Hidden Complication of Obesity and Diabetes: Is It Time to Put More Focus on Fatty Liver?

Authors:	*James Woijoo Kim,[1] Giada Sebastiani[2] 1. University of Calgary, Alberta, Canada 2. McGill University, Montréal, Quebec, Canada *Correspondence to jkim@vineyardmedicalclinic.com

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Abstract

Since the release of the EMPA-REG trial in 2015, the focus in diabetes management has been shifted from a glucocentric approach to a more organ-protective approach. Much of the focus has been on cardiorenal protections, thanks to the numerous landmark trials being published in recent years. However, the significance of what seems to be an innocuous fatty deposition in the liver has received less attention than it deserves for many years, especially in people living with diabetes and obesity, but its impact on health has slowly been highlighted more in the last decade. Bodies of research are now suggesting that non-alcoholic fatty liver disease (NAFLD) is a significant independent risk factor for cardiovascular disease, including myocardial infarction, heart failure, and atrial fibrillation, while it carries the increased risk of cirrhosis, hepatocellular carcinoma, and extrahepatic cancers. Numerous organisations have begun to publish guidelines focusing on screening and treating NAFLD in recent years in an effort to combat this underappreciated, underdiagnosed, and undertreated complication of diabetes and obesity. This review paper will provide an overview of NAFLD, highlighting the argument that NAFLD is indeed an independent cardiovascular risk factor, discussing the proposed pathophysiology of NAFLD being a cardiovascular risk factor, and suggesting a highly validated hepatic fibrosis screening tool, which is a simple, easy-to-use tool to screen for hepatic fibrosis, and can be used in primary care offices.

Key Points

1. Since the EMPA-REG trial in 2015, there has been a shift in diabetes management from a glucose-centred approach to one focused on organ protection, especially cardiorenal protection. The focus has shifted towards addressing complications that are often overlooked, such as non-alcoholic fatty liver disease (NAFLD).

2. NAFLD is not just a liver condition but is also an independent risk factor for cardiovascular disease (CVD). People with NAFLD, especially those with diabetes and obesity, are at an increased risk of various CVD outcomes, including myocardial infarction, heart failure, and atrial fibrillation.

3. Despite its prevalence and significance as a CVD risk factor, NAFLD is often underdetected, underappreciated, and undertreated. Healthcare providers, especially primary care providers, need more education and guidelines to improve the screening, detection, and management of NAFLD.

INTRODUCTION

Since the release of the EMPA-REG trial, in which for the first time an antihyperglycaemic agent demonstrated a reduction in major adverse cardiovascular events, the world of diabetes management has shifted from its glucocentric mentality into putting more emphasis on organ protection without discounting the importance of glucose management. After all, the most common cause of death amongst people living with Type 2 diabetes (T2D) is cardiovascular disease (CVD).[1] Starting with EMPA-REG, numerous research has been conducted and demonstrated that certain antihyperglycaemic agents are able to reduce cardiorenal outcomes, further providing cardiorenal protection. This includes the reduction in hard cardiovascular outcomes, such as cardiovascular death; hospitalisations for heart failure, as seen in EMPA-REG; and hard renal outcomes, as seen in CREDENCE. However, it seems that the diabetes world has been putting so much focus on cardiac and renal protection, that another metabolic condition, possibly a hidden complication of diabetes playing a significant role in CVD, has been almost forgotten and has not received the attention that it deserves. That is non-alcoholic fatty liver disease (NAFLD).

Global prevalence of NAFLD is 30%,[2] but the prevalence dramatically increases to 55% in patients with T2D.[2] This pandemic seems to be driven by the rise in T2D and obesity globally, including Canada. As matter of fact, the World Health Organization (WHO) made a gloomy prediction that the prevalence of global obesity will reach 1 billion, with close to 40% of Canadians being obese by 2030.[3] Given that the prevalence of NAFLD in the obese population is 75%,[4] it is unsurprising that the prevalence of NAFLD is expected to rise up to 35% globally.[5] One Canadian modelling study projected that by 2030, there would be an increase in the prevalence of NAFLD by 20% from 2019.[6] The same study forecasted a significant increased prevalence of advanced and end-stage NAFLD (i.e., decompensated cirrhosis, hepatocellular carcinoma) by 95%, while doubling of NAFLD-related deaths and need for liver transplantation would occur at the same time.[6] What seemed to be an innocuous fatty deposition in the liver, may result in hepatic cirrhosis and hepatocellular carcinoma in 10–20% of the individuals living with NAFLD.[2] NAFLD has now become the number one cause of liver transplant in the USA,[2] and is predicted to be the leading cause for liver transplant in Canada by 2025.[6] The condition is also associated with extrahepatic cancers. A meta-analysis by Mantovani et al.[7] in 2022 demonstrated a 1.5–2.0-fold increase in risk of developing gastrointestinal cancers, such as oesophageal, stomach, pancreas, or colorectal cancer; and 1.2–1.5-fold increase in developing lung, breast, urinary, or gynaecological cancers.[7]

Perhaps more importantly, NAFLD has demonstrated to be a significant cardiovascular risk factor by itself, as cardiovascular mortality is the leading cause of death in people living with NAFLD.[2,5] Despite NAFLD being common in the general population and carrying a significant

cardiovascular risk, it is underdetected, underappreciated, and, therefore, undertreated. This paper aims to address NAFLD as an independent cardiovascular risk factor, arguing that NAFLD should be viewed as one of the complications of T2D. The authors will also provide a brief overview of the pathophysiological link between NAFLD and CVD, and discuss ways to improve the detection of this frequent condition.

NON-ALCOHOLIC FATTY LIVER DISEASE-RELATED DEFINITIONS AND DISEASE PROGRESSION

NAFLD is defined as the presence of hepatic steatosis in more than 5% of the hepatocytes, with no other causes, including absence of excessive ongoing or recent alcohol consumption (i.e., <20 g/day for females and <30 g/day for males) without secondary causes of hepatic steatosis.[8,9] This terminology encompasses a disease spectrum from a simple state of hepatic steatosis without hepatocellular injury or fibrosis, known as non-alcoholic fatty liver, to non-alcoholic steatohepatitis (NASH), and finally cirrhosis.[8] NASH refers to the presence of >5% of hepatic steatosis with inflammation and hepatocyte injury (i.e., hepatocyte ballooning), with or without fibrosis, which then is further classified into Stages 1–4. Stage 4 fibrosis due to NASH corresponds to cirrhosis of the liver.[3,8]

There have been a number of terminology changes of NAFLD in recent years. In 2020, an international expert consensus decided to change the terminology from NAFLD to metabolic dysfunction-associated fatty liver disease, to demonstrate its clinical outcomes and its close association with metabolic syndrome.[10] More recently, a multi-society nomenclature change was agreed, where NAFLD and metabolic dysfunction-associated fatty liver disease were to be changed to metabolic dysfunction-associated steatotic liver disease.[11] However, for the purpose of this article, the older and more familiar terminology NAFLD will be used.

In general, the actual pathogenesis of NAFLD is not fully understood, as various hypotheses have been proposed. Multiple factors seem to occur simultaneously in the pathogenesis of NAFLD, and this has led to the development of multiple parallel hit hypotheses approximately a decade ago.[12] However, it is widely accepted that both hepatic and systemic insulin resistance play a central role in the development of NAFLD. Therefore, it is not surprising to find high prevalence of NAFLD in individuals living with obesity and diabetes.[13] Increase in a hepatic *de novo* lipogenesis, suboptimal uptake of circulating lipid, poor enhancement of compensatory fatty acid oxidation, and inadequate export of triglyceride-rich very low-density lipoprotein are the main pathways resulting in the imbalance between the lipid acquisition and lipid disposal, which, in turn, leads to hepatic fat accumulation and ultimately results in hepatic insulin resistance.[14] Ectopic fat accumulation also occurs in the pancreas, which is associated with systemic insulin resistance and β-cell dysfunction. This, in turn, will lead to the abnormal glucose metabolism and compensatory hyperinsulinaemia, which elevates the free fatty acid, and increases hepatic gluconeogenesis. NAFLD interestingly causes a reduction in hepatic insulin clearance, which will accentuate these effects.[14] The usual endocrine effect of the adipose tissues, including these ectopic adipose tissues, results in elevated adiponectin, which inhibits lipid accumulation, and regulates fatty acid oxidation, glucose homeostasis, and hepatic insulin sensitivity. Adiponectin has demonstrated anti-fibrotic and anti-inflammatory effects as well. Interestingly, patients with NAFLD or T2D have reduced adiponectin level, which will impair the fatty acid metabolism while promoting chronic inflammation of the liver.[15]

Fatty acid level decreases with the anti-lipolytic action and with the release of insulin. However, due to the insulin resistance in people with NAFLD, the level of circulating fatty acid tends to remain higher than usual. This results in increased uptake of fatty acid by the liver. Through complex processes, the liver is subjected to proinflammatory state, and profibrotic pathways are activated, which causes the progression of NASH.[16]

Numerous innate immune cells, such as neutrophils, Kupffer cells, dendritic cells, natural killer cells, and mast cells, are involved in developing NAFLD by producing proinflammatory cytokines, which ultimately progresses to fibrosis, cirrhosis, and hepatocellular carcinoma.[17]

Other factors, such as the alteration of the gut microbiome, are also believed to be main drivers in the pathogenesis of NAFLD. More recently, genetics and dietary components have been added to the list of contributors to NAFLD development.[12]

NON-ALCOHOLIC FATTY LIVER DISEASE AS AN INDEPENDENT CARDIOVASCULAR DISEASE RISK FACTOR

Firstly, the leading cause of death in people living with NAFLD is CVD,[2] and this should not come as a surprise since the typical person living with NAFLD frequently meets the diagnostic criteria for metabolic syndrome (i.e., obesity, diabetes, dyslipidaemia, hypertension), which are established risk factors for CVD.[18] Hypertension and NAFLD seem to have a bidirectional relationship.[19] A prospective study from Germany with 3,191 patients demonstrated prevalence of hypertension in NAFLD cohorts were three-fold higher (odds ratio [OR]: 3.1; 95% confidence interval [CI]: 1.7–5.8) than the cohorts without NAFLD.[20] Another prospective cohort study from Korea demonstrated that the incidence rate of hypertension was increased with increased severity of NAFLD (i.e., mild: 21.8%; moderate-to-severe: 30.1%).[21] An increased risk of CVD in people with NAFLD was evident in a recent large meta-analysis (hazard ratio [HR]: 1.45; 95% CI: 1.31–1.61).[22] The same meta-analysis further demonstrated the higher risk of NAFLD in non-fatal CVD (pooled random-effects HR: 1.40; 95% CI: 1.20–1.64), and fatal CVD (pooled random-effects HR: 1.30; 95% CI: 1.08–1.56).[22] When examining the various risk factors for CVD in people with NAFLD, diabetes was found to be the most important (OR: 2.18; 95% CI: 1.580–3.000; p=0.0004), followed by hypertension (OR: 1.67; 95% CI: 1.500–1.860; p<0.0001), and age (β: 0.100; 95% CI: 0.0576–0.142; p<0.0001).[23]

Multiple studies have demonstrated the relationship between higher CVD risk and worsening fibrosis, regardless of how the fibrosis was measured or even estimated. In a large meta-analysis, worsening fibrosis increased the risk of CVD 2.5 times (95% CI: 1.68–3.72).[22] Two validated fibrosis biomarkers using standard laboratory parameters, namely the Fibrosis-4 (FIB-4) index, which is a simple, highly validated non-invasive test calculated using age, alanine transaminase, aspartate aminotransferase (AST), and platelet; and NAFLD Fibrosis Score (NFS), were used in a prospective study by Baratta et al.[24] An NFS of >0.676 demonstrated a significant increase in CVD events after adjustment for comorbidities (HR: 2.29; 95% CI: 1.17–4.47; p=0.016). A FIB-4 score of >2.67 presented with a substantial increase in CVD events (HR: 4.57; 95% CI: 1.61–12.98; p=0.004).[24] Two other studies from Asia using the FIB-4 score demonstrated a high degree of association between advanced fibrosis (evaluated by a high FIB-4 score of >2.67) and CVD events.[25,26]

As matter of fact, simple hepatic steatosis alone is also associated with CVD risk. In 6,340 patients from PREVEND who had hepatic steatosis (i.e., Fatty Liver Index [FLI] >60) but without pre-existing CVD, hepatic steatosis was found to be a CVD risk factor after adjusting for traditional CVD risk factors.[27] Along the same lines, a population study from the UK also reported similar findings, where elevated FLI resulted in higher CVD events.[28] When examining the newly diagnosed patients with T2D with hepatic steatosis, once again defined by FLI ≥60, a Korean population study reported increased risk of myocardial infarction (HR: 1.28; 95% CI: 1.14–1.44), heart failure (HR: 1.17; 95% CI: 1.07–1.26), stroke (HR: 1.41; 95% CI: 1.25–1.56), and mortality (HR: 1.41; 95% CI: 1.32–1.51), even when adjusting for traditional CVD risk factors.[29] Ultrasonography was used to determine the presence of hepatic steatosis in a nested cohort study by Meyersohn et al.[30] Presence of hepatic steatosis resulted in an increased risk of CVD events compared with people without hepatic steatosis (HR: 1.69; 95% CI: 1.16–2.48; p=0.006), even after adjusting for the traditional cardiovascular risk factors, such as atherosclerotic CVD scores, metabolic syndrome, significant steatosis, or obesity.[30]

A Swedish nationwide cohort study involving over 10,000 individuals with biopsy-proven NAFLD were matched to 50,000 people for controls, demonstrating that NAFLD may be a risk factor for developing new onset of heart failure.[31] The risk of developing heart failure increased with worsening of NAFLD.[32] Valbusa et al.[33] reported that advanced liver fibrosis, calculated by liver fibrosis scores (i.e., FIB-4 and AST-to-Platelet Ratio Index [APRI]), was

associated with higher risk of hospital and post-discharge mortality in an elderly population admitted for acute heart failure.[33]

A review paper by Alkagiet et al.[34] examined the risk of ischaemic stroke in people with NAFLD. It was fascinating to note that NAFLD did not only increase the risk of ischaemic stroke, but also increased the severity of ischaemic stroke with worse clinical outcomes, concluding that NAFLD is an independent risk factor for ischaemic stroke, and suggesting that people with ischaemic stroke should be screened for NAFLD and treated aggressively.[34]

Large bodies of evidence demonstrate the relationship between NAFLD and atrial fibrillation. A recent meta-analysis by Jaiswal et al.[35] included 12 cohort studies with over 18 million patients and showed a significant increased likelihood of developing atrial fibrillation (relative risk: 1.42; 95% CI: 1.19–1.68) in people with NAFLD compared with the ones without NAFLD.[35] A population study from South Korea examined over 8 million people with NAFLD, and demonstrated the association between worsening hepatic steatosis with higher risk of developing atrial fibrillation.[36]

BRIEF OVERVIEW ON PATHOPHYSIOLOGY OF NAFLD'S EFFECT ON CARDIOVASCULAR DISEASE

A detailed overview of the pathophysiology on how NAFLD affects CVD is beyond the scope of this paper, and it is not fully understood. Therefore, a brief overview on pathophysiology of NAFLD's effect on CVD will be discussed. NAFLD seems to induce metabolic impairment, which is then also associated with systemic inflammation and increase in oxidative stress. Oxidative stress itself induces inflammation via endothelial dysfunction, which will predispose people with NAFLD to CVD events, resulting in impaired cardiac function and atherosclerosis.[37]

As obesity is closely associated with NAFLD, adiposity can trigger pro-inflammation through a number of mechanisms negatively impacting the production of anti-inflammatory cytokines while increasing the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This systemic inflammation arising from adipose tissue inflammation can lead to worsening of insulin resistance and CVD, which can result in worsening of NAFLD.[38]

Inflammation of the liver leads to the progression from simple hepatosteatosis (i.e., NAFLD) to NASH, and eventually to cirrhosis. During this process, systemic inflammation ensues at the same time. Hepatic necro-inflammation is thought to be an independent proatherogenic mechanism.[38]

Some of the major hallmarks of NAFLD are abnormal glucose metabolism and hepatic insulin resistance. Abnormal glucose metabolism can contribute to systemic inflammation and increased weight gain, including visceral obesity, leading to the accumulation of dysfunctional ectopic fatty tissue. These fatty tissues can accumulate in the pancreas, resulting in insulin resistance and β-cell dysfunction. Furthermore, insulin resistance leading to the negative metabolic status of a patient is also likely to be one of the main contributors to the development of CVD.[14] Ectopic fat can be deposited into the myocardium and surround the heart, which can be further classified into epicardial fat and pericardial fat. Epicardial fat plays a critical role in cardiac metabolism. The previously mentioned adiponectin, which is a protective hormone that mediates anti-fibrotic, anti-atherogenic, anti-inflammatory, and antioxidant cardioprotective effects, declines with NAFLD, while more proinflammatory cytokines are synthesised, including IL-6, IL-1β, and TNF-α. These changes lead to the promotion of atherosclerosis of coronary arteries and structural changes in the adjacent myocardium, including myocardial fibrosis, which ultimately leads to cardiac dysfunction.[14] Electrical and autonomic remodelling of the heart occurs, which increases the susceptibility to atrial fibrillation, ventricular arrhythmia, and prolongation of the QT interval.[37] It is likely that the epicardial adipose tissue may have placed itself at the centre of the pathophysiological link between NAFLD and CVD.[14] Other hypotheses have been implicated on the pathophysiology of NAFLD's effect of CVD. Numerous genes have been identified which increase the risk of developing NAFLD. Plaque formation increases due to increased activity of the pro-coagulation factors. Altered, dysregulated gut microbiome, which leads to the

production of certain metabolites, resulting in systemic inflammation, is also implicated in CVD development.[14]

SUGGESTED APPROACH TO NON-ALCOHOLIC FATTY LIVER DISEASE IN PRIMARY CARE CLINIC

A cross-sectional study by Islam et al.[39] revealed that primary care providers (PCP) are aware of the importance of fibrosis in NAFLD. Although time constraint was not found to be a barrier, lack of knowledge in diagnosis and management of NAFLD was a main barrier.[39] A similar survey was carried out in Canada by one of the authors, which demonstrated that a significant proportion of Canadian physicians and nurses were not familiar with this disease. The survey concluded that lack of educational programmes and national guidelines on NAFLD may be contributing to these results.[40] Several guidelines have been created to aid the healthcare providers in improving screening and management of NAFLD. The Calgary NAFLD pathway (based on the use of shear wave elastography) has shown that 92% of the referred patients for NAFLD were at low risk for fibrosis and were able to be managed within primary care. The implementation of such a pathway has reduced the NAFLD waitlist by 84%.[41] The Camden and Islington NAFLD pathways, which utilise sequential use of FIB-4 and the patent serum biomarker, Enhanced Liver Fibrosis (ELF) marker, recommended to screen for NAFLD in people with elevated liver enzymes.[42] However, this could still result in a significant number of people with NAFLD remaining undetected. A cross-sectional study conducted in 561 patients with T2D demonstrated that the proportion of people with hepatosteatosis with fibrosis having AST >40 units/L and alanine transaminase >40 units/L was only 6% and 10%, respectively.[43] The American Association of Clinical Endocrinology (AACE), American Association for the Study of Liver Diseases (AASLD), and American Gastroenterology Association (AGA) have similar guidelines and pathways which heavily rely on FIB-4 score. This non-invasive test has been highly validated is several clinical settings.[4,44,45] Most of these lab test results are readily available and the calculation is easy, providing risk stratification of the individual probability and severity of hepatic fibrosis status.

DISCUSSION

The prevalence of NAFLD has been underestimated and its sequelae have been largely underappreciated by PCPs. Many PCPs may have considered NAFLD to affect the liver alone, and yet, the leading cause of morbidity and mortality for people living with NAFLD remains CVD, just like any other typical metabolic condition. Seemingly, an innocuous fatty deposition in the liver can negatively affect the metabolic status, which can lead to various CVD events. Risk factors have been identified and although not fully understood, numerous pathophysiological links between NAFLD and CVD have been hypothesised. Treatments of NAFLD include non-pharmacological therapy such as weight loss, and reduction of cardiovascular risk factors. However, concrete and feasible evidence on pharmacotherapy targeting NASH and liver fibrosis for NAFLD treatment is still lacking. NAFLD in patients with T2D has been making enormous inroads in management of diabetes, where number of newer classes of antihyperglycaemic agents such as sodium-glucose cotransporter 2 inhibitors and especially glucagon-like peptide-1 receptor agonists are being researched vigorously with promising outcomes. Even older antihyperglycaemic agents, such as pioglitazone, have shown a positive therapeutic effect in NAFLD. Therefore, several societies have recommended the use of glucagon-like peptide-1 receptor agonists in treatment of T2D in people with NAFLD in their guidelines, and pioglitazone in people with or without NAFLD.[4,44] Anti-fibrotic medications are being developed currently and there will be more options in the treatment of NAFLD.

It is beyond the scope of this paper to describe all the anti-fibrotic medications that are in development, but it is worth noting a few of them. Farnesoid X receptor (FXR) is one of the nuclear receptors which plays a crucial role in metabolic pathways, such as glucose homeostasis, and inflammatory and fibrogenic processes. Activating FXR has positive impacts on the hepatic lipogenesis, glucose homeostasis, and production of bile acid, while protecting the hepatocytes against the bile acid-induced cytotoxicity.[46] In a rodent study by Fiorucci et al.,[47] FXR agonists promoted the reduction of hepatic fibrosis. Therefore, there are number

of FXR agonists being developed, such as tropifexor.[47] Certain fibroblast growth factors (FGF), such as FGF19, FGF21, and FGF23, are signalling proteins that regulate the metabolism of lipid, bile acid, and carbohydrates. Several studies have demonstrated histological improvement (i.e., fibrosis regression) and reduction in hepatosteatosis with FGF agonists.[45] Peroxisome proliferator-activated receptors are the nuclear receptors, playing an important role in regulating various metabolic processes, such as lipid transportation. Lanifibranor (Inventiva Pharma, Daix, France) and Saroglitazar (Zydus Cadila Healthcare Ltd, Ahmedabad, India) are two peroxisome proliferator-activated receptor agonists that are in development. Their Phase II studies have shown significant reduction in fat content, and, in some cases, resolution of NASH was noted in the interventional group.[47,48] Since the discovery of the link between hypothyroidism and NASH, many researches were dedicated to find the potential therapy to target this pathway, and it has led to the development of resmetirom, which is a thyroid hormone β-receptor agonist. A recent Phase III randomised control study demonstrated significant NASH resolution and improvement of hepatic fibrosis.[49]

It is important to note that several guidelines, such as those of the AASLD, strongly recommend statins to be used with people living with NAFLD for CVD risk reduction. The same guideline also emphasises the safety of statin in NAFLD disease spectrum, including compensated cirrhosis.[50]

CONCLUSION

NAFLD has been a hidden complication of obesity and diabetes, which has gone unnoticed for so long and is now affecting 30% of the general population. More educational programmes are required to inform the PCPs on this CVD equivalent condition. NAFLD algorithms created or endorsed by national organisations are crucial in improving the screening, detection rate, and management of patients with NAFLD and are urgently needed. This may be the first step towards addressing the silent pandemic of NAFLD. The diabetes world has made a huge step forward in cardiorenal protections. Now, it is time, although belated, to focus on NAFLD, which is evidently an independent CVD risk factor.

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