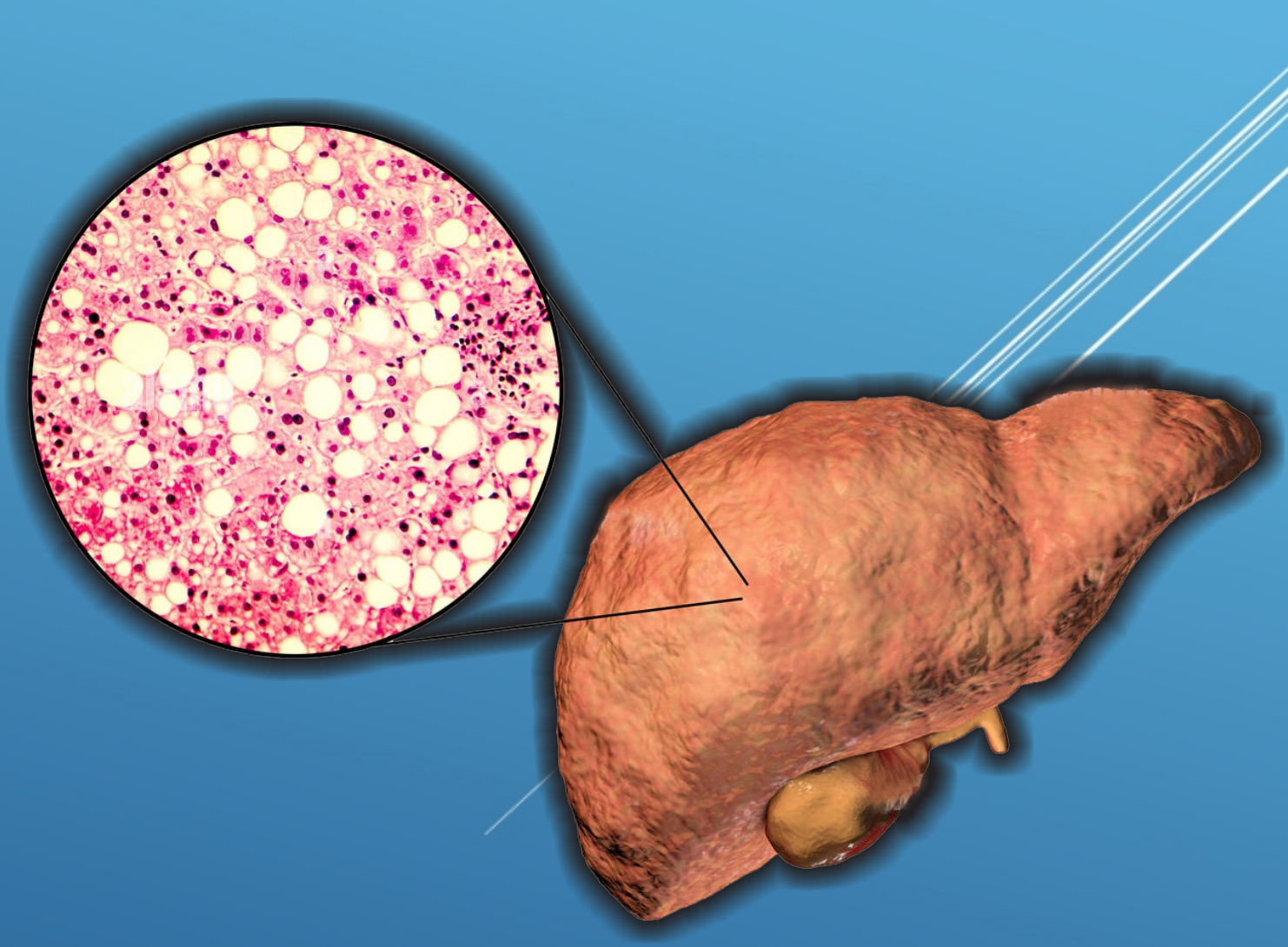

NON ALCOHOLIC FATTY LIVER DISEASE

CME Module for Medical Officers

State Institute of Health and Family Welfare
Uttar Pradesh

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MESSAGE

Shri Brajesh Pathak
Honorable Deputy Chief Minster
Honorable Minister of Medical
Health and Family Welfare Department
Government of Uttar Pradesh

Non-Alcoholic Fatty Leaver Disease (NAFLD) is a leading cause of chronic liver disease all over the world including India. As per estimates, the prevalence of NAFLD in our country is as high as 95 to 32%. This obviously is alarming because on one hand it causes morbidity and mortality which has social and economic costs in terms of loss of man days and on the other hand increases our expenditure on health care impeding socio-economic growth of our country.

In order to ease the implementation of the NAFLD programme, it has included under the "National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS)" because of the prevalence of similar risk factors and it is fact that identification of diabetes and obesity by NPCDCS will help in detection of NAFLD in a big way.

Considering the above stated facts, module on NAFLD is a minimum standard practice to be offered in a facility. Through this, medical officers will be exposed much needed training, thus ensuring that management of NAFLD is crucial and this could be achieved through staggered approaches.

I wish the team of State Institute of Health & Family Welfare, Uttar Pradesh and subject matter experts to continue developing such module for the medical officers in health services to create a significant impact on morbidity and mortality due to NDFLD.

(Brajesh Pathak)

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MESSAGE

Shri Mayankeshwar Sharan Singh
Hon'ble State Minister
Medical Health and Family
Welfare Department
Government of Uttar Pradesh

The liver is an important organ in the body which performs many vital functions. Unhealthy lifestyle, obesity, and uncontrolled diabetes are the major contributor to the development of Non-Alcoholic Fatty Leaver Disease (NAFLD). This is emerging as a cause of liver disease in India with various epidemiological studies suggesting the prevalence of around 9%-32% of the general population in India. An even higher prevalence is expected in those with overweight or obesity and those with hypertension, diabetes or pre-diabetes.

Once the disease develops, there is no specific cure available and health promotion and prevention aspects targeting weight reduction, healthy lifestyle and control of aforementioned risk factors are the mainstays to disease progression and prevent the mortality and morbidity due to NAFLD.

The state government has realized that existing NPCDCS programme strategies can be aligned to prevent the NAFLD through lifestyle changes, early diagnosis and management of associated non-communicable disease as well as NAFLD.

Accordingly, doable actions have been identified with main focus on health promotion and prevention of common NCDs which would also specifically cater to the identified needs of NAFLD. These issues have been considered in this manual to guide the state/UTs and stakeholders to support the NAFLD initiatives.

I am happy that the team at State Institute of Health & Family Welfare, Uttar Pradesh along with the subject matter experts has come up with such an intensified and detailed manual for medical officers in Uttar Pradesh.

I wish the team of SIHFW for success in their endeavors of aiding an improved medical service intervention through such CME on NAFLD.

(Mayankeshwar Sharan Singh)

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FOREWORD

Shri Partha Sarthi Sen Sharma, I.A.S
Principal Secretary
Department of Medical,
Health & Family Welfare
Government of Uttar Pradesh

Liver diseases are fast emerging as global health priorities. Fatty liver is described in the setting of non-alcoholic fatty liver disease (NAFLD) as well as alcoholic liver disease (ALD), the pathogenesis of excess fat being different in the two conditions while both are important components of the changing face of burden of liver diseases worldwide. They are intimately associated with a globalized economy and an increasingly homogenous socio- cultural order with a westernized lifestyle.

The accompanying adoption of a progressively sedentary life, consumption of diet dense in calories facilitate development of NAFLD while a spiraling upward trend in alcohol use along with earlier age of drinking as well as increased amount of per capita alcohol consumption increases the prevalence of ALD globally.

Adverse health outcomes in NAFLD as well as ALD are caused not only by progressive liver fibrosis that is the most significant factor for liver related and all-cause mortality in both but also by non-liver (cardiovascular, cancer, accidents, neurological) clinical outcomes that calls for a multidisciplinary and social approach to these conditions.

A broad-based integrated approach that incorporates social, behavioral as well as biological targets need to be undertaken at a health system level in a planned manner for these evolving liver health priorities that disproportionately challenges the low and middle-income countries of Asia, South America and Africa..

Considering the complexity and economic impact of NAFLD across population, this module on nonalcoholic fatty liver disease (NAFLD) for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh becomes exceedingly important not only from medical intervention perspective but it will also indirectly uplift the economic status of the state.

I congratulate the faculties of State Institute of Health & Family Welfare, Uttar Pradesh and subject matter experts for developing an impactful module that will enhance the capacity of Medical officers in managing cases of nonalcoholic fatty liver disease at their PHCs/CHCs.

(Partha Sarthi Sen Sharma)

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MESSAGE

Dr. Brijesh Rathor
Director General
Medical and Health Services
Uttar Pradesh

Non-Alcoholic Fatty Liver Disease (NAFLD), which affects one in three adults, is a contemporary public health challenge that demands strengthening of health systems worldwide. Although most countries are yet to develop a national strategy for tackling this public health threat, India became the first country globally to integrate NAFLD into the national non-communicable disease programme known as National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS).

Changes in lifestyle particularly dietary habits and sedentary living, rising incidence of obesity and diabetes have all contributed, leading to a epidemic of lifestyle liver disease known as Non-Alcoholic Fatty Liver Disease (NAFLD).

It is pertinent to note that to date, no effective medical interventions exist that completely reverse this disease and therefore lifestyle changes, dietary alterations remain the mainstay to avert the morbidity and mortality from NAFLD.

Considering the above stated facts, CME on NAFLD, State Institute of Health & Family Welfare, Uttar Pradesh with the help of subject matter experts has provided a comprehensive, coherent and insightful module for pharmacist.

I wish the team of State Institute of Health & Family Welfare, Uttar Pradesh and subject matter experts for such a commendable job.

(Dr. Brijesh Rathor)

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MESSAGE

Dr. Shailesh Kumar Srivastav
Director General Family Welfare
Directorate of Family Welfare
Uttar Pradesh

India is the seventh largest and second most populous country in the world. It has a rapidly developing economy with an estimated gross domestic product of US $2.87 trillion. Easy access to calorie-dense food and sedentary lifestyle together with the modern epidemics of diabetes mellitus (DM) and obesity have catapulted nonalcoholic fatty liver disease (NAFLD) into a substantial public health problem in India as in other parts of the world. NAFLD has emerged as one of the leading causes of cirrhosis, hepatocellular carcinoma (HCC), and liver transplant in India. Given its enormous population, the burden of NAFLD in India is likely to be substantial, which may significantly impact the limited health care resources in the country.

The prevalence of NAFLD among the general population in India ranges from 9% to 53%. Although differences in diagnostic techniques for NAFLD may partly account for the wide variation in reported prevalence, a possible rural-urban divide and geographical variation are evident from the available data. Most studies from urban centers have reported a higher prevalence as compared with those that cater to a largely rural population.

More recently, a population-based study from coastal south India reported an overall NAFLD prevalence rate of 49.8%; urban domicile was found to be associated with a higher risk for NAFLD. Other ongoing community-based cohort study in north India states that, prevalence of NAFLD was found to be higher in urban communities (53.7%) in comparison with rural communities (30.2%). Among the high-risk groups, prevalence has been reported to be higher among those with type 2 DM, pre-diabetes, obesity, and metabolic syndrome. Further worrisome are the recent data showing a high prevalence of NAFLD in obese Indian children.

Considering the above stated facts, this module on nonalcoholic fatty liver disease (NAFLD) for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, developed by the faculties of State Institute of Health & Family Welfare, Uttar Pradesh with the help of Subject Matter Experts, has provided a comprehensive, coherent and insightful module for Medical Officers thus equipping them with the required necessary knowledge for successful management of cases of NAFLD at their respective health facilities.

I congratulate the best to the faculties of State Institute of Health & Family Welfare, Uttar Pradesh and subject matter experts for such a commendable job.

(Dr. Shailesh Kumar Srivastava)

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MESSAGE

Dr. Narendra Agrawal
Director General-Training
Medical and Health Services
Uttar Pradesh

The entity of non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. The global prevalence of NAFLD is estimated to be 25%, with a higher prevalence in the Middle East and South America and the lowest in Africa. The prevalence of NASH is estimated to be 1.5%–6.5%. Global burden of disease (GBD) 2017 estimated the annual incidence of NASH cirrhosis to be 367,780 in 2017, which has almost doubled from that in 1990. In the future, NASH is expected to be the most common cause of chronic liver disease and indication for liver transplantation.

The presence of certain characteristics has been identified for the development of NAFLD. The prevalence of NAFLD is found to be higher among those with diabetes (55.5%–59.7%), overweight or obesity (64.6%–95%), and metabolic syndrome (73%). The prevalence of adult NAFLD in India has been reported between 6.7% and 55.1%. Of all cases with an asymptomatic elevation of liver enzymes, NAFLD may be responsible for almost one-third. Furthermore, explant histology data from liver transplant centers suggest that two-third of the patients with 'cryptogenic' cirrhosis had NAFLD. The prevalence of pediatric NAFLD in India varies from 7.3% to 22.4% in the healthy population. The prevalence of NAFLD increases with age.

The prevalence of pre-diabetes, diabetes, and metabolic syndrome among adults in India is increasing in both urban and rural areas. With the increasing prevalence of diabetes, obesity, and metabolic syndrome, NAFLD prevalence is expected to increase and cause an increased burden on health resources. To plan strategies for the future and be ready to address this public health problem, it is important to know the burden of the disease and its health impact.

Keeping the above facts in mind, State Institute of Health & Family Welfare, Uttar Pradesh with the help of Subject Matter Experts has developed an extensive and up to date module on nonalcoholic fatty liver disease (NAFLD) for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, State Institute of Health & Family Welfare, Uttar Pradesh, that deals with all the underlying nuances and provides a comprehensive, coherent and insightful module for Medical Officers.

I applaud the faculties of State Institute of Health & Family Welfare, Uttar Pradesh and subject matter experts for such a commendable job.

(Dr. Narendra Agrawal)

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ACKNOWLEDGMENT

Dr. Rajaganapathy R, I.A.S
Director
State Institute of Health & Family Welfare, UP
Government of Uttar Pradesh

More important than the mere presence of fatty liver is the prevalence of progressive nonalcoholic steatohepatitis (NASH) with or without hepatic fibrosis that adds to the significant liver disease and extrahepatic disease burden. Data from India corroborate that NAFLD is associated with several extrahepatic conditions, such as cardiovascular disease, chronic kidney disease, polycystic ovarian syndrome, obstructive sleep apnoea, vitamin D deficiency, and hypothyroidism.

NAFLD also has been shown to affect pathogenesis of Indian patients with NAFLD. Globally, multiethnic studies have suggested that Indians are more predisposed to insulin resistance and its consequences, including NAFLD. Most of the data from India suggest the presence of insulin resistance in patients with NAFLD; however, a small study suggested occurrence of NAFLD without insulin resistance.9 Earlier data from India had suggested certain subtle differences between Indian patients with NAFLD and their Western counterparts, with Indian patients having lower BMI and fewer cases of morbid obesity, diabetes, hypertension, or metabolic syndrome.

Indian data in lean patients with NAFLD suggest that although their total body fat is comparable with lean individuals without NAFLD, they are metabolically unhealthy, with an expanded visceral adipose tissue mass similar to overweight or obese patients with NAFLD. In addition to metabolic risk factors, studies from India have also suggested the role of small intestinal bacterial overgrowth, endotoxemia, and toll-like receptor expression in the pathogenesis of NAFLD.

In the light of these above stated facts, it is imperative the skills and knowledge of Medical Officers in Provincial Health & Medical Services in Uttar Pradesh is up to par to tackle the challenges posed by NAFLD in the state. This module on nonalcoholic fatty liver disease (NAFLD) for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, defines and facilitates the treatment protocols and treatment regimen for managing cases of NAFLD.

I acknowledge the sincere efforts made by the faculties of State Institute of Health & Family Welfare, Uttar Pradesh and by Dr Gaurav Pande, Additional Professor, Department of Gastroenterology, SGPGI-Lucknow, Dr Alka Sharma, Joint Director and State Nodal Officer, Directorate of Medical and Health, Swasthya Bhavan-Lucknow, Dr Akash Mathur, Assistant Professor, Department of Gastroenterology, SGPGI-Lucknow, Dr Piyush Mishra, Assistant Professor, Department of Gastroenterology, SGPGI-Lucknow, Dr. S. Rakesh Kumar, Assistant Professor, Department of Gastroenterology, SGPGI-Lucknow & Dr Abhinav Kadia, State NCD Consultant, World Health Organization in developing such a comprehensive, coherent and insightful module for Medical Officers.

(Dr. Rajaganapathy R.)

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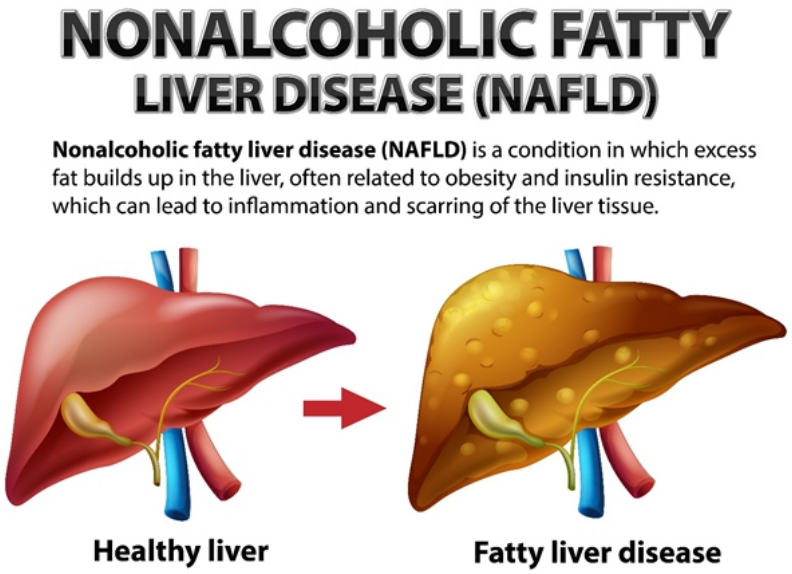
Introduction

Non-alcoholic fatty liver disease (NAFLD), a constellation of Non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), has emerged as a pressing global health concern, silently infiltrating homes and clinics alike (1). Once considered a niche medical issue, it has become a pervasive epidemic affecting millions worldwide. NAFLD encapsulates a spectrum of liver disorders, ranging from the benign accumulation of fat in the liver, known as simple steatosis or non-alcoholic fatty liver (NAFL), to the more aggressive Non-Alcoholic Steatohepatitis (NASH), characterized by liver inflammation and potential fibrosis. Left unchecked, NAFLD can progress to advanced stages, leading to cirrhosis, liver failure, and even hepatocellular carcinoma, significantly burdening healthcare systems and society (2).



The prevalence of NAFLD has surged in recent years. NAFLD has reached alarming proportions in India and worldwide, making it a significant public health challenge (3). It affects countries across the spectrum of economic development. Its prevalence varies, with higher rates in developed nations. Globally, estimates suggest that approximately 33% of the population may have NAFLD (4). India is grappling with a substantial burden of NAFLD, with studies suggesting that approximately one in three adults in India suffer from NAFLD (5). The prevalence of NASH in India varies from 9% to 53% based on the population studied and the criteria used (6,7).

The rising prevalence of NAFLD in India poses a substantial economic burden on the healthcare system due to increased hospitalizations, diagnostics, and treatments. It also leads to a loss of productivity. NAFLD can also progress to NASH and cirrhosis, increasing the burden on the country's liver transplantation programs. Also, NAFLD is closely associated with cardiovascular diseases, a leading cause of death in India (8). These further compounds the impact on national health. NAFLD is not merely a localized concern but a global health crisis with far-reaching consequences. Its prevalence in India and worldwide threatens the well-being of millions and places immense strain on healthcare systems, economies, and quality of life. Addressing NAFLD necessitates a comprehensive, multi-pronged approach encompassing public health initiatives, awareness campaigns, early diagnosis, lifestyle interventions, and continued research into effective treatments.

NAFLD is a complex condition influenced by genetic, metabolic, and lifestyle factors. Understanding the risk factors for NAFLD is essential for prevention and early detection. Here are some of the critical risk factors associated with the development of NAFLD (9,10):

Obesity: Obesity, particularly abdominal obesity, is one of the most significant risk factors for NAFLD. Excess body fat, especially in the abdomen, is closely linked to fat accumulation in the liver.

Type 2 Diabetes: People with type 2 diabetes have an increased risk of NAFLD due to insulin resistance and other metabolic disturbances. The body's impaired ability to regulate blood glucose levels contributes to fat accumulation in the liver.

Metabolic Syndrome: Metabolic syndrome is a cluster of conditions that includes high blood pressure, elevated blood glucose, abnormal lipid profile, and abdominal obesity. It significantly raises the risk of NAFLD.

High-Fat Diet: Consuming a diet high in saturated fats, trans fats, and added sugars can promote the development of NAFLD. These dietary choices contribute to weight gain and insulin resistance.

Rapid Weight Loss: Rapid weight loss, whether through crash diets or weight loss surgery, can lead to the quick breakdown of fat cells, which can overload the liver and trigger NAFLD.

Sedentary Lifestyle: Lack of physical activity is associated with obesity and insulin resistance, making it a risk factor for NAFLD. Regular exercise can help prevent and manage the condition.

Genetics: Some individuals may have a genetic predisposition to NAFLD. Specific genetic variants can increase the likelihood of developing the disease.

Medications: Some medications, such as corticosteroids, tamoxifen, and antiretroviral drugs, have been associated with an increased risk of NAFLD.

Polycystic Ovary Syndrome (PCOS): PCOS is a hormonal disorder that affects women and is associated with insulin resistance and a higher risk of NAFLD.

Age: While NAFLD can affect people of all ages, it is more common in middle-aged and older individuals.

Gender: Men are generally more prone to NAFLD than premenopausal women, although the risk in women increases after menopause.

Ethnicity: Some ethnic groups, such as Hispanics and South Asians, have a higher risk of NAFLD than others.

It is important to note that many individuals with NAFLD may have multiple risk factors. NAFLD is a complex interplay of genetic and environmental factors, and its development can vary from person to person. Lifestyle modifications, including a healthy diet and regular exercise, can help mitigate many of these risk factors and reduce the risk of NAFLD.

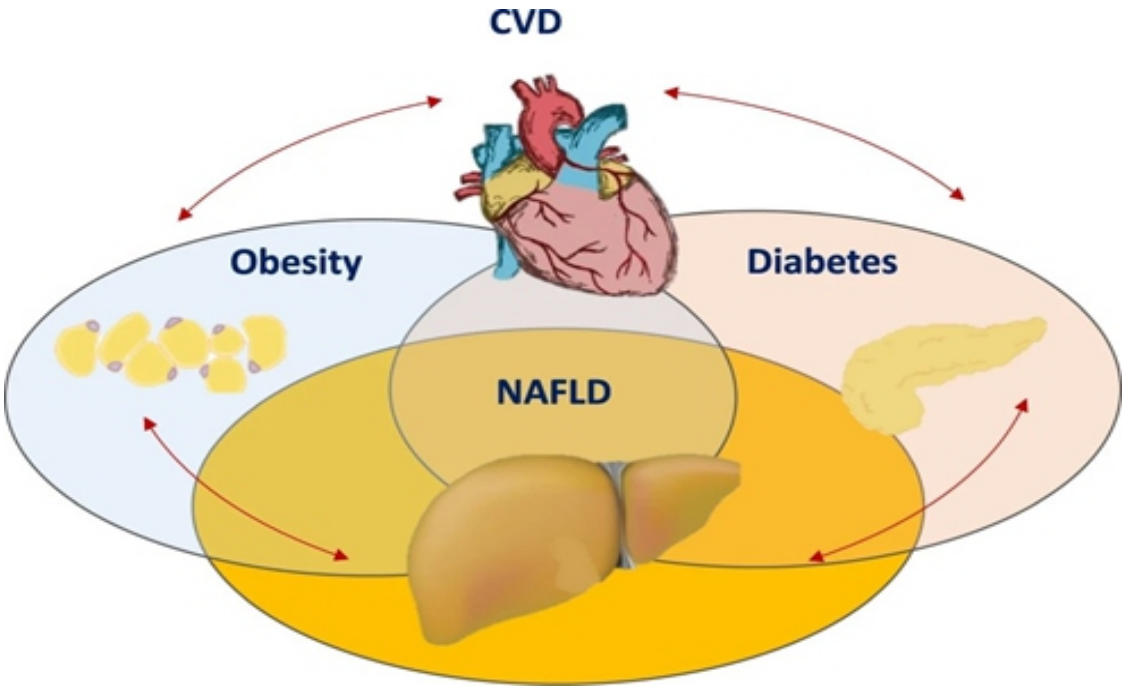
As we delve into the depths of these liver disorders, it becomes apparent that they are not isolated medical conditions but are intricately connected to broader health issues, such as cardiovascular disease, diabetes, and even mental health. Therefore, understanding NAFLD and NASH is not just a matter of liver health but a vital component of a holistic approach to overall well-being.

The rise of NAFLD mirrors the escalating global rates of obesity, type 2 diabetes, and metabolic syndrome (11). This monograph endeavours to delve deep into the intricate web of NAFLD, exploring its etiology, diagnostic challenges, therapeutic options, and broader implications for public health. NAFLD's complex pathogenesis, often intertwined with insulin resistance, inflammation, and genetic predisposition, remains a topic of intensive research and clinical scrutiny (12,13).

As we embark on this journey through the world of NAFLD, we will navigate the clinical landscape, from its subtle and asymptomatic beginnings to its dire consequences in advanced stages. We will also explore

the pivotal role of lifestyle modifications, medications, and emerging treatments in the fight against NAFLD, emphasizing the need for a multifaceted approach to combat this silent epidemic.

This monograph aims to provide a comprehensive understanding of NAFLD and underscore the urgency of addressing this global health crisis. It is a call to action for the medical community and society to raise awareness, foster early detection, and promote effective prevention and management strategies. Through this exploration, we hope to contribute to the evolving narrative surrounding NAFLD, enabling a future where liver health becomes a priority for all.



Chapter 2

Terminology

The controversy between NAFLD (Non-Alcoholic Fatty Liver Disease) and MAFLD (Metabolic Associated Fatty Liver Disease) revolves around the terminology used to describe this common liver condition characterized by the accumulation of fat in the liver, not caused by excessive alcohol consumption. This controversy stems from efforts to update and refine the nomenclature to reflect the diverse nature of the condition better and to include individuals who might not fit the traditional NAFLD criteria.

Amid the ongoing NAFLD vs. MAFLD controversy, numerous medical societies, including the American Association for the Study of Liver Diseases (AASLD), have taken significant steps to redefine and clarify terminologies within the realm of liver diseases characterized by steatosis. The term "steatotic liver disease (SLD)" has been introduced as a comprehensive and inclusive umbrella term aimed at encompassing the diverse etiologies contributing to steatosis. While striving to preserve the essential pathophysiological concept, the term "steatohepatitis" has been retained. Consequently, what was formerly known as non-alcoholic fatty liver disease (NAFLD) has now transitioned to "metabolic dysfunction-associated steatotic liver disease (MASLD)". MASLD is designed to encompass individuals exhibiting hepatic steatosis and presenting with at least one of five cardiometabolic risk factors.

A distinct subgroup has been identified and termed "MetALD" within this broader classification. This category is dedicated to individuals with MASLD who consume higher quantities of alcohol weekly, defined as 140 grams per week for females and 210 grams per week for males.

In line with this revised nomenclature, "metabolic dysfunction-associated steatohepatitis (MASH)" is now the preferred term replacing NASH. This alteration underscores the importance of metabolic factors in the condition's pathogenesis and aligns with evolving insights into its clinical characterization.

For those individuals presenting without discernible metabolic parameters or a known causative factor, the term "cryptogenic SLD" describes their condition. These changes in terminology aim to enhance precision and clarity in the classification of liver diseases characterized by steatosis, offering a more nuanced and comprehensive framework for understanding and managing these complex conditions (14).

Chapter 3

Pathogenesis of NAFLD

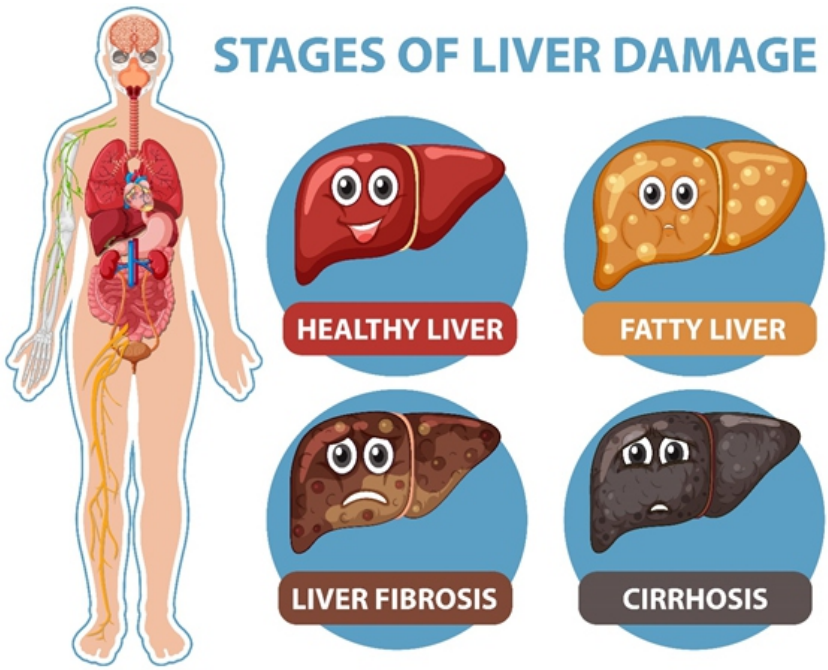
A diet high in fat causes obesity, which causes the body to accumulate ectopic fat, thereby increasing adipose tissue reserves. A constant pro-inflammatory state occurs due to macrophage infiltration in adipose tissue, causing insulin resistance (15). Due to unabated lipolysis in the setting of insulin resistance, the liver is overwhelmed by fatty acids and increased de-novo lipogenesis. When lipid metabolism is imbalanced, lipotoxic lipids are formed, which contribute to cellular stress (oxidative stress and endoplasmic reticulum stress), activate inflammasomes, and cause apoptotic cell death, thereby stimulating inflammation, regeneration, and fibrogenesis (16).

The liver plays a vital role in gut-liver signalling and is a hub for systemic metabolism, directly or indirectly impacted by gut dysbiosis (17). Studies show that gut bacteria can lead to steatosis and impaired insulin responses, which can be associated with NAFLD-like outcomes (18). Putative agents like Bacteroides and Escherichia enrichment consistently correlate with higher disease severity, especially advanced fibrosis (19).

Classification and Stages

There are a variety of potential factors that can contribute to NAFLD's heterogeneity in terms of disease progression and clinical outcome. It is a slowly progressive disease in most patients, though a small proportion develops advanced fibrosis, cirrhosis and hepatocellular carcinoma. Initially, NAFLD can manifest as NAFL (non-alcoholic fatty liver), which progresses to NASH (non-alcoholic steatohepatitis) with or without fibrosis, ultimately leading to cirrhosis and hepatocellular carcinoma (HCC). The non-alcoholic fatty liver (NAFL) is characterized by fat accumulation in the liver cells without inflammation. It is typically not associated with any clinical problems and/or complications. NASH, a more advanced form, is characterized by steatosis, hepatocellular ballooning, lobular inflammation, and almost always fibrosis. Due to necroinflammation, the fibrosis progression rate in NASH patients is more rapid and shows a linear correlation with time (20). Over time, a subset of patients enter the cirrhotic phase when repeated inflammation causes scarring and irreversible distortion in liver architecture. In patients with NASH cirrhosis, the likelihood of developing hepatocellular carcinoma is 10-6 per 1000 person-years. Cirrhosis is the most potent risk factor for hepatocellular carcinoma.

This fibrosis progression is dependent on multiple factors. The presence and severity of comorbid illness (Diabetes mellitus, obesity, hypertension, dyslipidemia, hyperpituitarism) determine the rapidity of NASH progression (21). Similarly, a few genetic loci (PNPLA3, TM6SF2, MBOAT7) contributed to the worsening of NAFLD, hepatocellular carcinoma progression and increasing all-cause mortality (22). Environmental factors drive this progression in protective (coffee, exercise) and harmful ways (alcohol, cholesterol and fructose-rich food). Advanced fibrosis prognosticates all subsequent liver-related outcomes. A meta-analysis showed that fibrosis worsens by one stage over 7.1 years for NASH and 14.3 years for NAFL patients (20).



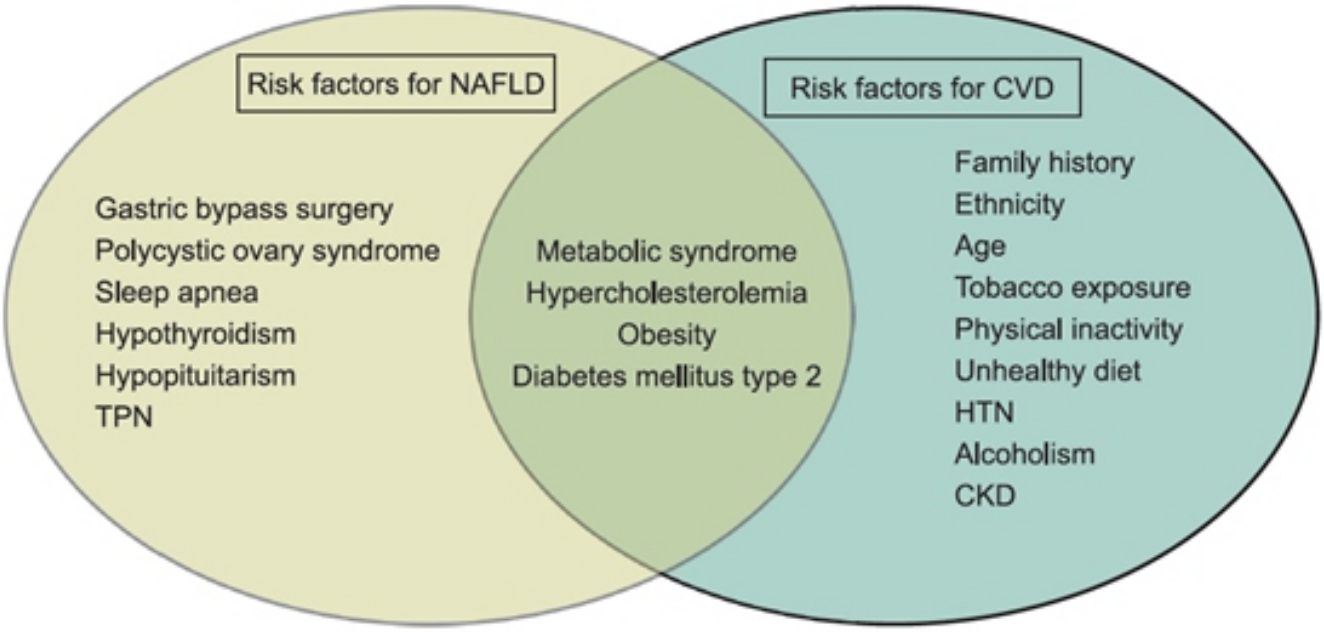
Chapter 5

Clinical presentation

Most patients with NAFLD do not experience symptoms; however, some may complain of fatigue, right upper quadrant discomfort, an increase in the size of the liver, acanthosis nigricans, and lipomatosis (23). A diagnosis like NASH or NAFLD is often discovered due to abnormal liver function tests such as aminotransferases (ALT and AST) or incidental findings of hepatic steatosis on radiologic abdominal findings. Hepatomegaly can be present during physical examination (23).

Most people with NAFLD have simple fatty liver, and these patients do not develop complications (24). In turn, NASH (liver inflammation) can lead to complications, such as cirrhosis and liver cancer. People with NASH have increased chances of dying from liver-related causes (25). If NASH leads to cirrhosis and further complications like fluid in the abdomen, altered mentation, jaundice, etc., one may need a liver transplantation to survive. Many patients with cirrhosis can present themselves with end-stage liver disease. Cardiovascular diseases are the leading cause of death in patients with NASH (25).

Complications



Diagnostic approaches

The diagnosis of NAFLD is usually suspected in an overweight or obese individual with mild elevation in liver enzymes on routine blood investigations or incidentally detected on routine abdominal imaging like ultrasound or CT scan. However, patients with NAFLD may also present with normal liver function tests, in which diagnosis is confirmed by imaging suggestive of fatty infiltration of the liver. Fat accumulation in the liver can also be found in conditions like excess alcohol intake, certain medications, viral hepatitis, autoimmune and metabolic or inherited liver diseases, which need to be excluded to confirm the diagnosis of fatty liver disease.

It is important to differentiate patients of NASH from simple steatosis and advanced fibrosis, for which liver biopsy is the only reliable method. However, it comes with limitations in invasiveness, rare but potentially life-threatening complications like bleeding, poor acceptability, sample variability and cost. Therefore, there is a need for non-invasive methods for the assessment of liver fat and grade of fibrosis.

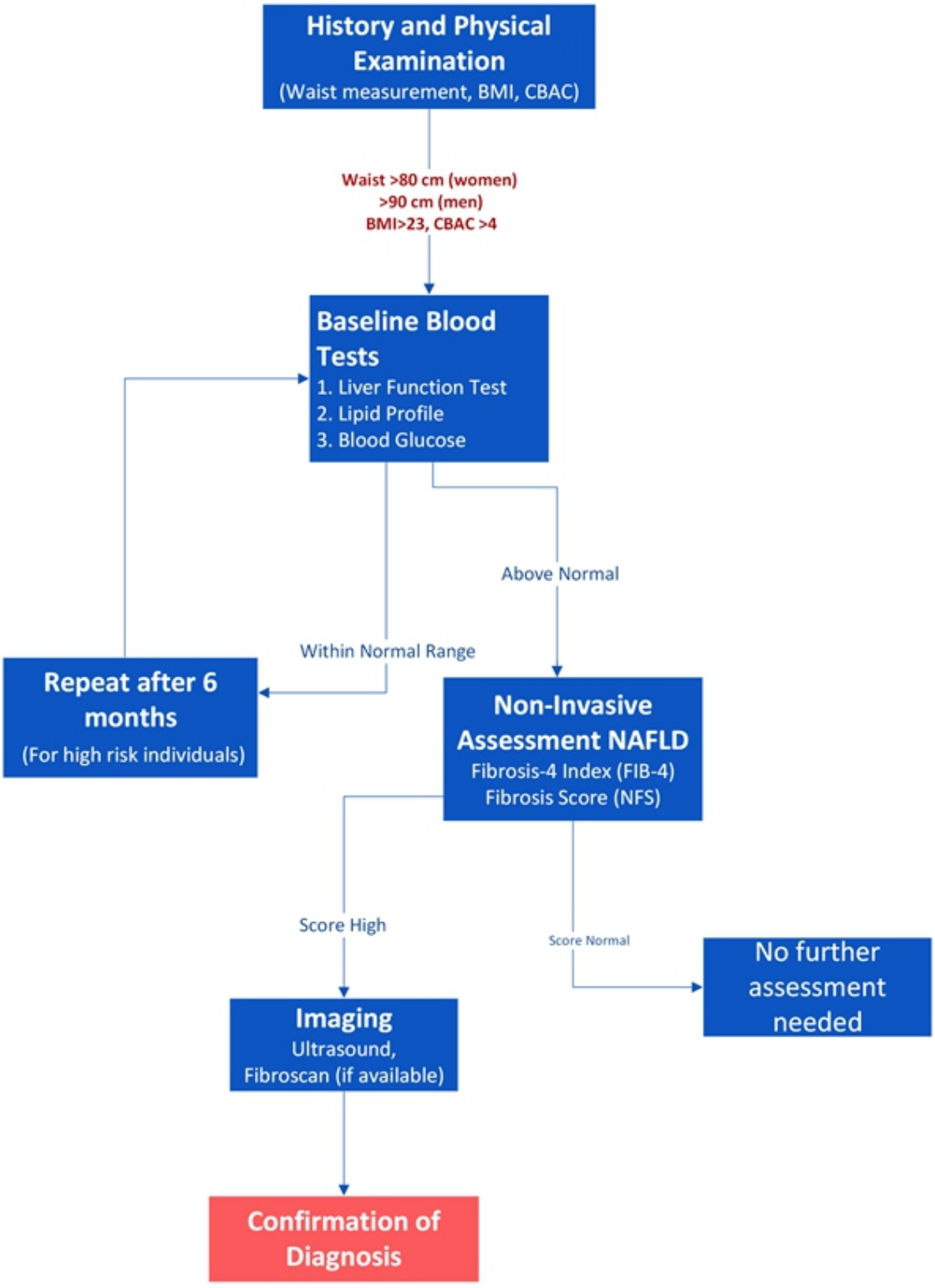
Among the biomarkers, fibrosis-4 (FIB-4) index and non-alcoholic fatty liver disease fibrosis score (NFS) have high predictive value (>90%) for ruling out advanced fibrosis and, hence, can be used in primary healthcare settings for detecting cases without advanced fibrosis who do not need further assessment. FIB-4 (age, platelet count and transaminase value) is easier to calculate and more attractive to primary healthcare physicians than the NFS score. In patients with intermediate or high-risk scores on FIB-4 and NFS, non-invasive assessment of liver fibrosis by transient elastography is recommended (26). A value between 2 to 6 KPa is normal. A value <8 KPa rules out cirrhosis (94-100% negative predictive value). Magnetic resonance imaging with proton density fat fraction (MRI-PDFF) can detect liver fat as low as 5% but is mainly used in research settings due to availability and cost concerns (27).

$$FIB\text{-}4 = \frac{\text{Age (years)} \times \text{ASTLevel } (U/L)}{\text{Platelet Count } (10^9/L) \times \sqrt{ALT}\ (U/L)}$$

Interpretation:

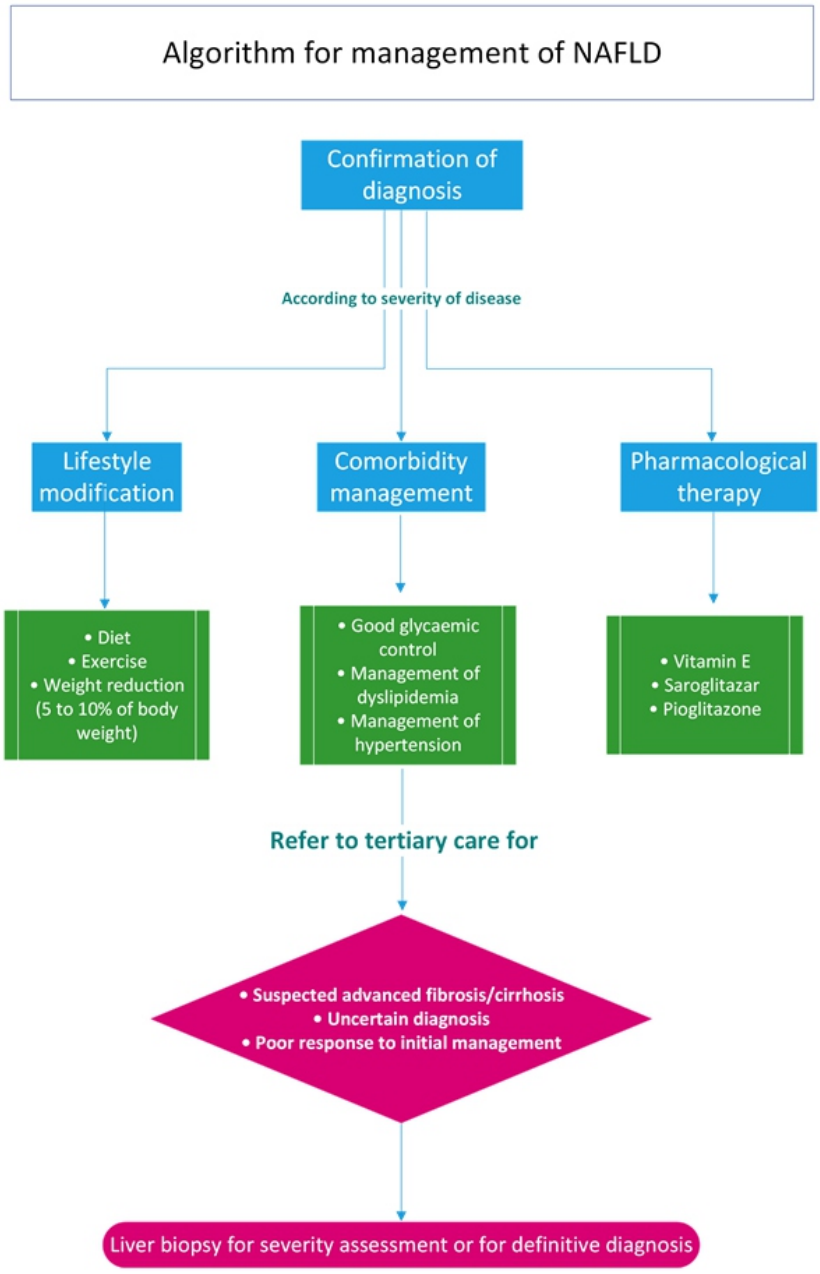
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Algorithm for evaluation for NAFLD



Treatment

Since primary care is the initial point of contact for most people with health concerns (including metabolic risk factors), primary care clinicians have a vital role in the prevention, diagnosis, risk stratification, and management of NAFLD. Studies suggest that improved diet quality and sustained or increased physical activity reduce the risk of developing NAFLD, even among individuals with high genetic risk (28,29).



To date, no effective medical treatment exists that can reverse the disease apart from dietary and lifestyle intervention to reduce weight and possibly bariatric surgery to some extent. Current guidelines endorse drugs like pioglitazone and vitamin E as a possible treatment in selected patients with NASH (25). Numerous drugs with different mechanisms of action, targeting lipid metabolism, inflammatory, or fibrotic pathways, are in development as a treatment for NASH (30).

New evidence suggests that food rich in mono-unsaturated fatty acids, like nuts, almonds, cashews, fish, eggs, coconut oil, safflower oil, etc., may be more beneficial than a low-fat diet. Drinking coffee has been shown to decrease the risk of fatty liver disease in large cohort studies. It is also essential to control and treat comorbidities like diabetes, hypertension, and dyslipidaemia simultaneously. These recommendations also apply to NASH, a more severe form of fatty liver disease.

Prevention strategies:

Preventing Non-Alcoholic Fatty Liver Disease (NAFLD) involves adopting a comprehensive approach that addresses its underlying risk factors. Some of the prevention strategies for NAFLD are (9,31–33):

a) Healthy diet:

- **Reduce Saturated Fats and Trans Fats:** Limit the intake of foods high in saturated fats (found in red meat, full-fat dairy, and some oils) and trans fats (found in many processed and fried foods). Replace these with healthier fats like mono-unsaturated and polyunsaturated fats in olive oil, avocados, and fatty fish.
- **Control Sugar Intake:** Minimize added sugars and refined carbohydrates, as excessive sugar consumption can contribute to NAFLD. Focus on whole grains, fruits, and vegetables.
- **Balanced Portions:** Be mindful of portion sizes to avoid overeating, which can lead to weight gain and liver fat accumulation.
- **Increase Fiber:** Including high-fiber foods like vegetables, fruits, and whole grains in the diet promotes a feeling of fullness and supports digestive health.

b) Maintain a Healthy Weight:

- **Gradual Weight Loss:** If overweight or obese, one should aim for gradual weight loss through dietary changes and regular exercise. Rapid weight loss can exacerbate liver fat accumulation.
- **Regular Physical Activity:** One should engage in regular exercise, such as brisk walking, swimming, or cycling, for at least 150 minutes per week to help control weight and improve insulin sensitivity.

c) Balanced Eating Habits:

- **Regular Meals:** Eat regular, balanced meals throughout the day to help stabilize blood sugar levels.
- **Limit Late-Night Eating:** Avoid late-night snacking, which can disrupt metabolism and contribute to weight gain.

d) Control Blood Sugar and Insulin Resistance:

- **Monitor Blood Sugar Levels:** In prediabetes or diabetes, work with the physician to manage blood sugar levels effectively and monitor blood sugar levels regularly.
- **Choose Low-Glycaemic Foods:** Select foods with a low glycaemic index to prevent rapid spikes in blood sugar levels.

e) Limit Medications and Supplements:

Use medications and dietary supplements only as prescribed or recommended by a healthcare professional, as some may harm the liver.

f) Regular Health Check-ups:

Schedule regular check-ups with your healthcare provider to monitor your liver health and address potential issues early.

g) Avoid Crash Diets:

Steer clear of extreme or crash diets that promise rapid weight loss, as they can lead to the rapid breakdown of fat cells and liver stress.

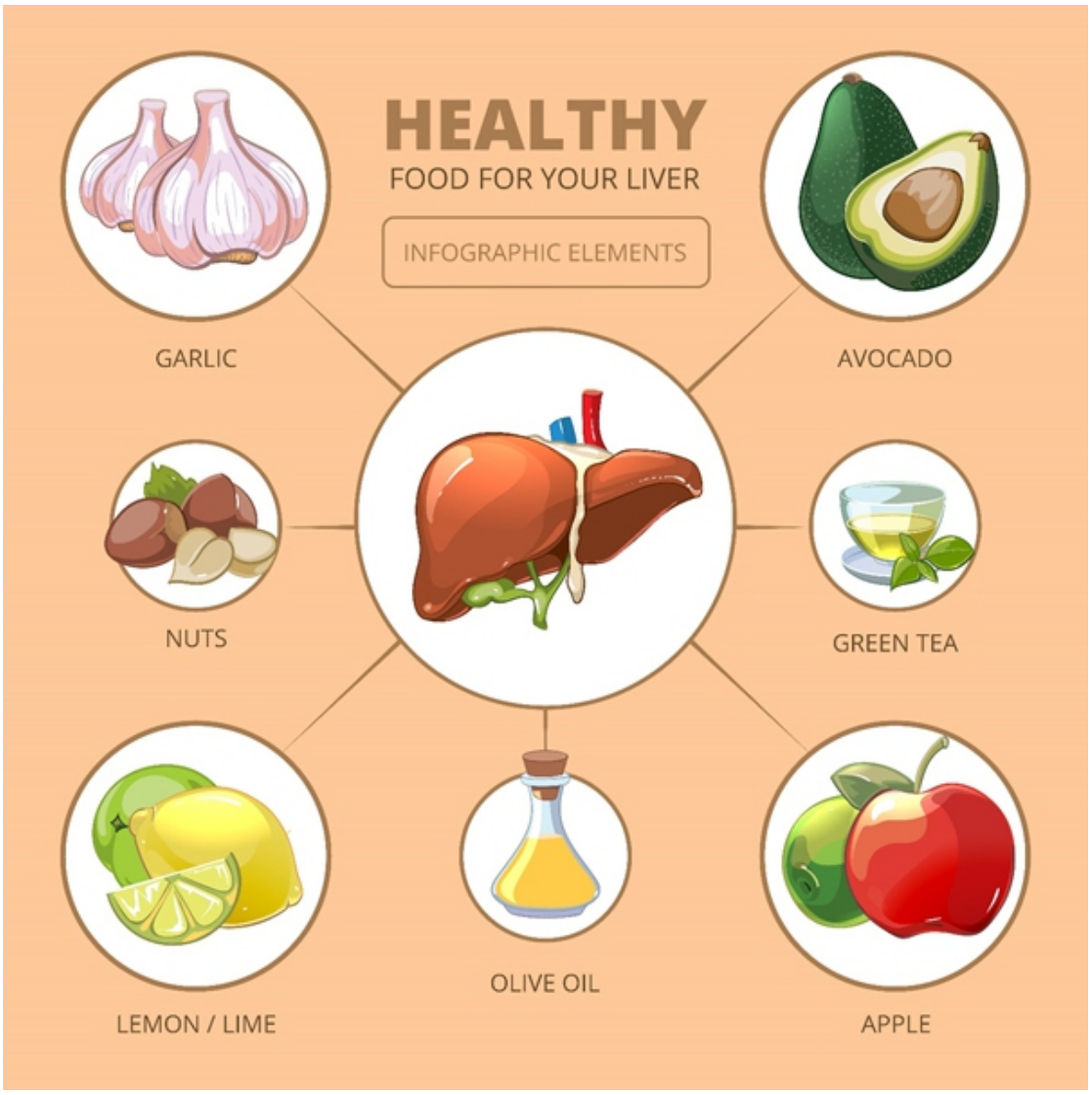
h) Stress Management:

Chronic stress can contribute to unhealthy eating habits and weight gain. Employ stress management techniques like meditation, yoga, or deep breathing exercises.

i) Seek Professional Guidance:

If you are at a higher risk due to genetics or other medical conditions, consult a healthcare provider, such as a hepatologist or nutritionist, for personalized guidance and monitoring.

Preventing NAFLD involves making sustainable lifestyle changes that promote a healthy weight, balanced nutrition, and overall well-being. A holistic approach encompassing dietary modifications, physical activity, and stress management is critical to reducing the risk of NAFLD and its associated complications (34). A healthcare professional should always be consulted before making significant changes to a diet or exercise routine, especially if one has underlying medical conditions.



Chapter 10

Future directions

The future directions for Non-Alcoholic Fatty Liver Disease (NAFLD) research, prevention, and management will likely focus on several key areas to address this condition's growing global health challenge. Here are some future directions concerning NAFLD (35–39):

a) Personalized Medicine:

Develop personalized treatment approaches based on an individual's genetic, metabolic, and environmental factors. Precision medicine could optimize therapies and improve outcomes for NAFLD patients.

b) Advanced Diagnostics:

Invest in non-invasive diagnostic methods, such as advanced imaging techniques and biomarkers, to accurately stage and monitor NAFLD progression, reducing the need for invasive liver biopsies.

c) Emerging Therapies:

Continue researching and developing new pharmacological treatments designed explicitly for NAFLD and NASH. Several potential drugs are in various stages of clinical trials.

d) Nutritional Interventions:

Explore the role of specific diets and dietary components in managing and preventing NAFLD. Research on interventions like intermittent fasting and low-carb diets may yield promising results.

e) Microbiome Modulation:

Investigate the gut-liver axis and the role of the microbiome in NAFLD development. Understanding how the gut microbiota influences liver health could lead to novel therapies.

f) Combination Therapies:

Study the potential benefits of combining pharmacological treatments with lifestyle interventions, as a multifaceted approach may be more effective in managing NAFLD.

g) Early Intervention in Children:

Focus on early detection and intervention in children and adolescents, as NAFLD is becoming increasingly prevalent in younger populations.

h) Public Health Campaigns:

Launch public health initiatives to raise awareness about NAFLD, emphasizing its connection to obesity, diabetes, and heart disease. Promote healthy lifestyles and early screening.

i) Telemedicine and Remote Monitoring:

Leverage telemedicine and digital health solutions for remote monitoring and managing NAFLD patients, especially in underserved or remote areas.

j) Patient Education and Support:

Provide comprehensive education and support programs for individuals with NAFLD, empowering them to make sustainable lifestyle changes and adhere to treatment plans.

k) **Health Equity:**

Address health disparities in NAFLD by ensuring access to healthcare, early diagnosis, and effective treatments for all populations, regardless of socioeconomic status or ethnicity.

l) **Comprehensive Research Consortia:**

Foster collaboration among researchers, clinicians, and pharmaceutical companies to accelerate the development of effective therapies and diagnostic tools.

m) Long-term Outcomes:

Investigate the long-term outcomes of NAFLD, including its impact on liver-related and cardiovascular morbidity and mortality.

n) Global Data Sharing:

Encourage international cooperation in sharing data and findings related to NAFLD to facilitate a deeper understanding of its global impact.

o) **Policy Initiatives:**

Advocate for policy changes that support healthier environments, such as sugar taxes, improved food labelling, and regulations on marketing unhealthy foods.

In conclusion, the future of NAFLD research and management holds promise as scientific understanding and technological advancements progress. A multi-pronged approach, including precision medicine, advanced diagnostics, lifestyle interventions, and public health efforts, will be essential in addressing the growing burden of NAFLD globally.

Chapter 11

Operationalization of NAFLD under NP-NCD

11.1 NAFLD as a component of NPCDCS: Broad Principles

The National Program for Prevention and Control of Cancer Diabetes Cardiovascular Diseases and Stroke (NPCDCS) is funded under the common NCD flexi-pool (consisting of NPCDCS, NMHP, NPCBVI, NTCP & NPHCE) of NHM. The States/ UTs, while formulating their interventions for NCDs, incorporate the budget for the same in the State NHM Programme Implementation Plan (PIP). The 'flexi-pool' allows States sufficient flexibility in providing funds to various components within the overall NCD allocation. Even under, the States /UTs are permitted to reassign funds among the various components to a certain extent after obtaining approval from the Government of India, but within the broad framework of NPCDCS.

Broad Activities permissible under NCD flexi-pool for NPCDCS are as follows:

- Health promotion including, IEC / BCC / SBCC
- Screening and case detection including Population-based screening
- Management of NCDs
- Integration with other programmes
- Monitoring & evaluation
- Capacity building
- Public- Private Partnership
- Innovations for NCD control

NAFLD is designed and included within the above broad structure of NPCDCS at each level of health care delivery.

11.2 Community Level

Through Community Based Assessment Checklist (CBAC) form, ASHA will obtain the following details for NAFLD:

- Abdominal obesity (waist circumference of >90 cm cm in men or > 80 cm in women)
- Family history of diabetes, hypertension, coronary heart disease, liver diseases, gallstones, and cancers

Those who are at risk with a history of diabetes combined with abdominal obesity will be referred to Sub Health Centre - Health and Wellness Centre by the ASHA as suspected of NAFLD.

11.3 Sub Health Centre - Health and Wellness Centre level:

Multi-Purpose Worker (Female/Male) enters the details of Household survey in the NCD application

MPW (Female or Male) / Community Health Officer (CHO) will validate all individuals referred by ASHA by assessing the presence of the following risk factors:

- Abdominal obesity (waist circumference of> 90 cm in men or> 80 cm in women)
- Personal &Family H/O diabetes, hypertension, heart diseases, and cancers
- Obesity (Classification based onBMI>=23kg/m2). Itwill require training along withthe provision of

auto calculation based on height (in meter) and weight (in kg) entered in the ANM application

- Screeningof diabetes, hypertension, and cancers. If cancer screening facilities are not available, then ANM will search for symptoms of cancer and refer to the higher center where cancer screening facilities are available
- Presence of Pedal Oedema

NAFLD is included in Population-based screening subsequently.

Referral:

1. All the patients with obesity and/or diabetes, validated by ANM, will be referred to Primary Health Centre - Health and Wellness Centre for further management., The follow up will be done for those patients who are under treatment for NAFLD.

11.4. Primary Health Centre - Health and Wellness Centre level

Diagnosis and management of common NCDs will be done either through PBS or direct at PHC.

The Medical Officer will examine the patient referred by Community Health Officer -

1) Abdominal obesity (waist circumference of >90 cm in men or> 80 cm in women)
2) Family H/O diabetes, hypertension, heart diseases, and cancers
3) Obesity (Classification based on BMI>=23kg/m2).
4) H/O or report of diabetes, hypertension, heart disease
5) The patient is provided with drugs for diabetes and hypertension
6) Emphasis on Signs of chronic liver disease like spider naevi, petechiae, purpura, palmar erythema, ascites, gynecomastia, asterixis, etc
7) Any patient with abnormal LFT report or incidental detection of hepatic steatosis on USG
8) The MO can undertake tele-consultation if needed. MOs may also utilize the hub and spoke model for diagnostics, if required .

Referral:

The patient will be referred to CHC Only if a specialist (MD Medicine) is available at the CHC. Otherwise, patient will be referred to the district hospital.

If there are any complications. No previously designed care is available for NAFLD. The Medical Officer will be sensitised through training.

11.5 CHC Level

Diagnosis and management of common NCDs will be done either through PBS or direct at CHC: The CHC Medical Officerwill perform a clinical examination and rule out other causes of chronic liver disease through history and examination and further perform USG.

Those diagnosed with NAFLD:

- Perform LFT and CBC; input data into the app and calculate FIB-4 or NFS score and do risk stratification for advanced liver fibrosis and manage the patient accordingly
- Calculate FIB 4 or NFS score on the application

Low risk for advanced liver fibrosis:

- Refer patients back to PHC for management of Diabetes, Dyslipidaemia, Hypertension, weight reduction

- The patient has to be reassessed after 3 years

High Risk for advanced liver fibrosis:

- Refer patients to the District Hospital or Tertiary care Centre for further management. Inclusion of NAFLD in patient referral card.

Indeterminate Risk for advanced liver fibrosis:

- Refer patients to the District Hospital for further evaluation. Inclusion of NAFLD in patient referral card.

11.6 District Hospital Level

Detailed investigation and management of the patient which referred through PBS will be done in District Hospital: Risk stratification for advanced liver fibrosis will be done if no facility for the same at CHC

For a patient with indeterminate risk for advanced liver fibrosis, the doctor will perform a Fibroscan

Low risk for advanced liver fibrosis:

- Refer patients back to PHC for management of Diabetes, Dyslipidaemia, Hypertension, weight reduction
- Patient to be reassessed after 3 years

High Risk for advanced liver fibrosis:

- Management of advanced fibrosis
- Screening and treatment of Portal hypertension
- Screening for HCC
- Referral to Tertiary care center for complicated cases or if facilities are not available at District Hospital. Inclusion of NAFLD in patient referral card.

Reporting

Routine monitoring mechanism through formats and with the existing apps.

The routine monitoring mechanism which is being adopted for NPCDCS will now include the indicators for NAFLD. Therefore, the following formats for monthly reporting from the facilities at various levels have been modified to include components of NAFLD:

Level	Reporting Form	Data generated from	Person responsible	Reporting to	Submission of previous month report by
Sub-centre	Form 1	ANM Screening Register	CHO of SHC-HWC	PHC	Last day of the month
PHC (including urban PHC-HWC	Form 2 & 2 A	PHC-HWC OPD Register & Compiled all Form-I	MO I/C PHCHWC	CHC NCD Clinic	5th of every month
CHC/ BPHC/ SDH	Form 3A	CHC NCD OPD Register	MO I/C CHC NCD Clinic	District NCD Cell	7th of every month
	From 3B	Compiled all forms 1 & 2	BPHC / SDH		
District Hospital	Form 4	DH-NCD OPD Register	MO I/C District NCD Clinic	District NCD Cell	7th of every month
District NCD cell	Form 5A	Form 5A Compiled all forms 3A & 4	District Nodal Officer (NCD)	State NCD Cell	10th of every month
	Form 5B	Form 5B Compiled all forms 3B			
State NCD Cell	Form 6	Form 6 Compiled all forms 5A &5B	State NodalOfficer (NCD)	National NCD cell	15th of every month

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