

Multimorbidity and polypharmacy in diabetic patients with NAFLD

Implications for disease severity and management

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Abstract

An observational study describing the number and type of chronic conditions and medications taken by diabetic patients with NAFLD and identifying characteristics that may impact liver disease severity or clinical management.

Adults with type 2 diabetes have a high prevalence of nonalcoholic fatty liver disease (NAFLD) and increased risk of developing advanced liver disease. Appropriate management should consider the characteristics of the diabetic NAFLD population, as comorbid conditions and medications may increase the complexity of treatment strategies.

Diabetic patients with NAFLD at risk of clinically significant liver disease (as assessed by the FIB-4 or NAFLD fibrosis scores) were recruited consecutively from the Endocrine clinic or primary care. Medical conditions, medication history, anthropometric measurements, and laboratory tests were obtained during assessment. NAFLD severity was classified by transient elastography and liver ultrasound into “no advanced disease” (LSM < 8.2 kPa) or “clinically significant liver disease” (LSM ≥ 8.2 kPa).

The most common coexistent chronic conditions were metabolic syndrome (94%), self-reported “depression” (44%), ischaemic heart disease (32%), and obstructive sleep apnoea (32%). Polypharmacy or hyperpolypharmacy was present in 59% and 31% of patients respectively. Elevated LSM (≥ 8.2 kPa) suggesting significant liver disease was present in 37% of this at-risk cohort. Increasing obesity and abdominal girth were both independently associated with likelihood of having significant liver disease.

There is a high burden of multimorbidity and polypharmacy in diabetic NAFLD patients, highlighting the importance of multidisciplinary management to address their complex health care needs and ensure optimal medical treatment.

Abbreviations: BMI = body mass index, CAMs = complementary and alternative medicines, CAP = controlled attenuation parameter, CI = confidence interval, CLD = chronic liver disease, CVD = cardiovascular disease, GORD = gastroesophageal reflux disease, HCC = hepatocellular carcinoma, IHD = ischaemic heart disease, LSM = liver stiffness measurement, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, OR = odds ratio, OSA = obstructive sleep apnoea, OTC = over-the-counter, PPIs = proton pump inhibitors, T2D = type 2 diabetes, TE = transient elastography.

Keywords: cirrhosis, liver disease, steatohepatitis, steatosis, transient elastography

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1. Introduction

People with type 2 diabetes (T2D) have a high prevalence of nonalcoholic fatty liver disease (NAFLD) (40–70%),^[1] characterized by steatosis in the presence of metabolic risk factors and the absence of significant alcohol intake (≥ 20 g ethanol daily). NAFLD is a spectrum of diseases ranging from steatosis alone to nonalcoholic steatohepatitis (NASH), which is characterized by inflammation and cellular damage, to fibrosis and cirrhosis. Patients with T2D and NAFLD are more likely to develop NASH, advanced fibrosis/cirrhosis and hepatocellular carcinoma (HCC)^[2] and diabetic patients have a 2 to 3 fold increased risk of mortality from chronic liver disease.^[3] In addition, the presence of NAFLD is associated with cardiovascular disease and increased atherogenic risk factors.^[4] Consequently, there is increasing interest in the identification and management of this common liver disease.^[5] Appropriate management however needs to consider the characteristics of the diabetic NAFLD population, as comorbid conditions and medications may increase the complexity of treatment strategies.

Multimorbidity is common in patients with T2D and is associated with increased healthcare service utilisation and polypharmacy.^[6] The most common chronic conditions coexisting with T2D include obesity-related disorders (hypertension, cardiovascular disease, dyslipidemia, obstructive sleep apnoea [OSA]) as well as conditions that do not share a common pathway, such as anxiety and arthritis.^[6,7] The presence of these co-morbidities may contribute to frailty or physical limitations that affect the nonpharmacological treatment of NAFLD with diet and exercise. Patients may experience challenges in managing complicated medication regimens, lifestyle modifications, and healthcare appointments, which may have a detrimental effect on outpatient attendance and ability to self-manage their disease. Furthermore, concomitant disorders may have a direct effect on NAFLD pathogenesis and liver disease progression. In particular, OSA has been implicated in exacerbation of the severity of both human and rodent models of NAFLD.^[8]

Coexistent diseases often require prescription of separate treatment regimens leading to a higher risk of polypharmacy and adverse drug interactions. NAFLD and obesity are reported to increase the risk of acute liver injury with some medications, via drug-induced oxidative stress or obesity-related increased activity of several cytochromes P450 that generate toxic metabolites.^[9–11] Conversely, aggravation of liver injury in NAFLD may be seen with drugs that worsen insulin resistance or activate lipogenic transcription factors.^[9] In many chronic diseases including liver disease, polypharmacy is associated with poor medication adherence and a greater chance for patient-clinician miscommunication about medications.^[12–15] Accurate information about the number and type of medications taken by diabetic patients with NAFLD is important to reduce the risk of adverse events and drug interactions when considering choice of pharmacological treatments for NAFLD. Although drug therapy for NAFLD is limited at present, many new compounds directed at multiple potential pathogenic pathways are in various stages of development.^[16]

The aim of this observational study was to describe the number and type of chronic conditions present in, and medications taken by, a cohort of diabetic patients with NAFLD at risk of clinically significant liver disease, attending a hospital or primary care diabetes service. In addition, we explored the association between specific comorbid conditions, medications, and the presence or absence of clinically significant liver disease.

2. Methods

A prospective cohort study was undertaken in diabetic patients recruited consecutively from the Endocrine clinic at the Princess Alexandra Hospital, Brisbane (n=74), or from primary care practices within the Metro South Hospital and Health Services District (n=21), between October 2015 and June 2016.

2.1. Case ascertainment/study eligibility

Patients were eligible to be included in the study if they had a diagnosis of type 2 diabetes defined using standard criteria,^[17] NAFLD, and an indeterminate or high score on the FIB-4^[18] (<http://gihep.com/calculators/hepatology/fibrosis-4-score/>) or NAFLD fibrosis scores^[19] (<http://www.naflscore.com/>). A diagnosis of NAFLD required demonstration of hepatic steatosis by liver ultrasound in the presence of metabolic risk factors and the exclusion of significant alcohol consumption (≥ 20 g/d) and other causes of hepatic steatosis or other chronic liver diseases. The NAFLD fibrosis and FIB-4 scores have good negative predictive values and can be used clinically to exclude advanced fibrosis in patients who have low scores.^[20] The study cohort therefore selectively recruited patients who were more likely to have clinically significant liver disease.

Patients were excluded if they had stage 5 chronic kidney disease (estimated glomerular filtration rate < 15 mL/min), renal replacement therapy, history of organ transplant, secondary causes of fatty liver, extrahepatic fibrosis, or if they had taken immunomodulators within the preceding 6 months.

2.2. Study population

Eligible patients were invited to attend the liver clinic at the Princess Alexandra Hospital, Brisbane for clinical assessment. Informed written consent was obtained from each patient and the protocol was approved by the Metro South Health and The University of Queensland Human Research Ethics Committees (HREC/15/QPAH/301; UQ2015001047).

2.3. Clinical data

Data were collected prospectively by the study clinician (PP). Medical history was obtained during the initial consultation in the liver clinic using a structured questionnaire. Interview items included self-reported socio-demographic characteristics, history of tobacco and recreational drug use, history of past and current alcohol intake, previously diagnosed liver disease and other medical conditions, and use of medications. Patients were asked to bring a list of or their current medications to the initial consultation. Subjects were asked to list the dose, frequency and indication for each of their medicines and specifically prompted for over-the-counter (OTC) and complementary and alternative medicines (CAMs). Patients' current medications were verified during the patient interview and corroborated with their nominated local pharmacy's dispensing history or General Practitioner's medical records.

Patients underwent a clinical assessment that included anthropometric measurements (weight, height, and waist circumference), laboratory tests (routine biochemical, haematological and serological assays), transient elastography, and liver ultrasound. Metabolic syndrome was defined as central obesity (waist circumference: Euroid male ≥ 94 cm, South Asian male ≥ 90 cm, female ≥ 80 cm), plus any 2 of the following 4 factors:

raised fasting plasma glucose or previously diagnosed type 2 diabetes, raised blood pressure or treatment of previously diagnosed hypertension, raised triglycerides or reduced HDL cholesterol or specific treatment for these lipid abnormalities.^[21]

Transient elastography with simultaneous Controlled Attenuation Parameter (CAP) was performed after a 3 hour fast using FibroScan technology (Echosens, Paris, France) using the standard M or XL probes. Examinations were performed by a trained clinical nurse (with experience performing more than 250 liver stiffness measurements [LSM]) and reviewed by a hepatologist (KAS) with extensive FibroScan experience (more than 2000 LSM performed). Recommended standard FibroScan operating procedures were followed along with adherence to criteria for definition of reliable LSM: minimum of 10 valid measurements with a success rate of $\geq 60\%$ and IQR $\leq 30\%$ of the final (median) result. The XL probe was used when the skin-capsule depth was ≥ 2.5 cm. Although optimal liver stiffness cut-off values in NAFLD remain under discussion, for the purposes of this study we used the following cut-off values: 8.2 kPa for severe fibrosis and 10.5 kPa for the diagnosis of cirrhosis, respectively for ruling out disease with at least 90% sensitivity, as described by Cassinotto et al.^[22]

Liver ultrasound was performed by one of the sonographers in the Department of Diagnostic Radiology, Princess Alexandra Hospital, Brisbane, trained in advanced liver imaging. The Princess Alexandra Hospital is the referral center for the state-wide liver transplant service and >1650 liver ultrasounds are performed in the department each year. Steatosis was determined by increased hepatic echogenicity and beam attenuation, resulting in the renal cortex appearing relatively hypoechoic to the liver parenchyma, absence of the normal echogenic walls of the portal and hepatic veins, and poor visualization of the diaphragm and deep portions of the liver.^[23] Evidence of cirrhosis or portal hypertension on liver imaging was determined by liver surface nodularity or signs of portal hypertension including portal vein dilatation, splenomegaly, portosystemic collaterals, and ascites.

NAFLD severity was broadly classified by transient elastography and liver ultrasound. Participants were divided into 2 groups: “no advanced disease” (LSM < 8.2 kPa and no evidence of cirrhosis or portal hypertension on liver imaging) and “clinically significant liver disease” (LSM ≥ 8.2 kPa). Liver biopsy was performed in a subset of the patients (n=24) for clinical indications, based on increased likelihood of advanced disease or patient interest in participating in clinical therapy trials. Histological changes of NAFLD (steatosis, lobular and portal inflammation, presence of ballooning, Mallory–Denk bodies, and fibrosis) were assessed and scored according to accepted criteria.^[24,25]

2.4. Data analysis

Data analysis was conducted using SPSS Inc version 24.0 (College Station, TX: StatCorp LP; 2013). Participant characteristics were presented as mean and standard deviation (data normally distributed), and proportions. Chi-square tests were used to compare proportions (Fisher exact test was used when cell counts were less than 5) and T tests to compare means. All *P* values were 2-sided and statistical significance was set at $\alpha=0.05$.

Bivariable logistic regression analysis was used to determine the odds of being categorized as having “clinically significant liver disease” compared with “no advanced disease.” Obesity or girth, age, gender, and number of co-morbidities, as variables of clinical

relevance, were included in the model. Odds ratio (OR) and 95% confidence interval (CI) were reported.

3. Results

3.1. Patient characteristics

Ninety-five “at-risk” patients with T2M and NAFLD were reviewed in the NAFLD clinic between October 19, 2015 and June 20, 2016. In all patients, the diagnosis of NAFLD was based on demonstration of hepatic steatosis by ultrasound in the presence of metabolic risk factors and the exclusion of significant alcohol consumption (≥ 20 g/d) and other chronic liver diseases. The demographic and clinical characteristics of the 95 subjects are summarized in Table 1.

3.2. Assessment of NAFLD severity

LSM were not obtained in 13 patients due to the presence of a defibrillator (n=3), failure of measurement (n=4) or were unreliable (i.e., did not meet manufacturer’s recommended criteria, n=6). LSM were considered acceptable/good quality in 81 of the remaining 82 (99%) patients, and required use of the XL probe in 87% (71 of 82). Median LSM was 6.9 kPa with a range from 2.6 to 63.9 kPa. 63% of the cohort (52 of 82 patients) had LSM < 8.2 kPa, suggesting the absence of severe fibrosis. Four patients (LSM 63.9, 40.9, 28.4, 14.6 kPa) had liver imaging consistent with cirrhosis (nodular liver surface and features of portal hypertension). Liver biopsy was performed in 24 patients for clinical indications (75% with liver stiffness measurements ≥ 8.2 kPa). All liver biopsies met histological criteria for NAFLD (steatosis grade 1 in 7 patients, grade 2 in 8, and grade 3 in 9); 75% of patients who underwent liver biopsy had bridging fibrosis/cirrhosis.

3.3. Coexistent chronic conditions

By definition, all patients had type 2 diabetes (3 diet controlled) and 94% had metabolic syndrome. In addition to the metabolic syndrome, 37 different chronic conditions were present in the cohort, summarized in Supplementary Table 1, <http://links.lww.com/MD/B675>. The number of co-morbidities (apart from metabolic syndrome) experienced by each patient ranged from 0 to 8 with a median of 3. Figure 1 illustrates “clustering” of the most prevalent combinations of co-morbidities. The most common coexistent conditions were self-reported “depression” in 42 of 95 (44%) patients, ischaemic heart disease (IHD) in 31 (32%), and OSA in 30 (32%) (Table 1).

3.4. Medication use

The number of regular medications taken by each patient ranged from 1 to 23, with a mean of 7.9 ± 3.2 . Ten percent of the 95 patients took <5 regular medications; polypharmacy (5–9 medications) was present in 59%; and hyperpolypharmacy (≥ 10 medications) in 31%. Patients who were older and those with a history of IHD or osteoarthritis were taking more medicines ($P=.01$, $P<.01$, and $P=.05$, respectively) (Table 2). Not surprisingly, there was a significant relationship between number of medications taken and number of co-morbidities (Spearman $r=0.358$, $P<.01$).

A total of 129 different medications were identified from all sources; 76% were classified as “conventional,” 6% as “conventional” CAMs, and 18% as alternative CAMs. The most common drug categories are listed in Supplementary Table 2,

Table 1
Demographic and clinical characteristics of patients with NAFLD and type 2 diabetes: all subjects (n = 95) and according to severity of liver disease*.

	All patients N=95 n (%)	Subgroup of patients with TE reading N=82		P values
		LSM ≥ 8.2 kPa n=30 [‡] (%)	LSM < 8.2 kPa n=52 (%)	
Age, years	59.6±9.4	58.9±10.4	59.6±8.8	.74
Gender (male), % [§]	61 (64)	20 (66.7)	35 (67.3)	.95
Ethnicity (Caucasian), %	75 (79)	27 (90)	37 (71.2)	.06
BMI, kg/m ²	36.2±8.4	39.4±8.3	32.6±6.2	<.01
Girth, cm	121.4±18.6	129.5±16.6	112.8±15.1	<.01
CAP, dBm	339.6±56.5	351.0±51.9	328.1±59.8	.08
HbA1c, %	8.3±1.6	8.0±1.4	8.4±1.6	.23
Co-morbidities				
Ischaemic heart disease [§]	31 (32)	8 (26.7)	20 (38.5)	.28
Obstructive sleep apnoea [§]	30 (32)	13 (43.3)	10 (19.2)	.02
Depression [§]	42 (44)	15 (50)	23 (44.2)	.61
Asthma [§]	21 (22)	8 (26.7)	11 (21.2)	.57
Osteoarthritis [§]	19 (20)	6 (20)	9 (17.3)	.76
Number of co-morbidities	2.9±1.7	3.4±1.9	2.5±1.6	.02
Number of medications [‡]	7.9±3.2	8.23±4.2	7.58±2.7	.39
Number of patients (%) taking:				
1–4 medications [§]	10 (10)	5 (16.7)	5 (9.6)	.24
5–9 medications (polypharmacy)	56 (59)	14 (46.7)	34 (65.4)	
≥10 medications (hyperpolypharmacy)	29 (31)	11 (36.7)	13 (25.0)	

BMI = body mass index.

[‡] TE includes 1 patient in whom poor quality images were obtained.

[§] Data presented categorically and analyzed using the χ^2 test.

^{||} Data presented categorically and analyzed using the Fisher exact test; all other variables presented as mean±standard deviation and statistically analyzed using the independent T test.

*Severity of liver disease: "no advanced disease", LSM < 8.2 kPa; n = 52; or "clinically significant liver disease", LSM ≥ 8.2 kPa; n = 30. TE unable to be calculated in 7 patients; TE score did not meet validity criteria in 6 patients; therefore data is not included.

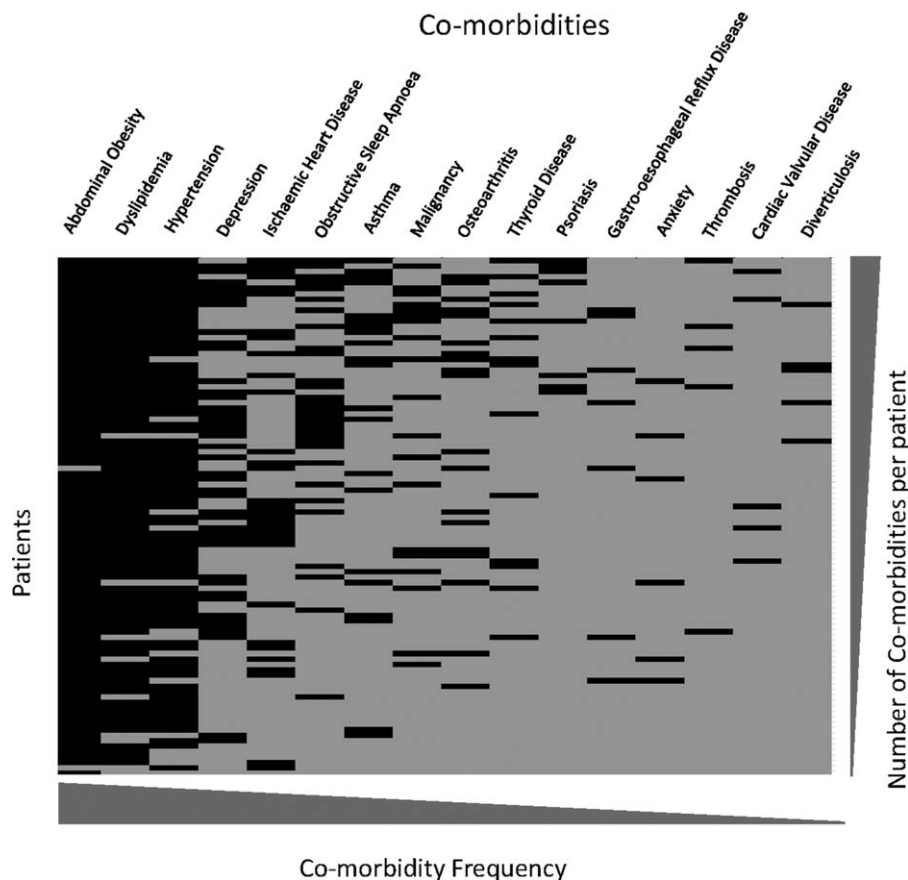


Figure 1. Heat map depicting frequency of most common co-morbidity (excluding co-morbidities with an incidence of <5 patients). Black cells represent the presence of a co-morbidity and gray cells represent the absence of the co-morbidity.

Table 2
Comparison of common co-morbidities and number of medications.

	<5 Medications N=10	Polypharmacy (5-9 medications) N=56	Hyperpolypharmacy (10+ medications) N=29	P values
Age, years*	57.8±11.8	57.7±9.4	64.0±7.2	.01
Gender (male)†, %	7 (70)	34 (61)	20 (69)	.73
Ethnicity (Caucasian)†, %	7 (70)	45 (80)	23 (79)	.71
BMI, kg/m ² *	37.9±8.6	37.2±9.8	33.9±4.9	.22
Co-morbidities†				
Ischaemic heart disease	1 (10)	14 (25)	16 (55)	<.01
Obstructive sleep apnoea	1 (10)	19 (34)	10 (34)	.35
Depression	3 (30)	23 (41)	16 (55)	.33
Asthma	4 (40)	11 (20)	6 (21)	.33
Osteoarthritis	2 (20)	7 (13)	10 (34)	.05
Number of co-morbidities*	2.4±2.7	2.7±1.6	3.7±1.3	.01

BMI=body mass index.

*Data presented as mean±SD and analyzed by one-way ANOVA.

†Data presented categorically (n, %) and analyzed using Fisher exact test.

<http://links.lww.com/MD/B675>. Figure 2 illustrates “clustering” of the most prevalent combinations of medications. 100% of the patient cohort were taking at least 1 medication that has been investigated as potential NAFLD pharmacotherapy; metformin^[26] was taken by 82 (86%) patients, incretin therapies^[27] by 30 (32%), statins^[28] by 81 (85%), and angiotensin therapies^[29] by 76 (80%). Apart from hypoglycemic and cardiovascular medications, the most commonly prescribed drug category was proton-pump inhibitors that were taken by 41 (43%) patients.

3.5. Clinical variables associated with NAFLD severity

The demographic and clinical characteristics of subjects with “no advanced disease” (TE <8.2 kPa and no evidence of cirrhosis or portal hypertension on liver imaging) or “clinically significant liver disease” (TE ≥ 8.2) are listed in Table 1. Body mass index (BMI), girth, and OSA were associated with NAFLD severity (Table 3). For every 1 unit increase in BMI, the likelihood of having significant liver disease (TE ≥ 8.2) increased by 1.14 times (95% CI 1.06–1.23); after controlling for age, gender, and

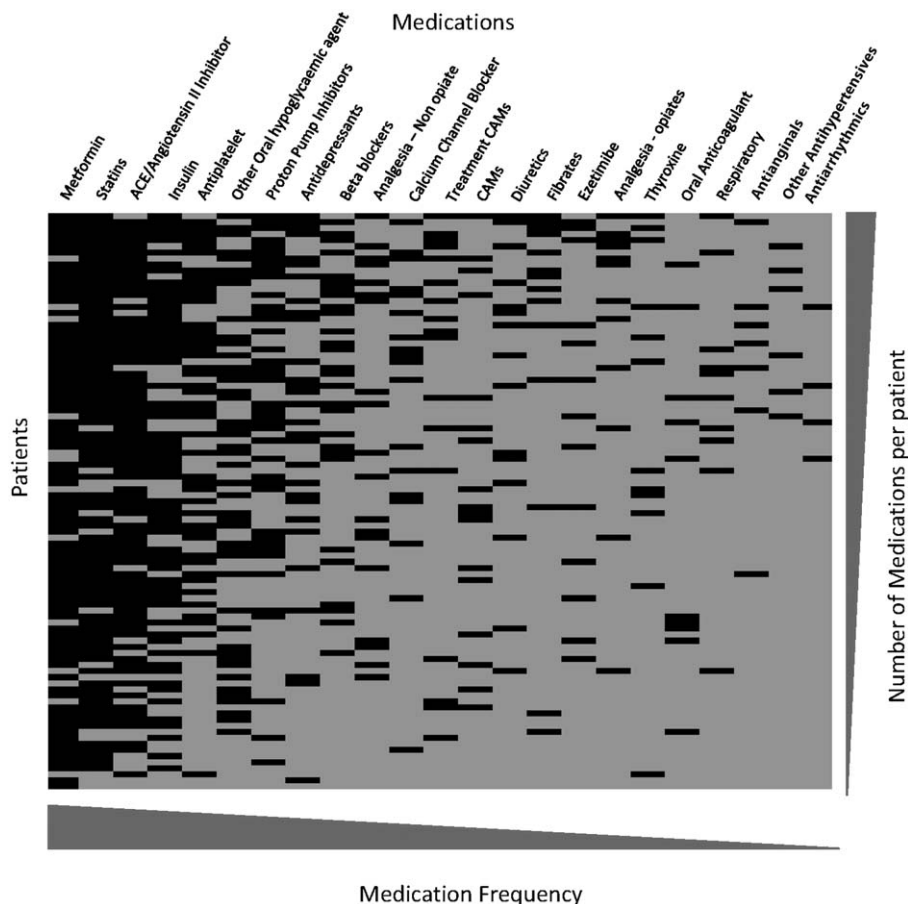


Figure 2. Heat map depicting frequency of most common medications. CAMs= complementary and alternative medications. Black cells represent the presence of a medication and gray cells represent the absence of the medication.

Table 3**Crude and adjusted odds ratio for common co-morbidities according to baseline LSM < or ≥8.2 kPa.**

	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Girth (cm)	1.07 (1.03–1.11)	1.08 (1.03–1.12)
BMI (kg/m ²)	1.14 (1.06–1.23)	1.16 (1.06–1.26)
BMI (categorical)		
<30	1.00	1.00
30.0–39.9	1.33 (0.36–4.88)	1.56 (0.40–6.12)
>40.0	9.38 (2.19–40.11)	15.00 (2.78–80.88)
Ischaemic heart disease	0.58 (0.22–1.56)	0.40 (0.11–1.42)
Obstructive sleep apnoea	3.21 (1.18–8.72)	1.37 (0.38–4.89)
Depression	1.26 (0.51–3.10)	1.04 (0.36–3.04)
Asthma	1.36 (0.48–3.86)	1.01 (0.24–4.32)
Osteoarthritis	1.19 (0.38–3.76)	0.80 (0.2–3.26)

BMI = body mass index.

*Adjusted for age, gender, number of co-morbidities, and BMI (continuous variable).

number of co-morbidities the association remained (adjusted OR = 1.16, 95% CI 1.06–1.26). Patients with BMI over 40 were 15 times more likely to have significant liver disease compared with their counterparts (adjusted OR = 15.0, 95% CI 2.78–80.88). For every centimeter increase in girth, the likelihood of having significant liver disease increased by 1.08 times, after controlling for the other factors in the model. OSA was found to be associated with NAFLD severity (OR = 3.21, 95% CI 1.18–8.72) in bivariable analysis; but the association disappeared after controlling for age, gender, number of co-morbidities, and BMI (adjusted OR = 1.37, 97% CI 0.38–4.89). ORs were also adjusted for age, gender, number of co-morbidities, and girth yielding similar estimates: OR = 0.50 (95% CI 0.14–1.81) for ischaemic heart disease, OR = 1.05 (95% CI 0.30–3.74) for OSA, OR = 0.90 (95% CI 0.30–2.68) for depression, OR = 0.76 (95% CI 0.18–3.13) for asthma, and OR = 0.74 (95% CI 0.18–3.11) for osteoarthritis.

The only medications found to be associated with NAFLD severity were the statins. In bivariable analysis, statin use was higher (92%) in patients with LSM < 8.2 kPa, compared with their use by 73% of patients with LSM ≥ 8.2 ($P = .03$, Supplementary Table 3, <http://links.lww.com/MD/B675>). However, the association disappeared after controlling for age, gender, number of co-morbidities, and BMI (adjusted $P = .34$).

4. Discussion

Due to the high prevalence of NAFLD and increased risk of advanced fibrosis in people with type 2 diabetes, there is a critical need for novel drug therapies for NAFLD and for cross-disciplinary guidelines to aid clinical management. This study was undertaken to describe the number and type of chronic conditions and medications taken by a cohort of diabetic patients with NAFLD and to identify characteristics of this population that may impact clinical management. The present study indicated that in addition to metabolic syndrome, 81% of people with NAFLD and type 2 diabetes had 2 or more chronic conditions, with the largest burden generated by IHD, OSA, and self-reported depression.

In this “at risk” cohort of diabetic NAFLD patients with indeterminate or high scores on the FIB-4 or NAFLD fibrosis scores, 37% had an elevated LSM (≥8.2 kPa), consistent with clinically significant liver disease. Increasing obesity and abdominal girth (as a surrogate marker of visceral adiposity) were both independently associated with likelihood of having significant liver disease. This supports a previous study reporting

an independent association between visceral adipose tissue area (measured by CT imaging) and fibrosis in NAFLD patients.^[30] Compared with subcutaneous adipose tissue, visceral fat produces more inflammatory cytokines such as TNF- α and IL-6 and less adiponectin, and this inflammatory profile may contribute to its increased metabolic risk.^[31]

Not surprisingly, components of the metabolic syndrome (increased waist circumference, dyslipidemia, hypertension) were present in more than 90% of the cohort, reflecting the multisystem nature of NAFLD with insulin resistance and activation of inflammatory pathways.^[32] Similarly, over 30% of the cohort reported a history of cardiovascular disease (CVD), consistent with other hospital-based studies showing that the prevalence of CVD is increased in patients with NAFLD.^[32] Obstructive sleep apnoea (OSA), another obesity-related condition, was present in almost one-third of the cohort. OSA may contribute to NAFLD pathogenesis through hypoxia-related effects on insulin resistance, lipid metabolism, and inflammation.^[33] Importantly, our study found that other conditions not directly related to the presence of metabolic risk factors were also common in this population. In particular, depression was the most prevalent discordant condition, reported by 44% of our cohort. Emerging evidence suggests an association between metabolic abnormalities, hypercholesterolemia, and the pathogenesis of affective disorders.^[34,35] In a recent study of patients with biopsy-proven NAFLD, subclinical and clinical depression was identified in 53% and 14% of patients respectively, along with a dose-dependent relationship between severity of depressive symptoms and severity of hepatocyte ballooning.^[36]

Recognition of the high burden of multimorbidity in these patients is important because of the impact on health status, level of functioning, and approach to NAFLD management. Previous studies in people with diabetes have shown that co-morbidities increase utilization of healthcare services^[7] and negatively affect quality of life and ability to self-manage disease.^[37] The health priority attributed to NAFLD by patients and their clinicians needs to be addressed in future studies, since in the setting of co-morbidities, patients report selectively attending to the management of conditions based on their perceived severity or importance.^[38] Patients may allocate a low priority to NAFLD because it has a substantial latency period without obvious signs or symptoms of disease until the development of complications of end-stage liver disease or hepatocellular cancer. Although the cornerstone of NAFLD treatment remains lifestyle changes, physical exercise may need to be individually tailored for the 24% of our cohort with coexisting musculoskeletal conditions^[39]

or 32% with ischaemic heart disease. In addition, the presence of depression has been associated with higher weight over a 6-month standard care follow-up in individuals with NAFLD.^[40] These issues highlight the need for an integrated multidisciplinary approach to the treatment and coordination of care in these medically complex patients.

Another important consequence of multimorbidity is the coprescription of several drugs in order to meet disease-specific treatment goals. In our patients with NAFLD and type 2 diabetes, polypharmacy was present in 90% of the cohort. In addition to their diabetic medications, the majority of the cohort was taking medications for management of dyslipidemia (85%) and hypertension (84%). Patients without evidence of advanced liver disease were more likely to be taking statins, although this association disappeared after adjustment for other clinical variables. Previous cross-sectional studies have shown statin-treated diabetic patients with NAFLD have a lower risk of advanced fibrosis.^[28,41] The clinical significance of this association remains unclear however, as trials of statin therapy in NAFLD have been underpowered and provided limited histologic data.^[42,43]

Apart from treatment of the metabolic syndrome, the most commonly prescribed drugs were antiplatelet agents in 48% of the cohort and proton pump inhibitors (PPIs) in 43%. PPIs block gastric acid secretion and are widely used for treating gastroesophageal reflux disease (GORD), peptic ulcer disease and for prevention of low-dose aspirin-induced ulcers.^[44] The specific indications for PPI prescriptions could not be addressed in our study. Of the patients prescribed a PPI, only 7 patients reported a history of GORD and 65% were also prescribed an antiplatelet agent or anticoagulant. Consensus statements and guidelines for prevention of gastrointestinal complications in patients taking antiplatelet agents have been jointly released by several craft groups and recommend strategies based on patient risk profiles.^[45] If not required for optimal patient benefit, consideration could be given to reducing dose and/or ceasing PPIs to decrease the risk of possible adverse effects. Prolonged hypochlorhydria due to long-term PPI use may predispose to enteric infections including *Clostridium difficile*,^[46] and malabsorption leading to hypomagnesemia and metabolic bone disease.^[47] Future studies should address whether the changes in gut microbiota seen with PPI use^[48] influence the metabolic and disease phenotype of patients with NAFLD and type 2 diabetes.^[49]

Nonadherence to prescribed medications is a significant concern for the management of diabetic patients with multiple co-morbidities.^[50] Miscommunications about medications between patients and clinicians occur more frequently with complicated medication regimens, polypharmacy and in patients with poor adherence.^[51] Multimorbidity and polypharmacy also has implications for compliance with new drug treatments for NAFLD, particularly in diabetics who are at greatest risk of liver disease progression and liver cancer. Coexisting chronic diseases will also influence the clinical relevance of “off-target effects” of new NAFLD therapies such as obeticholic acid, where treatment-induced changes in the serum cholesterol pool and insulin resistance may exacerbate atherogenesis.^[51]

While these results provide insight into the complexities of managing this cohort of patients, the results must be interpreted within the limitations of the study. One such limitation is sample bias as a high proportion of participants were recruited from within a tertiary diabetic center which may include many patients who are experiencing current or ongoing difficulties with their

diabetes. Another potential limitation is that although patients' current medications were corroborated with external sources, active reconciliation with the patient present did not occur, as this was not standard clinical practice at the time. In addition, NAFLD severity was broadly classified into 2 groups, patients with and without advanced fibrosis on the basis of liver stiffness measurements. In patients with NAFLD, liver stiffness measurements have a high negative predictive value and a modest positive predictive value for detecting advanced fibrosis.

This study highlights the importance of multidisciplinary management of NAFLD patients to address their complex health care needs, and ensure optimal medical treatment. NAFLD cannot be considered in isolation when developing clinical management guidelines, and, conversely, nonhepatology specialists will increasingly need to consider the prevalence and impact of NAFLD in their patient populations. The study also has implications for health service planning and resource allocation, which should take into account the complexity of this group of patients with multiple chronic medical problems. Coordinated care strategies could be investigated to improve outcomes for this group of patients.

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