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How should Endocrinologists diagnose and treat nonalcoholic fatty liver disease?

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Nonalcoholic fatty liver disease (NAFLD) was first described in 1980 in a report from the Mayo clinic that described the characteristics of non-alcoholic steatohepatitis in 20 patients[1]. A liver biopsy showed 'the presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates; and evidence of fibrosis in most specimens'. Most of the patients were moderately obese, and many had type 2 diabetes mellitus (T2DM) and cholelithiasis[1]. The report concluded 'currently, we know of no effective therapy'[1]. Forty years later, it is gratifying to note that although there are still areas of uncertainty, there has been considerable progress in our understanding of the aetiology and pathogenesis of NAFLD, the non-invasive diagnosis of NAFLD, and how NAFLD can be treated. Moreover, in contrast to 40 years ago, there is now little need to resort to invasive, expensive and potentially risky liver biopsies to diagnose NAFLD, and there are now licensed treatments for the management of T2DM and obesity, that are also of proven benefit in the treatment of NAFLD.

In the 21st century, NAFLD has become a very common condition for both Endocrinologists/Diabetologists and Primary Care physicians. Risk of NAFLD is markedly increased with obesity, T2DM and features of the metabolic syndrome. Over the last ~5 years it has also become clear that NAFLD is a 'multisystem disease' that not only affects the liver, but also increases risk of developing important extra-hepatic complications, such as T2DM, cardiovascular disease (CVD), chronic kidney disease and certain extra-hepatic cancers[2,3]. In particular, it should be noted that the leading causes of death among patients with NAFLD is CVD, followed by extra-hepatic cancers and liver-related complications[2,3].

NAFLD represents a spectrum of conditions that is defined by the presence of ~5% liver fat accumulation, and progresses over time to (nonalcoholic) steatohepatitis that may occur with, or without the presence of liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). NAFLD occurs in up to ~70% of patients with obesity or T2DM; and, importantly, NAFLD is usually an asymptomatic condition until late in the course of disease. Consequently, it is really important for Endocrinologists/Diabetologists to know how best to diagnose and monitor NAFLD early in the disease process, identify those patients who may benefit from available treatment options, and recognise those patients who need to be referred to specialist Hepatology services.

Recently, the American Association of Clinical Endocrinology conducted a literature search for relevant articles published between January 1, 2010 and November 15, 2021. A task force of medical experts that also included representatives from the American Association for the Study of Liver Diseases, developed evidence-based recommendations based on a review of the clinical evidence, expertise, and informal consensus, according to an established American Association of Clinical Endocrinology protocol for guideline development[4]. As the diagnosis, monitoring and treatment of NAFLD is sub-optimal in people living with T2DM and/or metabolic syndrome, there are a number of recommendations in this Consensus Document (CD) that are worth highlighting and discussing.

The CD focussed on diagnosis and management of NAFLD in both adults and children[4]. Age (>50 years), insulin resistance, and features of the metabolic syndrome were highlighted as key risk factors that increase the likelihood of developing NASH, advanced fibrosis or cirrhosis; and it is important to recognise that all of these key risk factors often occur in T2DM[4]. It is well established that advanced fibrosis and cirrhosis are also key risk factors for developing HCC, and people with T2DM and NAFLD are at markedly higher risk (~20 fold) of developing HCC (compared to their counterparts without NAFLD)[5]. Consequently, it is clinically important to establish whether a person living with T2DM has liver fibrosis. In a very useful summary table of the recommendations within the CD, the authors state ‘clinicians should consider persons with obesity and/or features of metabolic syndrome, those with prediabetes or T2DM, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be “high risk” and should be screened for NAFLD and advanced fibrosis’[4].

Liver fibrosis is classically staged according to four levels of histological severity (stages F1-F4) and, as highlighted by the authors, F2-F4 should be considered high-risk states that

require identification[4]. In considering the important question 'what blood tests (e.g. diagnostic panels and specific biomarkers) can be used to diagnose NAFLD with clinically significant fibrosis (stages F2-F4) in adults', the authors conclude that 'clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis'[4]. They state that 'the preferred non-invasive initial test is the Fibrosis-4 (FIB-4) score and clinicians should consider persons belonging to the "high-risk" groups (defined above) who have an indeterminate or high FIB-4 score, should have further work up with an vibration-controlled transient elastography (VCTE) or an Enhanced Liver fibrosis (ELF) test, as available'[4]. In our opinion, it remains uncertain whether the ELF score adds further diagnostic value to a FIB-4 score, but we agree that is essential that high-risk patient groups undergo VCTE to determine whether they have clinically significant fibrosis. Additionally, modern VCTE scanners also contain an ultrasonography component (i.e., the controlled attenuation parameter) allowing the assessment of steatosis severity. With the cost of these scanners falling, the widespread use of VCTE scanning in all persons with T2DM is becoming a realistic possibility that could become feasible within the routine assessment of most patients with T2DM in Endocrinology clinics. Although the use of the ELF test has not gained much traction in health care, it should be noted that some centres do use the ELF test, and this test was also the preferred liver fibrosis biomarker recommended in the 2016 UK NICE NAFLD Guideline (ng49)[6].

When considering what medications have proved to be effective for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH, the authors of the CD conclude 'pioglitazone and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are recommended for persons with T2DM with biopsy-proven NASH'[4]. Importantly, the authors go on to state 'clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and non-invasive tests'[4]. With regard to the use of sodium-glucose cotransporter (SGLT-2) inhibitors, the authors state 'to offer cardiometabolic benefit in persons with T2DM and NAFLD, clinicians must consider treatment with GLP-1 RAs, pioglitazone, or SGLT2 inhibitors; however, there is no evidence of benefit for treatment of steatohepatitis with SGLT2 inhibitors'[4]. For other commonly used anti-hyperglycaemic drugs, the authors also state 'due to the lack of evidence of efficacy, metformin, acarbose, dipeptidyl peptidase IV inhibitors, and insulin are not recommended for the treatment of steatohepatitis, but may be continued as needed for the treatment of hyperglycemia in persons with T2DM and NAFLD'[4].

The burden that NAFLD creates for health care and for economies is considerable for all countries and especially for those countries where there is an increasing prevalence of obesity and T2DM. Recently, the lifetime costs of all patients with NASH in the USA in 2017 were

estimated to be $222.6 billion, and amongst this group of patients, the costs attributed to advanced NASH were $95.4 billion[7]. The excellent CD discussed above is a very helpful publication that we would encourage all Endocrinologists/Diabetologists and Primary Care Health Care Professionals to read. The views expressed are largely congruent with other recent Guidelines and Consensus documents that have been published in the last year[8-10]. The CD should also act as a call to arms to all Endocrinologists/Diabetologists and their Professional Societies to develop their own strategies to address NAFLD, and we suggest this should now happen as quickly as possible, at both a national and global level.

References

1. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**(7): 434-8.
2. Byrne CD, Targher G. NAFLD: A multisystem disease. *J Hepatol* 2015; **62**(1S): S47-S64.
3. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. *The lancet Gastroenterology & hepatology* 2021; **6**(7): 578-88.
4. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 2022; **28**(5): 528-62.
5. Wild SH, Walker JJ, Morling JR, et al. Cardiovascular Disease, Cancer, and Mortality Among People With Type 2 Diabetes and Alcoholic or Nonalcoholic Fatty Liver Disease Hospital Admission. *Diabetes Care* 2018; **41**(2): 341-7.
6. Glen J, Floros L, Day C, Pryke R. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. *Bmj* 2016; **354**: i4428.
7. Younossi ZM, Tampi R, Priyadarshini M, Nader F, Younossi IM, Racila A. Burden of Illness and Economic Model for Patients With Nonalcoholic Steatohepatitis in the United States. *Hepatology* 2019; **69**(2): 564-72.
8. McPherson S, Armstrong MJ, Cobbold JF, et al. Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group. *The lancet Gastroenterology & hepatology* 2022.
9. Duell PB, Welty FK, Miller M, et al. Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol* 2022: 101161atv0000000000000153.
10. Non-alcoholic fatty liver disease in adults 2021: A clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO). *Nutr Metab Cardiovasc Dis* 2022; **32**(1): 1-16.