Conference Report

The Global Burden of Non-alcoholic Steatohepatitis

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is growing globally in parallel to the epidemics of obesity and type 2 diabetes mellitus. Presently, 25% of the adult population is affected globally but in those with Type 2 diabetes mellitus (T2DM), the global prevalence is 55.5%. Despite the very high prevalence of NAFLD, it is the subtype of non-alcoholic steatohepatitis (NASH) that predominantly leads to the development of fibrosis, cirrhosis, hepatocellular carcinoma (HCC), liver transplantation and/or death. Currently, the prevalence of NASH in general population ranges from 1.5–6.5% but can be as high as 37.3% in those with T2DM. As such, NASH is now among

the top indication for liver transplantation and is increasingly linked to HCC in the United States. To date, there are no approved pharmaceutical agents to treat NASH and management relies on life style modifications. In this review, we discuss NASH, its pathophysiological, patients reported and economic outcomes as well as potential therapeutic targets.

Keywords: Non-alcoholic Steatohepatitis.

Introduction

Non- Alcoholic Fatty Liver Disease (NAFLD) is part of a multisystemic disease which has been considered the hepatic manifestation of metabolic syndrome due to its close associations with obesity, insulin resistance, type 2 diabetes mellitus, hypertension, and dyslipidemia. An individual is considered to have NAFLD if >5% of the liver cells are comprised of fat in the absence of excessive alcohol use or other causes of liver disease. For the most part, the so called the “simple steatosis” type of NAFLD, also referred to as NAFL, does not progress past the early stages of liver disease. However, approximately 20% of those with NAFLD have underlying Non-alcoholic steatohepatitis (NASH), whose liver biopsies show hepatic steatosis as well as ballooning of the hepatocytes, necroinflammation of the liver with or without peri-sinusoidal fibrosis. NASH is considered progressive type of liver disease leading to fibrosis, cirrhosis, hepatocellular carcinoma, the potential need for a liver transplantation.[1,6] Furthermore, research has demonstrated that it is the stage of fibrosis and the presence of certain metabolic disorders (eg, type 2 diabetes mellitus) that are most closely associated with death. In fact, stage 2 or higher stage of fibrosis has been found to be an independent predictor of liver-related mortality. [3-5]

Recent studies have also indicated that NASH is now among the top indications for liver transplantation and is the fastest growing cause of hepatocellular carcinoma. [2, 7] The rate for the development of HCC in those with NASH and fibrosis to be approximately 2% to 3% which does make screening for HCC necessary for these patients. In contrast, non-cirrhotic NAFLD can also progress to HCC in about 0.5% of patients which is low enough to make screening for HCC not a recommended option. [8,9]

Due to the lack of fully validated non-invasive diagnostic methods, therein lies another dilemma as to how best to determine the presence of NASH and the stage of fibrosis. Further research into the best non-invasive tools for the diagnosis of NASH and fibrosis are an immediate need and concern in the oncoming front of NASH in the background of the obesity epidemic. [9] However, a recent publication provided some much-needed guidance on how to incorporate the already developed non-invasive tools into clinical practice while also citing the many areas of research still needed. For example, the authors have suggested that in the primary care setting using tests that are simple, inexpensive and easily obtained with commonly blood serum tests make up the best choices. [9] Currently, the FIB-4 or NAFLD fibrosis scores (NFS), both which have > 90% negative predictive value for ruling out advanced fibrosis and a positive predictive value 75% to 90%, should be used as first-line tests when screening for fibrosis. Patients are considered to be at low risk of advanced fibrosis if FIB-4 score of <1.3 or NFS < –1.455 and do not warrant further assessment with additional tests but should receive life style modification counseling. All others whose scores fall outside of the low scores should be considered for further testing and assessment by expert practices. It is important to note that approximately 55% of patients will be low risk, 30% of patients may be at an intermediate fibrosis risk while 12%-15% may be at high risk for fibrosis. [10-12]

NASH Prevalence

Until recently, focus has been on determining the prevalence and incidence of NAFLD but as our understanding of this disease process has rapidly expanded, NASH has become the focal point of interest. However, given the limitations of the diagnostic methods available to determine the presence of NASH outside a liver biopsy, there is a paucity of data on the global prevalence and incidence of NASH but the following will provide the available data on the prevalence and incidence of NASH. [12,13]

Globally, the total prevalence of NAFLD has been cited at 25%, while the prevalence of NASH has been estimated to range from 1.5% to 6.45% with the global prevalence of NASH among persons with type 2 diabetes estimated at 37.3%.[14-16] (Fig. 1) A literature review from 1985-

2017 which returned 30 studies reported that biopsy-confirmed NASH ranged from 16%-70% among the NAFLD population while the prevalence of NASH among type 2 diabetic patients ranged between 57%-64% and between 14-47% for those considered obese. [17] In a study among pathologists who read liver biopsies from patients with NAFLD, the prevalence of NASH was found to be 45%.[18]

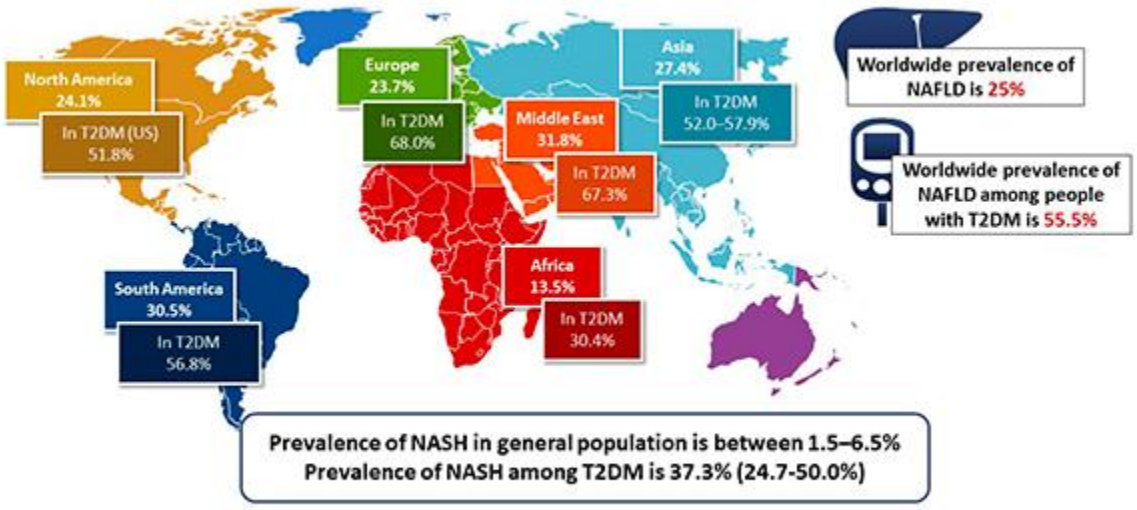

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Fig. 1 - Prevalence of NAFLD and NASH

In the US, the prevalence of NASH has been reported to be 12% with certain sub populations more at risk. The prevalence of NASH for Hispanics has been reported to be 19.4% while for Caucasians the prevalence has been reported to 9.8%. Among those with obesity, the prevalence of NASH has been estimated to be 25% to 30% while a recent study using liver biopsies suggested that among those with NAFLD and Type 2 diabetes mellitus, the prevalence of NASH was 65.26%. [16] Another study investigating the prevalence of NASH in those with biopsied proven NAFLD within the US determined that the prevalence of NASH was 69.2% while the prevalence of advanced fibrosis was 41.0%. [19] Given that these patients were scheduled for biopsy, there is inherent

selection bias. Given these data, the estimated prevalence of NASH (1.5%-6.5%) in the general population seems to be accurate.[14]

In addition to the meta-analysis of the general population estimates, another meta-analysis was conducted among patients with Type 2 diabetes mellitus. This analysis found that the global prevalence of NAFLD among this group was 55.5% with Europe and the Middle East having the highest prevalence at 68.0%[20]. The estimated the prevalence of NASH among person with type 2 diabetes mellitus was found to be 37.3% with an estimated prevalence of advanced fibrosis to be 17.0%.[20] Finally, a US study using data from the National Health and Nutrition Examination Survey (NHANES) data found that over only a decade (1999-2002 to 2009-2012) the rates of obesity, insulin resistance, and diabetes increased alongside a 2.5-fold increase in the prevalence of NASH cirrhosis that when extrapolated was equal to 417,524 adults in the US.[21] This explains the recent data that NAFLD is the most rapidly growing liver disease in the United States over the past 30 years.[6]

As noted, due to the lack diagnostic methods for determining the prevalence of NASH, researchers are using modeling methods to provide estimates of NASH for many countries. One modeling study analyzed data for eight countries (China, France, Germany, Japan, Spain, UK, US, and Italy) in 2016 and reported that within the general population to include children the NASH prevalence ranged from a low 2.4% for China to a high of 5.3% for the US. Researchers also forecasted that by 2030 the prevalence of NASH will increase with 7.6% of the US population presenting with NASH followed by 6.3% of the Italian population having NASH to only 3.4% of China's population having NASH. Among those with NAFLD, the prevalence of NASH ranged from 13.4% for China to 20.3% for the US. These researchers also applied the same model in 2017 to data from Saudi Arabia and the United Arab Emirates (UAE). The results were similar for both countries among the general population where in Saudi Arabi the NASH prevalence was estimated to be 4.2% and 4.1% for UAE. The NASH prevalence for both countries is expected to increase to greater than 6% by 2030. In those with NAFLD, the NASH prevalence rates were 16.2% and 16.4%, respectively.[10, 22-28]

Turkey also reported that the prevalence of NAFLD was a shocking 48.3% which led investigators to quantify the presence of NASH. In a total of 468 patients with biopsy-proven NAFLD where

histological classification of the biopsies was performed according to the Steatosis, Activity and Fibrosis (SAF) scoring and Fatty Liver Inhibition of Progression (FLIP) algorithm along with the NAFLD Activity Score (NAS) scoring system, they found that according to the SAF criteria 90.4% had NASH. The prevalence of significant fibrosis (≥F2) was found to be 35%, advanced fibrosis (≥F3) of 17.5% and cirrhosis (F=4) was 3.8%. Over 60% of this group was obese while 63% had metabolic syndrome and 33.5% had type 2 diabetes. Most disturbing is that over less than a decade from 2009 to 2017, the prevalence rates of NASH increased by 30% whereas the prevalence of advanced fibrosis almost tripled.[31]

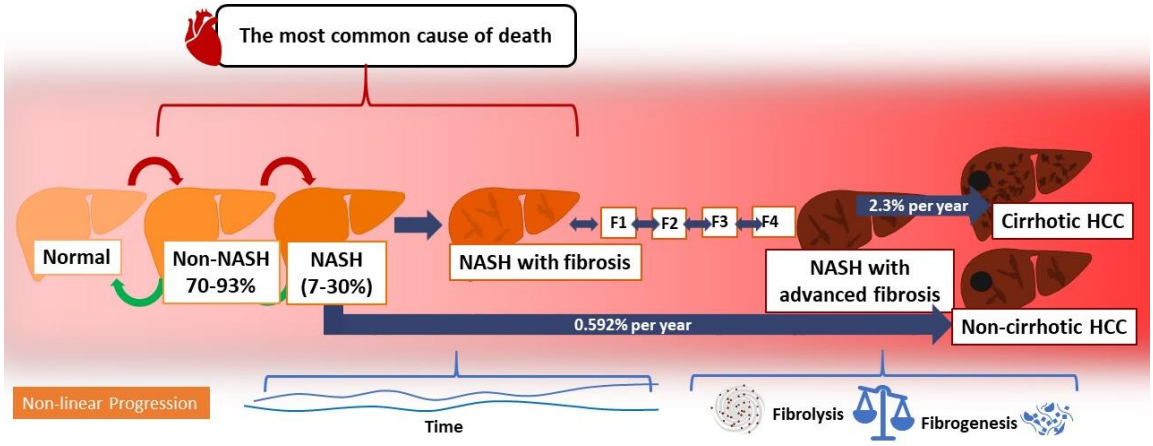
Researchers from Australia studied the prevalence of NASH among the morbidly obese undergoing bariatric surgery. They found the NASH prevalence to be 17.1%. [32]

Incidence of NASH

Determining the prevalence of NASH is challenging given the above cited obstacles but determining the incidence is NASH is even more difficult since NAFLD itself can be a silent disease until a patient presents with advanced fibrosis or cirrhosis. However, using modeling techniques and known data, it is estimated 20% of people with NAFLD will develop NASH. [3] Based on US data a recent modeling study estimated that the prevalence of NASH in the United States will increase 63% by 2030. Data from Europe and some parts of Asia are showing almost exactly the same type of trends. [33]

Projected Clinical Outcomes of NASH

NASH is an important cause of cirrhosis and hepatocellular carcinoma globally. This burden is expected to increase as epidemics of obesity, diabetes and metabolic syndrome continue to grow. A recent forecasting model suggested that by 2020, NASH will be the number one reason for liver transplantation and 2–12% of people with NASH cirrhosis will develop liver cancer per year. NASH prevalence will increase 15-56%, while liver mortality and advanced liver disease will more than double as a result of an aging/increasing population even if the prevalence of obesity and diabetes mellitus level off in the future (Fig. 2). [33]



HCC, hepatocellular carcinoma.

Younossi ZM et al. *Hepatology*. 2018;68:349–360; Younossi ZM et al. *Hepatology*. 2018;68:361–371. Younossi ZM. *J Hepatol*. 2019;70:e17–e32. Jie Li et al. Lancet Gastroenterol Hepatol. May 2019

Fig. 2 – Clinical Outcomes: Natural History of NAFLD and NASH

The same modeling study which projected a 63% increase of NASH by 2030 also projected that this increase will lead to an increasing incidence of NASH-related decompensated cirrhosis by 168%, HCC by 137%, liver related deaths by 178% causing approximately 800,000 excess liver deaths. [34] As noted in **Figure 3**, the number of NASH related mortality around the world appears to double by the year 2030.[34]

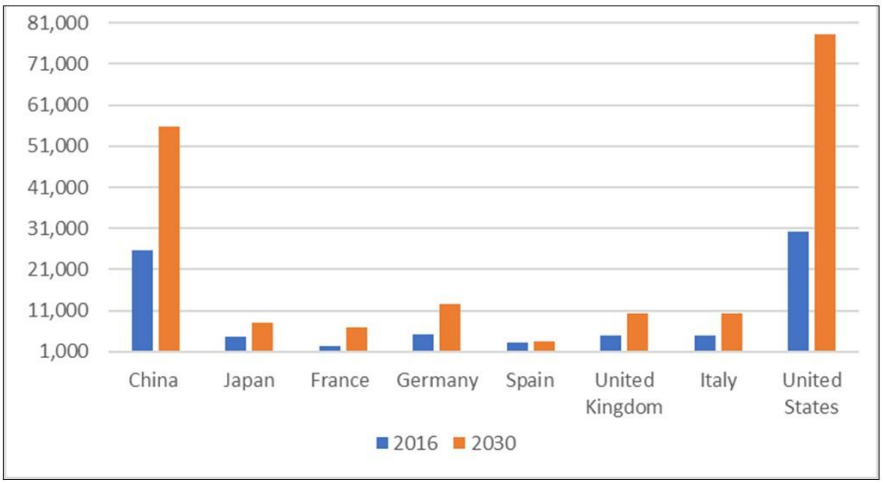


Fig. 3 - Number of NASH Related Deaths by Country for 2016 and 2030

A similar study was conducted in Saudi Arabia and the United Arab Emirates (UAE). Results of the model indicated that by 2030, there will be an estimated 12,534,000 NAFLD cases in Saudi Arabia and 372,000 cases in UAE with higher increases in NASH cases due to aging of the population and the high incidence of obesity and diabetes mellitus present in both countries. In addition, compensated cirrhosis and advanced liver disease are projected to at least double by 2030, while annual incident liver deaths will also increase in both countries which will equal 4800 deaths in Saudi Arabia and 140 deaths in UAE. [35]

Characteristics of those with NASH

Studies have suggested that patients with NASH tend to be metabolically unhealthy where as the number of metabolic syndrome components present increased so did the odds of complications, including mortality [36]. In addition, those affected with NAFLD/NASH have been found to have a two times higher risk for death related to cardiovascular disease and non-liver cancers compared to those without NAFLD. [36-39]

In a recent multicenter study of 1058 patients with biopsy proven NAFLD investigators studied the impact of metabolic factors (diabetes mellitus, low HDL, hypertriglyceridemia, arterial hypertension) beyond obesity on NASH, development of fibrosis, chronic kidney disease, and cardiovascular risk.[40] They determined that those who were metabolically unhealthy but not obese were almost 4 times as likely to develop NASH and significant fibrosis. The metabolically unhealthy outside of obesity also showed more chronic kidney disease and an impaired atherogenic profile. [40]

In the study from Australia conducted among 216 bariatric surgery patients (75.5% female) where the prevalence of NASH was found to be 17.1%, researchers found that NASH prevalence was significantly greater among those with diabetes, hypertension and dyslipidemia. In addition, though obesity played a significant role in the prevalence of NASH, the odds of having NASH were 9 times greater in those with a BMI>50 and metabolic disease. Interesting, they did not find that visceral adiposity had a significant association with NASH. [32]

Thus, those with NASH may or may not be obese but do have more advanced liver disease with fibrosis, increased levels of ALT due to necroinflammatory activity, and one or more metabolic diseases to include diabetes mellitus, insulin resistance, hypertension, hyperlipidemia, or metabolic syndrome. NASH is more prevalent in the older adult though it cannot be ruled out in children especially in our nutrient dense environment of today. In fact, in a study of 742 children who died accidently, 13% were found to have NAFL and among this group 23% had NASH and severe fibrosis or cirrhosis was found in 9% of those with NASH. [41]

Pathophysiology of NASH (Figure 4)

NAFLD, as already noted, is a term used to describe a spectrum of a fatty liver disease that is caused by the accumulation of fat within the liver cells which exceeds five percent when no other liver disease is present and alcohol consumption is determined to be minimal. Non- alcoholic fatty liver (NAFL) is the first stage of this disease and where the majority of people will stay throughout their life after diagnosis. However, 20% of people will progress to the next stage of disease, NASH.

NASH is the stage where further progression of the disease can be accelerated so understanding its' pathophysiology is important.

However, this understanding is still not fully matured and remains quite complex due to the interface of genetics, hormones, and environment. Presently, there is accumulating data which indicate that the total amount of triglycerides stored in hepatocytes is not the major determinant of the dysregulation of the lipid environment which can lead to cell injury or death (lipotoxicity). Rather, it may be the impact of free fatty acids (lipotoxic agents) such as palmitic acid, cholesterol, lysophosphatidylcholine, and ceramides which affect the liver cells via multiple mechanisms, including activation of signaling cascades and death receptors, endoplasmic reticulum stress, modification of mitochondrial function, and oxidative stress. The increased delivery of the free fatty acids comes from several sources which include the insulin-resistant adipose tissue, intrahepatic de novo lipogenesis, and dietary fat which when combined are the major mechanisms underlying triglyceride accumulation. The gut hormones, such as incretins GIP and GLP-1, also appear to have a profound effect on hepatic glucose and lipid metabolism which adds to the fat accumulation within the cells. Furthermore, fatty liver disease development may also be affected by gut bacteria such that the gut microbiome is disrupted through the dysbiosis-induced dysregulation of gut endothelial barrier function which allows for the translocation of bacterial components leading to hepatic inflammation (Fig. 4).[42-44]

As the disease progresses from steatosis to NASH, the risk for the development of stage 2 fibrosis or higher may increase up to seven-fold and appears to occur because of chronic, uncontrolled necroinflammation. However, it is important to note that NASH does not have to be present prior to fibrosis development as it has recently been determined that it is the presence of fibrosis but not steatohepatitis that is associated with an increased risk of mortality.[45-48]

Macrophages and humoral factors, such as adipokines and cytokines, also appear to play a role in inflammation of the peripheral adipose tissues which trigger a cascade of events that can lead to NASH and or fibrosis. NASH also appears to have an epigenetic center which will allow for gene expression and phenotypic variation not caused by changes in the DNA sequence but rather allows any alteration as a result of an environmental exposure to impact one's lineage cell division such that when exposed to a fibrosis stimuli, NASH is more likely to rapidly progress. The epigenetic

center theory also helps to explain why diet and especially diets high in omega-6 fatty acids and carbohydrates, mainly fructose, play such an important role in the progression of NAFLD to NASH and fibrosis. [49] Finally, studies have demonstrated that polymorphisms of a number of candidate genes, including those encoding for immunoregulatory proteins, proinflammatory cytokines and fibrogenic factors appear to influence the appearance of NASH and the development of liver fibrosis. Of particular importance are the variations of the gene PNPLA3 which appear to be associated with the histological severity of NASH.[50-52]

Adding to complexity of trying to understand the pathophysiology of NASH is that NASH can regress. Recently, a panel of experts released a consensual statement addressing the resolution of NASH which is the disappearance of hepatocyte ballooning and either the disappearance lobular inflammation or at the very least only minimal lobular inflammation is found. As such, it is this definition that is now being used as a regulatory outcome in several large, international, phase III studies and recent therapeutic trials.

Treatment

Currently, there are no approved pharmaceutical interventions available to treat NASH. Therefore, losing weight (at least 10% of body weight) through diet and exercise is the goal of treatment where diet and exercise remain the cornerstone of obtaining this goal. [53] However, even in this area there is much study going on in order to quantify what a healthy diet consists of, how much and what type of exercise is needed, can a person exercise alone to lose weight or is diet and exercise the best combination, how to motivate people to lose weight and then maintain their weight loss. Until these questions are answered, the success rate of this approach will remain very low. Other interventions that have been discussed as treatment agents among the professional organizations include oral hypoglycemic agents (insulin-sensitizing drugs), vitamin E, lipid-lowering agents, and bariatric surgery. All which appear to have some capacity in treating NAFLD (Fig. 4).[54-57]

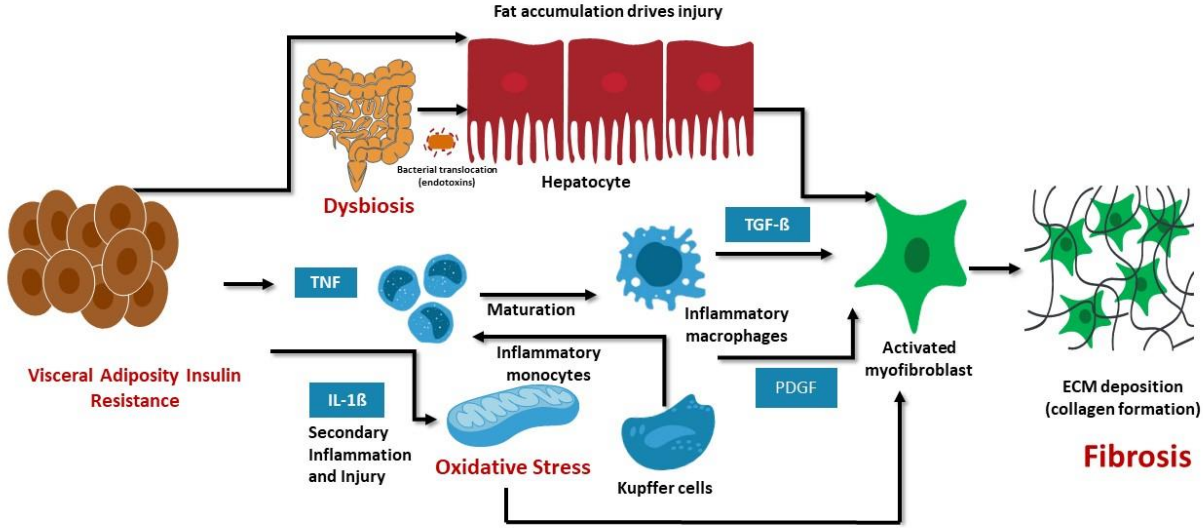


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Fig. 4 - Pathophysiology of NASH

Recognizing this, intense research is now ongoing to find a pharmaceutical agent that will target the inhibition of fibrogenesis and the development of cirrhosis. Currently, many of the trials are targeting potential areas in the fibrinogenesis development which include: chemokine receptor 2 and 5, galectin-3 protein; toll-like receptor 4, fibroblast growth factor 19, selective thyroid hormone receptor-beta, apoptosis signal-regulating kinase 1 (ASK-1), acetyl-coenzyme A carboxylase, farnesoid X receptor, and inflammasomes. [54]

However, work remains to better understand the non-modifiable risk factors related to genetic and epigenetic variations associated with NAFLD for each ethnicity. A better appreciation and understanding of the ethnic differences and reasons why will add needed information on how best to treat NAFLD both through environmental, cultural and pharmacological interventions. [58]

Patient Reported Outcomes

Health-related quality of life (HRQL) is an important patient related outcome. HRQL is a multidimensional concept that includes self-reported accounts for the influence of health, environment, freedom, economy, as well as aspects of one's culture, values, and spirituality on an individual's well-being. [59] HRQL has now become a mandatory measure in investigative interventional studies. [59] To that end work, has been ongoing in trying to understand the impact of NAFLD and NASH on a person's HRQL. Since HRQL cannot be measured directly, they are estimated using validated instruments or questionnaires that are divided into general measures (generic instruments) and disease specific instruments.[60-67] The two most commonly HRQL tools used in patients with liver disease are the generic tool the Short Form-36 v2 and the disease specific tool, Chronic Liver Disease Questionnaire (CLDQ). [61,62] Recently, the CLDQ was specifically designed to measure HRQL in patients with NAFLD and with NASH (CLDQ-NAFLD and CLDQ-NASH). Both tools have been validated.[60, 67]

Studies completed on patients with NAFLD have found that they report a lower HRQL than those without NAFLD especially in their physical functioning. Patients with NAFLD also report higher rates of depression when compared to those with depression. In a small study of patients with NASH, investigators found that both the physical and mental health functioning domains were significantly lower for those with NASH than the age and gender matched controls.

HRQL results for patients (n=1,667 patients) with NASH and bridging fibrosis or with compensated cirrhosis (metavir scores, F3 or F4) who were enrolled in the phase 3 STELLAR trials of selonsertib were recently reported. Selonsertib is an ASK-1 inhibitor whose goal was to reduce the stage of fibrosis at least one stage without worsening NASH. HRQL was measured using the SF-36 and the CLDQ-NASH. Researchers found that the mean physical health-related scores were significantly lower than those of the general population and that patients with cirrhosis had the largest score reductions in 75% of HRQL domains while those with F3 fibrosis had score reductions in 50% of the HRQL domains. In multivariate regression analysis, factors independently associated with lower HRQL scores were having cirrhosis, female sex, having a higher body mass index, having a history of smoking, diabetes or other comorbidities.[69]

Economic Burden of NASH

NASH carries an economic burden which has recently been quantified to some extent. A formal economic analysis for the United States and Europe (Germany, France, Italy, and United Kingdom) was conducted using Markov modeling to estimate the clinical and economic burden of NAFLD. Patients with NAFLD were allowed to transition between nine different stages of disease which included NAFL, NASH, NASH-fibrosis, NASH-compensated cirrhosis, NASH-decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, post-liver transplant, and death. For the United States, the model estimated that 64 million people had NAFLD which resulted in a potential annual direct medical cost of about $103 billion ($1,613 per patient). In Europe, it was estimated that ~52 million people had NAFLD with an annual cost of about €35 billion (from €354 to €1,163 per patient). The model estimated that within the US about 3-4 million patients who were at the greatest risk for progression had NASH and fibrosis which totaled an annual expenditure of $10-15 billion.[72]

Another modeling study conducted for those in the US with NASH and advanced NASH used seven different health states. Cost inputs for the model came from the Center for Medicare and Medicaid Services Fee Schedule 2017 and published data and included inpatient, outpatient, professional services, emergency department, and drug costs. All future costs were discounted at an annual rate of 3%. Using these model inputs, 6.65 million adults (18+ years old) were estimated to have NASH in the US with approximately 232,000 new (incident) cases in 2017. In 2017, lifetime costs for all NASH patients in the United States was $222.6 billion while the cost for the advanced NASH population was $95.4 billion.[73]

Conclusions

In summary, although our understanding of NASH has come a long way in a few short years, data are still missing to answer many unanswered questions such as what is the true rate of progression to NASH, who will progress to NASH, who will not progress to NASH, how does NASH effect one's work productivity and activities of daily living completion, what current treatments provide the longest term benefit, and should we screen all patients for NAFLD and NASH and or screen

for NASH hepatocellular carcinoma. A group of investigators and several professional organizations have attempted to address many of these questions. However, until more data are collected from many diverse populations, complete answers to these questions will remain unanswered. Therefore, we suggest that focused efforts for clinicians and researchers should be directed to gathering bedside data in collaboration with the Global NASH Registry to provide robust and real-world database answers.

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Author contributions to manuscript

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