative to the reference level; for a continuous predictor, a coefficient value of β corresponds to a $100 \times (\exp(\beta) - 1)$ percent change in the outcome per unit increase in the predictor.

The effect of LSM on the odds of a patient having CKD and IHD was tested using two univariate logistic regression models.

R (version 4.2.2) was used to conduct all statistical analyses.

Institutional Review Board Approval and ethical compliance

Specific site approval was granted by Metro South Research Governance Queensland Australia. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects.

Results

During the study period, 1,129 patients underwent fibroscan, primarily prompted by LFTs. Of these, 437 patients fulfilled the inclusion criteria for MAFLD, yielding a prevalence of 38.71% in this cohort. There was a male-to-female predominance (42.78% vs. 35.16%). Additionally, males exhibited 1.38 times higher odds of having MAFLD (95% confidence interval (CI): 1.08 - 1.77, P = 0.010). A significant association between T2DM and MAFLD was found (P < 0.001). Individuals with T2DM experienced 4.81 times increased odds of having MAFLD (95% CI: 3.65 - 6.38), with a prevalence of 51% in individuals with T2DM in this cohort. The demographic and clinical characteristics of general patient variables and T2DM-specific variables are described in Tables 1 and 2.

General predictors of LSM in MAFLD

Statistical analysis demonstrated that age (P = 0.006) and T2DM (P < 0.001) exert an influence on LSM. For each year increase in age, there was an estimated 0.7% increase in LSM (95% CI: 0.2 - 1.21). Moreover, patients with T2DM were estimated to exhibit a 31% increase in LSM compared to individuals without diabetes (95% CI: 15.95 - 47.99). Notably, other cardiometabolic risk factors (obesity, dyslipidemia, hypertension) did not show significant impact on LSM (Table 3). LSM was significantly elevated (P < 0.001) in MAFLD patients with diabetes (median: 7.7; IQR: 5.6 - 13.1) in comparison to those without diabetes (median: 6.0; IQR: 4.6 - 8.3).

Predictors of LSM in MAFLD with T2DM

There was statistically significant evidence that the use of GLP-1a (P = 0.013), SGLT-2i (P = 0.001) and insulin (P < 0.001)

Table 1. Summary Statistics of General Patient Variables for MAFLD Patients

Characteristic	MAFLD (N = 437)	Non-MAFLD (N = 692)
Age (years)	58 (13)	
Sex		
Female	212 (49%)	391 (57%)
Male	225 (51%)	301 (43%)
Ethnicity		
Asian	19 (4.3%)	
Caucasian	413 (95%)	
Other	5 (1.1%)	
BMI (kg/m^2)	34 (7)	
Unknown	3	
Obesity class[a]		
Normal BMI	16 (3.7%)	
Overweight	100 (23%)	
1	143 (33%)	
2	100 (23%)	
3	75 (17%)	
Unknown	3	
Hypertension		
Yes	237 (54%)	
No	200 (46%)	
Dyslipidemia		
Yes	266 (61%)	
No	171 (39%)	
IHD		
Yes	84 (19%)	71 (10%)
No	350 (81%)	621 (90%)
Unknown	3	
CKD		
Yes	176 (40%)	115 (17%)
No	261 (60%)	577 (83%)
LSM (kPa)	7 (5, 10)	
T2DM		
Yes	223 (51%)	123 (18%)
No	214 (49%)	569 (82%)

[a]Defined by BMI in kg/m^2. Underweight: < 18.5; normal 18.5 - 24.9; overweight: 25 - 29.9; class 1: 30 - 34.9; class 2: 35 - 39.9; class 3: > 40. For Asians class 1: 27.5 - 30. Mean (SD) is reported for age and BMI; median (IQR) is reported for LSM; counts and corresponding percentages are reported for categorical variables. BMI: body mass index; CKD: chronic kidney disease; IHD: ischemic heart disease; IQR: interquartile range; LSM: liver stiffness measurement; MAFLD: metabolic dysfunction-associated fatty liver disease; SD: standard deviation; T2DM: type 2 diabetes mellitus.

Table 2. Summary Statistics of T2DM-Specific Patient Variables for MAFLD Patients With T2DM

Characteristic	N = 223
HbA1c	7.35 (1.70)
Unknown	8
Metformin	
Yes	187 (84%)
No	36% (16%)
Sulfonylurea	
Yes	53 (24%)
No	170 (76%)
DPP4i	
Yes	42 (19%)
No	181 (81%)
GLP-1a	
Yes	62 (28%)
No	161 (72%)
SGLT-2i	
Yes	69% (31%)
No	153 (69%)
Unknown	1
Insulin	
Yes	49 (22%)
No	173 (78%)
Unknown	1

Mean (SD) is reported for HbA1c; counts and corresponding percentages are reported for categorical variables. DPP4i: dipeptidyl peptidase-4 inhibitors; GLP-1a: glucagon-like peptide-1 receptor agonists; HbA1c: hemoglobin A1c; MAFLD: metabolic dysfunction-associated fatty liver disease; SGLT-2i: sodium-glucose co-transporter 2 inhibitors; T2DM: type 2 diabetes mellitus.

has an impact on LSM. Patients using GLP-1a exhibited an estimated -20.55% lower LSM compared to those not on this therapy (95% CI: -33.63, -4.88). Similarly, individuals taking SGLT-2i had an estimated -25.17% lower LSM compared to those not taking SGLT-2i (95% CI: -37.5, -10.42). Conversely, patients administering insulin therapy showed a significant 101.38% increase in LSM (95% CI: 64.87 - 148.43). In contrast, the use of metformin, sulfonylurea, DPP4i and HbA1c did not demonstrate a significant effect on LSM (Table 4). LSM was found to have moderate effect on the total daily dose of insulin (P = 0.028), with a 1-unit increase in LSM leading to a 0.94 unit increase in the total daily insulin dose (Table 5).

Microvascular and macrovascular complications of MAFLD

A statistically significant association between MAFLD and CKD (P < 0.001) was found, with a 3.38 times increase in the

Table 3. Linear Regression Results for Testing the Effect of Patient Characteristics on Log-Transformed LSM in MAFLD Patients

Characteristic	Beta	95% CI	P-value
Age	0.007	0.002, 0.012	0.006
Sex			
Female	-	-	
Male	0.056	-0.060, 0.171	0.3
T2DM			
No	-	-	
Yes	0.270	0.148, 0.392	< 0.001
Obesity			
Non-obese	-	-	
Obese	0.218	-0.088, 0.524	0.2
Hypertension			
No	-	-	
Yes	-0.048	-0.179, 0.083	0.5
Dyslipidemia			
No	-	-	
Yes	0.015	-0.114, 0.144	0.8

Coefficient estimates (beta) and the corresponding 95% CI and P-value for each predictor variable are reported. For each of the diabetic treatment predictors, the disuse of a treatment was taken as the baseline value for each predictor variable. CI: confidence interval; LSM: liver stiffness measurement; MAFLD: metabolic dysfunction-associated fatty liver disease; T2DM: type 2 diabetes mellitus.

odds of having CKD (95% CI: 2.54 - 4.50).

Due to the limited number of patients with advanced CKD stages 4 or 5, ordinal regression was not feasible to assess whether CKD worsens with higher LSM. Instead, we examined the impact of LSM on the binary CKD variable and observed a significant effect (P = 0.003) and estimated that each unit increase in LSM was associated with a 1.05-fold increase in the odds of having CKD (95% CI: 1.02 - 1.08) (Table 6).

A significant association between MAFLD and IHD was also observed (P < 0.001), with patients with MAFLD having 2.10 times increase in the odds of having IHD (95% CI: 1.47 - 3.00). However, there was no statistically significant evidence that LSM has an effect on the odds of a patient having IHD (Table 7). Both CKD and IHD were observed more in T2DM with MAFLD (Table 8).

Table 4. Linear Regression Results for Testing the Effect of HbA1c and the Use of Diabetic Treatments on Log-Transformed LSM in MAFLD Patients With T2DM

Characteristic	Beta	95% CI	P-value
HbA1c	-0.02	-0.08, 0.03	0.4
Metformin	0.03	-0.20, 0.26	0.8
Sulfonylurea	0.07	-0.14, 0.28	0.5
DPP4i	0.09	-0.13, 0.30	0.4
GLP-1a	-0.23	-0.41, -0.05	0.013
SGLT-2i	-0.29	-0.47, 0.11	0.001
Insulin	0.70	0.50, 0.91	< 0.001

Coefficient estimates (beta) and the corresponding 95% confidence interval and P-value for each predictor variable is reported. For each of the diabetic treatment predictors, the disuse of a treatment was taken as the baseline value for each predictor variable. CI: confidence interval; DPP4i: dipeptidyl peptidase-4 inhibitors; GLP-1a: glucagon-like peptide-1 receptor agonists; HbA1c: hemoglobin A1c; LSM: liver stiffness measurement; MAFLD: metabolic dysfunction-associated fatty liver disease; SGLT-2i: sodium-glucose co-transporter 2 inhibitors; T2DM: type 2 diabetes mellitus.

Table 5. Linear Regression Results for Testing the Effect of LSM, BMI, HbA1c % on MAFLD Patients' Total Daily Insulin Dose

Characteristic	Beta	95% CI	P-value
LSM (kPa)	0.94	0.11, 1.8	0.028
BMI	0.12	-2.3, 2.6	> 0.9
HbA1c	9.7	1.9, 18	0.016

BMI: body mass index; CI: confidence interval; HbA1c: hemoglobin A1c; LSM: liver stiffness measurement; MAFLD: metabolic dysfunction-associated fatty liver disease.

Table 6. Logistic Regression Results for Testing the Effects of LSM on Odds of CKD

Characteristic	OR	95% CI	P-value
LSM (kPa)	1.05	1.02, 1.08	0.003

CI: confidence interval; CKD: chronic kidney disease; LSM: liver stiffness measurement; OR: odds ratio.

Table 7. Logistic Regression Results for Testing the Effects of LSM on Odds of IHD

Characteristic	OR	95% CI	P-value
LSM (kPa)	1.02	1.00, 1.03	0.079

CI: confidence interval; IHD: ischemic heart disease; LSM: liver stiffness measurement; OR: odds ratio.

Table 8. Proportions of CKD and IHD in Patients With T2DM and Non-T2DM

Characteristic	Diabetic (N = 223)	Non-diabetic (N = 214)	P-value*
CKD			0.011
Yes	103 (46%)	73 (34%)	
No	120 (54%)	141 (66%)	
IHD			
Yes	63 (28%)	21 (10.0%)	< 0.001
No	160 (72%)	190 (90%)	
Unknown	0	3	

Data are expressed as n (%). *Fisher's exact test. CKD: chronic kidney disease; IHD: ischemic heart disease; T2DM: type 2 diabetes mellitus.

Discussion

This study adds to the available literature on prevalence of MAFLD and the association with comorbid conditions. In particular, a high prevalence of MAFLD was observed in individuals with T2DM in this cohort. All MAFLD patients were defined to have hepatic steatosis based on fibroscan CAP score ≥ 248 dB as utilized in other studies [13] along with the presence of metabolic risk factors. As all individuals in our study had at least one metabolic risk factor, our findings support the proposition of transitioning the terminology from NAFLD to MAFLD, encompassing metabolic risk factors. MAFLD was observed predominantly in males as compared to females (42.78% vs. 35.16%) as found in other studies [17]. In our analysis of predictors for clinically significant fibrosis (LSM > 8.0 kPa), T2DM emerged as the most influential factor, consistent with existing studies on MAFLD assessed with elastography [18, 19].

The strong association between IHD and MAFLD indicated a twofold increase in risk, particularly pronounced in patients with diabetes underscoring synergistic effects between MAFLD and diabetes. Despite the absence of statistically significant evidence linking LSM to the odds of developing IHD, IHD remains a significant cause of mortality in individuals with MAFLD [20]; nevertheless, the precise extent to which MAFLD autonomously contributes to IHD remains uncertain [10]. Prioritizing the optimization of cardiovascular (CV) risk factors management, aiming to decrease CV morbidity and mortality, is imperative for enhancing outcomes in patients with MAFLD [21, 22].

Furthermore, our findings indicate compelling evidence of an association between CKD and MAFLD, with 3.38-fold increased risk particularly in individuals with diabetes, highlighting collegial effects in the underlying pathophysiology. Although the study's limited number of advanced CKD cases hindered the analysis of high LSM effects on CKD stages, significant evidence indicated that elevated LSM is associated with increased odds of CKD (Table 6). Previous research has suggested a connection between MAFLD and microvascular complications especially CKD [23, 24] and a meta-analysis confirmed a twofold increased prevalence of CKD in individuals with MAFLD [25]. Recent findings also support an elevated risk of CKD with progressive fibrosis [26].

During the evaluation of the impact of antiglycemic therapy on LSM, it was observed that individuals using either GLP-1a or SGLT-2i exhibited significantly lower LSM (-20.55% and -25.17%, respectively), while insulin users showed higher LSM. Our findings align with a recent large-scale study conducted in the United Kingdom, suggesting that the use of SGLT-2i or GLP-1a may be associated with a reduced incidence of MAFLD and hepatic transaminase elevation in individuals with T2DM (hazard ratio (HR): 0.86, 95% CI: 0.73 - 1.01 and HR: 0.78, 95% CI: 0.68 - 0.89, respectively) [27]. Additionally, a study with 637 Italian T2DM patients demonstrated that GLP-1a and SGLT-2i, but not DPP4i, improved non-invasive biomarkers for steatosis and fibrosis (fatty liver index and FIB-4 score) [28].

In recent years, GLP-1a and SGLT-2i have shown benefits in glycemic control and positive effects on CV and renal profiles [29]. These results underscore the potential utility of these therapies in managing MAFLD, aligning with emerging evidence of their efficacy in diabetes and associated liver complications. In a phase 2 trial, semaglutide has shown reversal of NASH in higher percentage as compared to placebo [30]. Similarly, in phase 3 trial, tirzepatide showed significant reduction in liver fat content as compared to insulin degludec [31]. Empagliflozin has also been shown to reduce liver fat content and improve liver transaminases [32-34]. While the favorable impacts of GLP-1a and SGLT-2i on steatosis and features of steatohepatitis are likely attributed to weight loss and enhanced glycemic control, additional indirect mechanisms may encompass anti-inflammatory effects, modifications in hepatic substrate supply, and amelioration of gut dysbiosis [35]. Ongoing investigations explore the potential synergistic effects of combining GLP-1a with other enteropancreatic hormones to enhance their metabolic effects [36].

The influence of glycemic control on the progression of MAFLD remains a topic of contention. While two small studies have indicated an association between inadequate glycemic control and hepatocellular injury along with liver fibrosis, other investigations have not substantiated this observation [10]. Our study did not reveal a significant association between LSM and HbA1c. However, it is noteworthy that insulin doses were higher in patients with elevated LSM.

Limitations

As a retrospective study, data were extracted from electronic health records, and its reliability hinges on documentation quality. The exact recording of comorbidities and medications might not have been consistent. The obtained dataset included listed indications, which were relied upon for case selection. Incomplete or incorrect data may have led cases being inadvertently excluded from the study. Factors like medication adherence, treatment duration accuracy, and potential supply issues remained unconfirmed. History of smoking was also not recorded due to inconsistent documentation. It is crucial to recognize that these limitations are inherent to retrospective studies and necessitate resolution through comprehensive large-scale prospective investigations.

Conclusion

Our study characterizes a notable prevalence of MAFLD within the cohort from Logan catchment area. MAFLD exhibits a robust association with CV co-morbidities, especially in the presence of diabetes. The utilization of GLP-1a and SGLT-2i is associated with lower LSM (< 8.0 kPa) and has demonstrated efficacy in CV and renal outcomes in various trials. These findings support the continued assessment of these therapies in patients with MAFLD.

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Conflict of Interest

The authors declare that no potential conflict of interest relevant to this article was reported.

Informed Consent

A waiver of consent and ethical clearance were sought and granted approval by the human research ethics committees of Metro South Health and the University of Queensland (HREC/2023/QMS/98122).

Author Contributions

Muhammad Imran Butt: study design, data collection, literature review, data interpretation, and writing up manuscript. Gaurav Puri: supervision, study conception, reviewing and drafting manuscript. Kathryn Berkman: supervision, study conception, reviewing and drafting manuscript. Simon Ryder: supervision, study design, reviewing and drafting manuscript. Muhammad Asif Shahzad: reviewing and drafting manuscript. Joshua Knowles: data analysis and interpretation, reviewing and drafting manuscript. Muhammad Amer Malik: data collection, reviewing and drafting manuscript. Noa Shalev: data collection, reviewing and drafting manuscript. Jo Sexton: data collection, reviewing and drafting manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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