



**An Australian Diabetes Society Clinical Care
Consensus Living Guideline for Specialist
Assessment, Referral and Treatment of Metabolic
Dysfunction-Associated Fatty Liver Disease
in People with Diabetes.**

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An Australian Diabetes Society Clinical Care Consensus Living Guideline for Specialist Assessment, Referral and Treatment of Liver Disease in People with Diabetes.

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Summary:

People with type 2 diabetes mellitus (T2DM) have increased risk of dysmetabolic liver disease and liver fibrosis, linked with increased morbidity and mortality. In recent years, non-invasive methods for assessment of liver fibrosis in people with T2DM have been developed. Concurrently, referral recommendations to hepatologists are being refined and new treatments for liver fibrosis in dysmetabolic disease such as T2DM are being developed. International clinical care guidelines for assessment and management of liver fibrosis in diabetes have been developed, reflecting an increasing evidence base. This Australian Diabetes Society (ADS) living clinical guideline has both adapted an international clinical care guideline to the Australian situation and harnessed expert consensus through a modified Delphi process. The consequent 14 recommendations target an endocrinology audience managing a defined patient phenotype and have been integrated with the 2024 published collaborative Gastroenterology Society of Australia (GESA) consensus statement for patient assessment in primary care. It is envisaged that these ADS living guidelines will assist endocrinologists/diabetologists to develop local liver assessment, referral and treatment pathways for their patients with T2DM.

Introduction:

Complications of diabetes account for significant morbidity, which is associated with reduced quality of life, disability and premature mortality [1].

Recently it has become evident that metabolic dysfunction-associated fatty liver disease (MAFLD) is relatively common in people who are overweight or obese, especially those who have metabolic syndrome or type 2 diabetes mellitus (T2DM) [2]. Of clinical importance to diabetes care, the presence of T2DM is a major independent risk factor for the presence and development of severe liver fibrosis, hepatocellular carcinoma (HCC) and liver failure [3]. Advanced liver fibrosis can lead to the development of cirrhosis that is associated with increased mortality – T2DM worsens this liver-related mortality [4]. An emerging evidence base indicates that advanced liver fibrosis may be identified by non-invasive tests [5]; if present, it can be stabilised, and perhaps even reversed, using intensive lifestyle measures, targeted pharmacological approaches or bariatric surgery [6].

In 2019, the American Diabetes Association made its first consensus recommendations in screening for liver fibrosis in people with T2DM. In subsequent years, the strength of the recommendations has increased as higher quality research evidence for rational case finding and screening has strengthened [7]. In 2024, via a fast-track process, the United States of America Food and Drug Administration (USA FDA) approved the first pharmacological agent targeting liver fibrosis, resmetirom, with subsequent recommendations for its access and usage [8]. Other agents are likely to follow suit.

There are subtypes of MAFLD which have traditionally been defined histologically from liver biopsy, with the pathological changes of steatosis (lipid accumulation), inflammatory cellular infiltrates (inflammation), hepatocyte injury (ballooning), and, in some cases, various degrees of liver fibrosis (scarring) [9]. Although MAFLD with liver fibrosis is more likely to be associated with increased liver-related and cardiovascular mortality [10], people without liver fibrosis are also at increased risk of cardiovascular

events. In people with T2DM who have metabolic risk factors, assessing the presence of fibrosis and its severity is particularly important, since the presence of diabetes substantially increases cardiovascular mortality.

Acronyms with greater clinical utility than non-alcoholic fatty liver disease (NAFLD), including MAFLD and metabolic dysfunction associated steatotic liver disease (MASLD), have been defined and used in recent years, as they have a metabolic dysfunction focus and can also include (rather than exclude) people with added adverse hepatic impact from excessive alcohol intake [11,12]. The related term metabolic dysfunction associated steatohepatitis (MASH) is defined by the presence of hepatic inflammation and injury, with or without liver fibrosis.

In albeit limited cross-sectional studies through diabetes centres in Australia, ~15-20% of people with T2DM were found to have severe liver fibrosis in MASH, based mainly on transient elastography measures [13]; these severe liver disease prevalence rates accord with those reported internationally [14]. In contrast, extensive prospective community-based studies of people with T2DM in Australia have published that clinically overt hepatobiliary disease-causing mortality is infrequent [15], as explored in a related commentary [16]. Reconciling the apparent disparate findings may be that diabetes centres may assess people with a more severe T2DM phenotype than in the general community. Moreover, considering the covert, commonly silent nature of dysmetabolic liver fibrosis, this condition will not be diagnosed preclinically unless deliberate screening or case-finding is undertaken, as is recommended in this living guideline. Natural history longitudinal studies in people with MAFLD through liver services indicate that in those with any liver fibrosis, a significant minority, ~30-40% of people, will progress to more severe liver fibrosis across ~8 years, and some, especially those with T2DM, may progress more rapidly to the more severe forms of liver fibrosis, cirrhosis and HCC [17,18]. Larger natural history studies from people with T2DM who have earlier liver fibrosis are required to more comprehensively define rates of disease progression.

In 2024, the Gastroenterology Society of Australia (GESA) published a collaborative interdisciplinary consensus statement on MAFLD, based on a process involving a systematic review of published literature followed by serial Delphi rounds for the assessment of clinical recommendations [19]. That guideline targets primary care. It also makes its main recommendations in assessment and referral, focusing less on treatment of dysmetabolic liver disease. It included membership nominated by the Australian Diabetes Society (Professor Stephen Twigg).

This current living guideline, developed by the Australian Diabetes Society, has also involved a systematic approach. In early 2022, a Diabetes and Liver Disease Subgroup (DLDS), a working group of the ADS Clinical Guidelines/Standards Advisory Committee (CAC), was commenced as commissioned by the ADS [20]. Chaired by Prof. Stephen Twigg and Prof. Jonathan Shaw, it included expressions of interest from the ADS membership to nominate to join the DLDS to develop a clinical care guideline to complement GESA in its MAFLD targeting of primary care consensus statement. The DLDS also sought membership through leaders in the GESA position statement development to align in guideline development. As the living guideline targets a clinical care audience and uses many medical terms, it deliberately did not have a consumer membership.

Methods:

To develop a living guideline, DLDS determined that it would use a high quality international clinical care guideline for MAFLD, which had as its target audience endocrinologists and diabetologists. After an international clinical care guideline published scoping process, the source document selected for use by the DLDS was the American Association of Clinical Endocrinology (AACE) Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings [21].

To determine if Individual Recommendations in that publication should be taken forward to a Delphi process in Australia, two members of DLDS (SP, TC) independently reviewed the Practice Recommendations made in the AACE clinical care guideline [21]. The Recommendations were 'excluded', 'adopted', or the text was 'adapted'. A third planned reviewer (ST) was not required in excluding or adopting recommendations, as there was concordance across the two independent reviewers. The recommendations that were excluded from the AACE guideline from further consideration were those that focused on paediatrics/adolescents or type 1 diabetes, as the level of evidence and strength of recommendation was considered to be low compared with that for T2DM, and too low for subsequent recommendation. The text for the adapted recommendations was developed by consensus across the three reviewers and further reviewed and refined by the DLDS co-chairs. The adopted and adapted recommendations were then developed into an online Delphi survey by the ADS. The Delphi survey method was used as an iterative two-stage process, designed to transform opinion into group consensus using methods broadly described including: iterative Delphi rounds, consensus criteria, analysis of consensus, closing criteria [22].

As a result of the initial process of exclusion, adopting or adapting recommendations, a series of 15 recommendations were taken forward to a Delphi survey involving all expert members of the DLDS and ADS CAC membership (n=18 total). Each recommendation was assessed in the first round of the Delphi independently online by each participant using a 5-point Likert scale comprising: 'strongly agree', 'agree', 'neutral (neither agree or disagree)', 'disagree' or 'strongly disagree' using methods previously published [19,23]. Recommendations for which there was at least 80% agreement (either 'strongly agree' or 'agree') in the DLDS membership were confirmed as realising consensus and thus 'adopted', as in the GESA methodology [19]. For any recommendation that did not realise consensus in round 1, text comment could be provided by Delphi participants to aid refinement in text wording to bring forward into a consensus Delphi round 2.

Across the 15 Recommendations assessed, 11 were adopted by consensus (Table 1) and 4 were rejected as they did not realise the 80% agreement threshold. Those rejected are given in Supplementary Table 1. Among the 4 rejected, text was then

adjusted as per participant comments, and a second round of Delphi occurred online. In one case, the text adjustment resulted in two separate recommendations being made from the one original in round 1 to refine and simplify the recommendation being made and minimise combinations and caveats. In the second round of Delphi, again with independent participation, from 6 recommendations proposed, 3 were adopted by consensus (Table 2) and 3 were rejected. Those rejected in the second round are presented in Supplementary Table 2. As per the original planned methodology, only the two rounds of Delphi occurred, and no further iteration was made for the 3 rejected in round 2. Those rejected recommendations occurred through a lack of consensus as, by definition, there was not adequate agreement to support them with the second Delphi round.

Thus, in total, 14 recommendations were made by the Delphi consensus process. These are given below. They align with categories of: Assessment, Referral, and Treatment of Diabetes and Liver Disease. Each of these recommendations will be briefly explored in its clinical context.

Recommendations - Assessment:

R1. Clinicians should consider people with obesity or features of metabolic syndrome and those with prediabetes or T2DM, to be at “increased risk” and in each case, screen for the presence of MAFLD with advanced liver fibrosis.

R2. Clinicians should use liver fibrosis prediction calculations to assess the risk of MAFLD with advanced fibrosis. The preferred **non-invasive initial test** is the Fibrosis-4 Liver index test, known as FIB-4*. *FIB-4 Ref:

<https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis>

R3. Clinicians should consider people belonging to the higher risk groups for advanced liver fibrosis, based on an “indeterminate” or “high FIB-4 score”, for further assessment with a liver stiffness measurement (LSM) (by transient elastography, such as Fibroscan®), or by a blood enhanced liver fibrosis (ELF™) test, as available.

In overall summary comment for ‘assessment’, in those with a phenotype of increased liver fibrosis risk, screening for the presence of significant liver fibrosis should occur (R1). The preferred first line risk stratification clinical algorithm is FIB-4 (R2). Unless a ‘low risk’ FIB-4 score occurs, then a non-invasive further assessment is indicated (R3).

Recommendations - Interdisciplinary Referral:

R4. People with “**high risk**” of MASH with fibrosis based on first- or second-line tests, including blood tests or imaging (FIB-4, >2.67; or LSM, >12 kPa; or ELF test, >9.8), should be referred to a hepatologist for further assessment, which may include a liver biopsy.

R5. Following an appropriate **first line test** (FIB-4) people with T2DM and an “**indeterminate risk**” of having MASH with liver fibrosis (FIB4 score 1.30-2.67) should receive a **second line test**, or if such is not accessible, they should be considered for referral to a physician with expertise in liver disease, usually a hepatologist.

R6. Following an appropriate **second line test**, people with T2DM and an “**indeterminate risk**” of having MASH with liver fibrosis (LSM, 8-12 kPa; or ELF test, 7.7-9.8), should be considered for referral to a physician with expertise in liver disease, usually a hepatologist.

R7. Clinicians should refer people with clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, oesophageal varices, or evidence of hepatic synthetic dysfunction) to a hepatologist for further care.

In summary, for ‘referral’ those assessed as “high risk” for liver fibrosis should be referred to an hepatologist (R4). Those with an “indeterminate risk” of having MASH with liver fibrosis after a first- or second-line test depending on test accessibility, should be considered for referral to an hepatologist (R5, R6). In any patient with clinical advanced liver disease referral to an hepatologist is indicated (R7).

Recommendations - Treatment with a MAFLD and MASH focus:

R8. In people with MAFLD, clinicians should recommend regular physical activity. Participation in a structured exercise program is recommended, when possible, tailored to the individual's lifestyle and personal preferences.

R9. Clinicians should consider the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals who have obesity and MAFLD or MASH, using an approach that is aligned with the Australian Obesity Management Algorithm. Ref: www.diabetessociety.com.au/wp-content/uploads/2024/07/Australian-Obesity-Management-Algorithm-July-2024.pdf

R10. Clinicians should consider the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals who have obesity and MAFLD or MASH with a goal of at least 5%, preferably $\geq 10\%$, sustained weight loss, as more weight loss is often associated with greater liver histology and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone.

R11. For chronic weight management in individuals with a BMI of $\geq 27 \text{ kg/m}^2$ and MAFLD or MASH, clinicians should give preference to semaglutide 2.4 mg/week (best evidence) or twincretin therapy such as tirzepatide, over other obesity pharmacotherapy and subject to availability.

R12. Clinicians should consider bariatric surgery as an option to treat MAFLD and improve cardiometabolic health in persons with MAFLD and a BMI of $\geq 35 \text{ kg/m}^2$ ($\geq 32.5 \text{ kg/m}^2$ in Asian populations), particularly if T2DM is present.

R13. Due to the lack of evidence of efficacy on steatohepatitis, metformin, sulphonylureas, acarbose, dipeptidyl peptidase IV inhibitors, SGLT2i, and insulin, are not recommended for the treatment of steatohepatitis (as they have no benefit on

hepatocyte necrosis or inflammation or fibrosis), but may be used as needed for the treatment of hyperglycaemia in people with T2DM and MAFLD or MASH.

R14. While statin therapy can rarely through an adverse effect elevate liver enzymes, the presence of MAFLD does not contraindicate the use of HMG CoA reductase (statin) therapy to treat dyslipidaemia.

In summary, in ‘treatment’ lifestyle management with nutrition and exercise (R8) aiming for body weight loss, per Australian obesity guidelines (R9), are mainstays in managing obesity in MAFLD/MASH, with enhanced well-evidence based options such as pharmacotherapy with incretin mimetics [24] or related agents such as twincretins [25] (R10) and bariatric surgery [26] (R11) to realise the higher percentage of sustained weight loss required in people with MASH who have significant liver fibrosis. In terms of obesity pharmacotherapy, incretin mimetics are evidence-based preferred agents (R11). In contrast, other glucose lowering therapies in people with T2DM and obesity have not been shown to have efficacy on steatohepatitis (R13). Finally, in people with obesity and MASH fibrosis, use of statin therapy for lipid lowering is not contraindicated (R14).

Discussion:

These ADS DLDS Clinical Care Recommendations have a number of intrinsic strengths. Firstly, they are based on a reasonably contemporaneous systematic review leading to an evidence-based international clinical care guideline. Secondly, they have been adapted to Australian clinical care conditions by specialist clinicians using a systematic consensus-based process. Thirdly, the clinicians involved were highly engaged in the consensus building process and were aware of the rationale of the living guideline in its practical targeting of the endocrinologist and diabetes centre audience in Australian care and including assessment, referral, and clinical care, aligned with the GESA process of screening and diagnosis targeting primary care [19].

There are also several significant limitations of the current guideline. Firstly, it does not address type 1 diabetes mellitus nor paediatric or adolescent diabetes, nor specifically

prediabetes. This is because the volume of high-quality evidence linking these phenotypes to severe liver fibrosis is currently determined by the ADS DLDS to be very limited and questionable; indeed, some data suggest much weaker links to liver fibrosis compared with T2DM [27]. Secondly, the sample size of the Delphi membership was not large, even though the DLDS membership were highly engaged in the process. Finally, the second line methods of assessment, Fibroscan®, and blood biomarkers are limited in their accessibility and neither has a current Medicare Benefit Schedule indication in Australia. However, the recommendations do enable consideration of the lack of accessibility to these second line assessment methods.

Other considerations are noteworthy in relation to the use of this living guideline. In people with T2DM, the post-assessment risk for the majority of patients will not be found to be 'low' (i.e. FIB-4 <1.3) after non-invasive assessment. This means that the majority of people with T2DM would be referred to an hepatologist (or physician with liver disease expertise) for further assessment or clinical trial invitation. The practising clinician and diabetes service will need to determine whether those with only 'high-risk' liver fibrosis will be referred (which would be the minority assessed for liver fibrosis) or if those with 'indeterminate risk' will also be referred. The accessibility of local services for referral to an hepatologist, and hepatologist preference, will be key to making such determination in referral criteria and patient numbers. In terms of treatment, these clinical care guidelines have made recommendations for therapy based on the Australian Obesity Management Guidelines, including the use of very low energy diets (VLEDs) and pharmacologic agents, such as incretin-based treatment [28].

The time frame for reassessment in those with 'low risk' of severe liver fibrosis has not been addressed in this living guideline, as the original evidence-based international clinical care guideline [21] did not address the topic. The 2024 GESA developed clinical guidelines have suggested between 1 and 3 years be utilised in individual reassessment [19], noting that the non-invasive assessments are imperfect and in those with T2DM, liver fibrosis can progress rapidly.

The topic of dysmetabolism and liver fibrosis, especially in those with T2DM, is developing rapidly. It is envisaged that more predictive non-invasive assessment methods will be recognised that use synergistic combinations of, for example, liver stiffness by transient elastography and blood fibrosis markers, and that combinations of antifibrotic therapies along with lifestyle change and targeted surgery will be defined in an increasingly cost-effective and accessible manner.

Table 1: Clinical Care Recommendations developed by consensus in Delphi

Round #1:

[with total % Agree or Strongly agree]

- 'Clinicians should consider people with obesity and/or features of metabolic syndrome, those with prediabetes or T2DM, to be at "increased risk" and in each case, screen for the presence of MAFLD/NAFLD with advanced liver fibrosis.' [94%]
- 'Clinicians should use liver fibrosis prediction calculations to assess the risk of MAFLD/NAFLD with fibrosis. The preferred non-invasive initial test is the Fibrosis-4 Liver index test, known as FIB-4*. *FIB-4 Ref: <https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis>.' [100%]
- 'Clinicians should consider people belonging to the higher risk groups for liver fibrosis, who thus have an indeterminate or high FIB-4 score, for further assessment with a liver stiffness measurement (LSM) (by transient elastography, such as Fibroscan®), or by a blood enhanced liver fibrosis (ELF™) test, as available.' [94%]
- 'People with "high risk" of MASH/NASH with fibrosis based on blood tests and/or imaging (FIB-4, >2.67; or LSM, >12 kPa; or ELF test, >9.8), should be referred to a hepatologist for further assessment, which may include a liver biopsy.' [100%]
- 'Clinicians should refer people with clinical evidence of advanced liver disease (ascites, hepatic encephalopathy, esophageal varices, or evidence of hepatic synthetic dysfunction) to a hepatologist for further care.' [100%]
- 'Clinicians should consider the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals with obesity and MAFLD or MASH with a goal of at least 5%, preferably ≥10%, sustained weight loss, as more weight loss is often associated with greater liver histology and cardiometabolic benefit, when this is not effectively achieved by lifestyle modification alone.' [89%]

- 'In people with MAFLD, clinicians should recommend regular physical activity. Participation in a structured exercise program is recommended, when possible, tailored to the individual's lifestyle and personal preferences.' [94%]
- 'Due to the lack of evidence of efficacy on steatohepatitis, metformin, sulphonylureas, acarbose, dipeptidyl peptidase IV inhibitors, SGLT2i and insulin, are not recommended for the treatment of steatohepatitis (as they have no benefit on hepatocyte necrosis or inflammation or fibrosis), but may be used as needed for the treatment of hyperglycaemia in people with T2DM and MAFLD or MASH.' [89%]
- 'While statin therapy can rarely through an adverse effect, elevate liver enzymes, the presence of MAFLD does not contraindicate the use of HMG CoA reductase (statin) therapy to treat dyslipidaemia.' [94%]
- 'For chronic weight management in individuals with a BMI of ≥ 27 kg/m² (≥ 25 kg/m² for Asian people or Aboriginal and Torres Strait Islander people) and MAFLD or MASH, clinicians should give preference to semaglutide 2.4 mg/week or incretin therapy such as tirzepatide, over other obesity pharmacotherapy and subject to availability.' [83%]
- 'Clinicians should consider bariatric surgery as an option to treat MAFLD and improve cardiometabolic health in persons with MAFLD and a BMI of ≥ 35 kg/m² (≥ 32.5 kg/m² in Asian populations), particularly if T2DM is present.' [89%]

Table 2: Clinical Care Recommendations developed by consensus in Delphi round #2:

[with total % Agree or Strongly agree]

- 'Following an appropriate first line test (FIB4) people with T2DM and an "indeterminate risk" of having MASH with liver fibrosis (FIB4 score 1.30-2.67) should receive a second line test, or if such is not accessible, they should be considered for referral to a physician with expertise in liver disease, usually an hepatologist.' [86%]
- 'Following an appropriate second line test, people with T2DM and an "indeterminate risk" of having MASH with liver fibrosis (LSM, 8-12 kPa; or ELF test, 7.7-9.8), should be considered for referral to a physician with expertise in liver disease, usually an hepatologist. [93%]
- 'Clinicians should consider the use of obesity pharmacotherapy as adjunctive therapy to lifestyle modification for individuals who have obesity and MAFLD or MASH, using an approach that is aligned with the Australian Obesity Management Algorithm. Ref: www.diabetessociety.com.au/wp-content/uploads/2024/07/Australian-Obesity-Management-Algorithm-July-2024.pdf [100%]

Supplementary Table 1:

Non-supported recommendations assessed in Delphi #1 (<80% agree or strongly agree)

- ‘People with hepatic steatosis on imaging and an “indeterminate risk” of MASH with liver fibrosis (FIB-4, 1.3-2.67; or LSM, 8-12 kPa; or ELF test, 7.7-9.8), should be considered for referral to a hepatologist, as available.’
- ‘ People undergoing bariatric surgery should be evaluated for the presence and severity of MASH, and a liver biopsy should be considered at the time of bariatric surgery. Liver biopsy should be recommended if presurgical stratification suggests “indeterminate” or “high risk” of liver fibrosis.’
- ‘Clinicians should consider treating T2DM with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having MASH with fibrosis based on non-invasive tests (FIB-4, 1.3 or greater; or LSM, 8 kPa or greater; or ELF test, 7.7 or greater).’
- ‘Metformin or SGLT2i may improve hepatic steatosis in people with MAFLD but are not recommended for such treatment; they may be used as needed for the treatment of hyperglycaemia in persons with T2DM and MAFLD or MASH.’

Supplementary Table 2:

Non-supported recommendations assessed in Delphi #2 (<80% agree or strongly agree)

- ‘Clinicians should consider treating T2DM with GLP-1 RAs when there is an elevated probability of having MASH with fibrosis based on non-invasive tests (FIB-4, 1.30 or greater; or LSM, 8 kPa or greater; or ELF test, 7.7 or greater). FIB-4 Ref: <https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis>.’
- ‘Whilst Metformin or SGLT2i may improve hepatic steatosis in people with MAFLD they are not recommended as a primary treatment for MAFLD in the presence or in the absence of T2DM.’
- ‘People undergoing bariatric surgery should be assessed before surgery for the presence and severity of MASH, and if they are determined to be at “high” or “indeterminate” risk of MASH with fibrosis by non-invasive tests (FIB-4, 1.30 or greater; or LSM, 8 kPa or greater; or ELF test, 7.7 or greater), then a liver biopsy should be considered at the time of bariatric surgery.’

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