Addressing NAFLD as a type 2 diabetes complication using the emerging paradigms in diagnostic and management techniques

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About the Author

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Introduction

Several critical epidemiological facts underscore the urgent need to address non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes (T2D):

1. NAFLD is the most common liver disease in Canada, affecting approximately one in four Canadians[1,2]
2. NAFLD is projected to become the number one leading indication for liver transplant by 2025[3]
3. Individuals with T2D are at the greatest risk of liver disease progression in NAFLD; T2D is the main predictor of NAFLD-related liver fibrosis and mortality[4,5]

To put this into clinical perspective, consider the following fictitious case: A 45-year-old teetotaler, Caucasian woman with T2D and a body mass index (BMI) of 32 kg/m^2, with no microvascular or macrovascular complications, was incidentally found to have "fatty liver" on abdominal ultrasound. ALT and AST were both within normal range. She was recommended to lose weight and control A1C. Twelve years later, she developed hematemesis and liver biopsy confirmed end-stage liver cirrhosis, with hepatocellular carcinoma. She was scheduled to undergo a liver transplant at age 59.

Despite the three established facts presented above and an abundance of cases similar to the one presented here, currently NAFLD is not being addressed during routine diabetes care as a complication of T2D. The primary reasons for this surprising clinical omission are:

1. NAFLD does not fit into the classical picture of the microvascular or macrovascular complications of T2D that are traditionally taught in undergraduate medical, residency, and continuing professional programs.
2. Early stages of NAFLD are asymptomatic (silent), with normal levels of liver enzymes and other liver function tests. Most cases are clinically diagnosed at a late stage of fibrosis, cirrhosis, or hepatocellular carcinoma.
3. Liver biopsy, the gold standard method of NAFLD diagnosis, is invasive, may not be readily accessible to all patients, and has several limitations.

4. Non-invasive methods to diagnose NAFLD, such as biomarker testing and imaging modalities, are evolving and screening algorithms are not yet standardized.
5. Most non-invasive screening methods for NAFLD are not easily accessed by Canadians, as they are either restricted or not covered by provincial health plans.
6. No guideline recommendations currently exist in Canada for screening of NAFLD in T2D.
7. No pharmacologic treatment is approved by Health Canada for NAFLD.
8. The majority of Canadian physicians and allied health care professionals have insufficient clinical knowledge about NAFLD.[6]

The changing paradigms

Fortunately, the majority of the above described clinical challenges are being resolved. Medical societies worldwide are now recommending systematic screening of NAFLD for individuals with T2D as an approach that has been demonstrated to be cost-effective.[7-10] Simultaneously, there is a growing consensus on non-invasive algorithms for NAFLD screening, coupled with recent positive outcome results from therapeutics directed at NAFLD.

Below are some of the most pertinent clinical background features of NAFLD in T2D (pathophysiology, terminology, epidemiology, diagnostics, and treatment) of which health care providers, including endocrinologists and other diabetes specialists, should be aware.

Definition, pathophysiology and terminology of NAFLD

NAFLD is defined as the accumulation of hepatic fat (steatosis) in ≥5% of hepatocytes in the absence of excessive alcohol consumption (<20 g/day for women and <30 g/day for men). NAFLD is characterized by fat accumulation in the liver, which can subsequently cause inflammation and fibrosis (scarring), leading to irreversible damage, cirrhosis, and eventually hepatocellular carcinoma. In addition to life-threatening hepatic events, NAFLD is associated with an increased risk of cardiovascular disease, extrahepatic cancers and renal disease.[7,9]

NAFLD is a progressive disease that encompasses two distinct histologic entities:

1. Nonalcoholic fatty liver (NAFL): Signified by a relatively benign histology; characterized by hepatic steatosis without evidence of hepatocellular injury.
2. Nonalcoholic steatohepatitis (NASH): A more serious process defined by steatosis accompanied by lobular inflammation and hepatocyte ballooning (cell death), without or with fibrosis (stages F1-F4 on liver biopsy).

Evolving diagnostic and therapeutic inter-disciplinary clinical care pathways

Figure 1 describes a roadmap for the diagnosis of NAFLD in T2D, emphasizing the need for an inter-disciplinary approach that places the chief onus of case finding on primary care and diabetes care teams. Referral to hepatology (or gastroenterology, depending on local access/options) should be considered for diagnostic challenges or for screening and managing liver complications in individuals at high risk for NASH.

Within the primary care and diabetes care teams, FIB-4 (Fibrosis Index based on 4 factors: age, AST, ALT and platelet count) calculation can be integrated into electronic medical records (EMRs) to screen and categorize individual as being at low, intermediate or high risk for NASH (available at www.hepatitisc.uw.edu/page/clinical-calculators/fib-4).

For those with intermediate risk on FIB-4, Vibration Controlled Transient Elastography (VCTE e.g., FibroScan®) performed in community diagnostic or hepatology centres may be utilized as a second step to further evaluate the risk of NASH. Low-risk liver stiffness is often considered for those individuals with VCTE <8 kPa, while those with VCTE ≥12 kPa are likely to have high-risk liver stiffness for NASH fibrosis.

As no pharmacotherapy is approved by Health Canada for NAFLD or NASH, health behavioural changes with emphasis on weight loss[11] and avoidance of alcohol remain the cornerstones of clinical management. Selected individuals with NAFLD together with T2D and high BMI may benefit from bariatric surgery.[12]

Certain antihyperglycemic medications, including glucagon-like peptide 1 receptor agonists (GLP-1RAs),[13] sodium-glucose co-transporter-2 (SGLT2) inhibitors,[14,15] and pioglitazone,[16] have demonstrated randomized clinical trial (RCT) evidence of reversal of liver steatosis and reduction of progression of fibrosis. However, no effect of these diabetes medications on reversing fibrosis has been observed in these short-term studies.

Recently, interim analyses from two large, randomized trials with NASH-targeted therapies—one with obeticholic acid[17] (a semi-synthetic bile acid analog) and another with resmetirom (a liver-directed selective thyroid hormone receptor agonist)—have reported positive results on the primary endpoint of

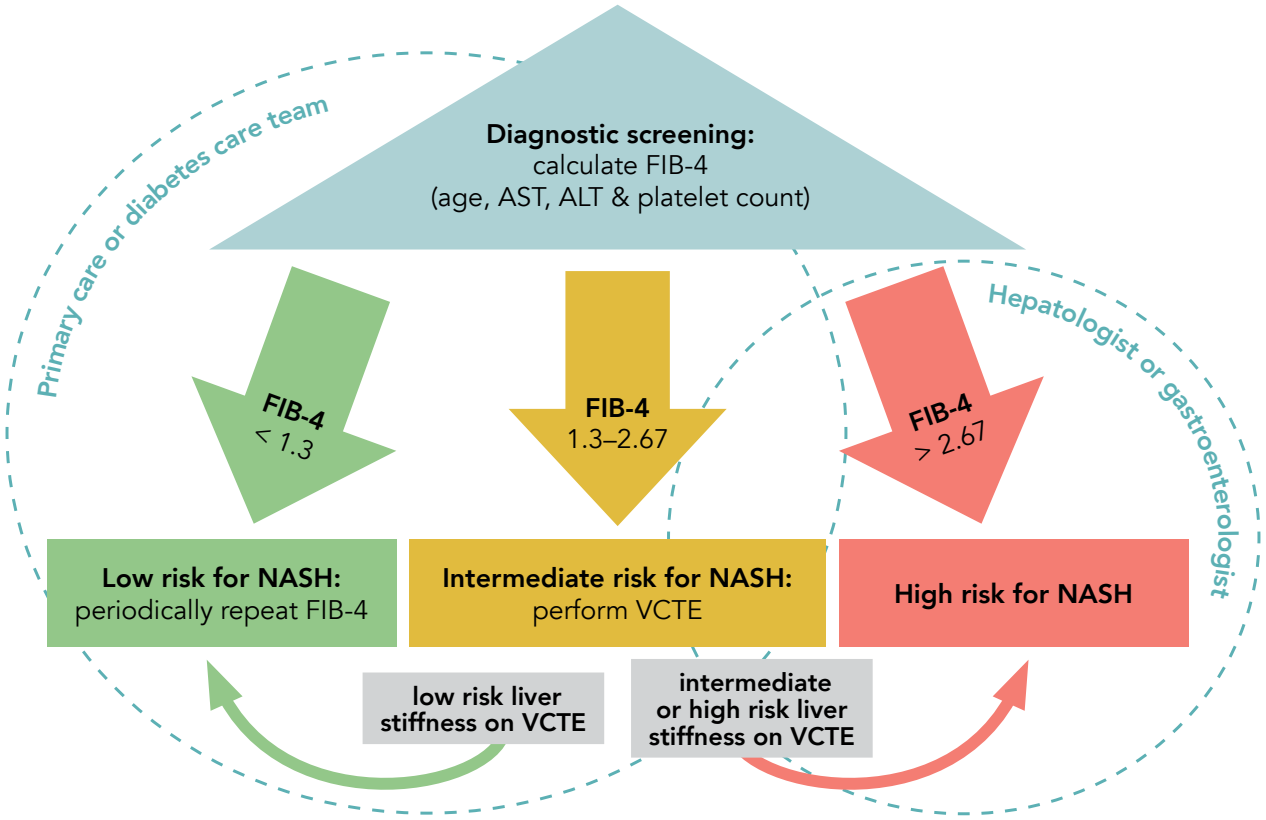

Figure 1: Interdisciplinary pathway for integration of NAFLD screening in clinical practice for individuals with type 2 diabetes. **FIB-4**: Fibrosis Index Based on 4 Factors; **ALT**: alanine transaminase; **AST**: aspartate transaminase; **VCTE**: vibration controlled transient elastography.
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fibrosis improvement (≥1 stage) with no worsening of NASH. These positive outcome results may lead to regulatory approval of these and other new classes of NASH therapeutics in the near future.

Summary

NAFLD is a prevalent, yet undiagnosed complication of T2D. Non-invasive diagnostic testing methods and consensus concerning NASH screening algorithms are rapidly evolving. It is anticipated that biomarker testing, the FIB-4 index, for example, may soon become the standard of care for NAFLD screening in individuals with T2D, similar to the utility of urinary albumin-creatinine ratio for nephropathy screening. Large randomized trials with NASH therapeutics, including antihyperglycemic medications and liver-targeted therapies, are underway and offer hope for regulatory approval of treatment options in the near future. Canada-wide, collaborative educational efforts are urgently needed to fill the existing clinical care gaps so that healthcare professionals can begin to evaluate and manage NAFLD as a common non-microvascular, non-macrovascular complication of T2D.

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