Non-alcoholic fatty liver disease in Morocco: The situation, the determinants and the challenges for health care

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Abstract
Non-alcoholic fatty liver disease (NAFLD), a health problem growing in parallel to the epidemic of obesity and type 2 diabetes (T2D) worldwide. This pathology leads to an accumulation of triglycerides and free fatty acids in the liver. The accumulation of these fats depends on several factors that act in synergy. Among these factors, metabolic syndrome, visceral adiposity, alteration of the intestinal microbiota, diet, malnutrition, physical inactivity, oxidative stress and genetic predisposition are cited. NAFLD is a silent and progressive pathology with serious economic and social consequences. It represents a public health challenge due to its associated hepatic and extra hepatic complications. The multidisciplinary nature of both obesity and NAFLD management has guided research to identify appropriate non-invasive diagnostic methods and effective treatments for NAFLD. Considering the association of this disease with obesity and diabetes and the trend of the continuous increase of these latter problems in Morocco, this review presents the situation the evolution, the determining factors, complications and etiologies of non-alcoholic fatty liver disease in Morocco.

Keywords: Non-Alcoholic Fatty Liver Disease; Prevalence; Obesity; Morocco

1. Introduction
Non-alcoholic fatty liver disease (NAFLD) is defined by an accumulation of lipids in at least 5% of hepatocytes in the absence of significant alcohol consumption (<20 g / day for women and <30 g / day for the man). The pathology encompasses a histological spectrum ranging from non-alcoholic fatty liver disease (NAFL) characterized by a so-called simple steatosis without inflammation, to non-alcoholic steatohepatitis (NASH) with inflammation and swelling. NASH corresponds to the aggressive form of the disease which promotes fibrosis in the hepatic parenchyma progressing to cirrhosis and its complications (liver failure, ascites, rupture of varicose veins, hepatocarcinoma [1]. Non-alcoholic fatty liver disease (NAFLD) is a worldwide chronic disease of the liver, parallel to the epidemic of obesity and type 2 diabetes (T2D) [1, 2]. Recent studies show that NAFLD is associated with cardiovascular disease, chronic kidney disease, type 2 diabetes, osteoporosis, endocrinopathies and colorectal neoplasms [3]. People with NAFLD have co-morbidities with considerable clinical and economic consequences [2]. The progression of NAFLD is an indicator of liver transplantation [4]. However, any increase in the demand for liver transplants leads to a high level of disability [5] and economic costs [5, 6]. In addition, chronic liver disease being a major cause of mortality [2], liver transplantation may be limited as a treatment option in patients with multiple co-morbidities [5, 6]. Research is underway to identify appropriate non-invasive diagnostic means and effective treatments that have not existed to date. In addition, knowing the pathology of NAFLD, its risk factors and prevalence, will be used to take preventive measures to decrease the incidence of this condition in the years to come.

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Indeed, NAFLD is a complex disease with great heterogeneity in its progression and its severity depending on the individual. Its development results from an interaction of genetic and environmental factors, in particular food and the intestinal microbiota.

2. Epidemiological situation of NAFLD in the World

2.1. The prevalence of NAFLD

NAFLD has become the leading cause of liver disease [2]. Indeed, due to the growing global epidemic of obesity and type 2 diabetes, predictions estimate liver deaths due to NASH by 178% in 2030 [4]. This will make it the next pandemic in the future with challenges and implications for the health system [7].

At present, the prevalence of NAFLD exceeds 25% of the world population. It affects both developed countries with 25-30% in industrialized countries and developing countries [2]. Estimates report 10 to 30% in the USA, 24% in Europe [8, 9] 25% in Asia [8, 10], 20-30% in Australia [8, 10] and the highest rates in the Middle East and in South America, and the lowest in Africa [11].

In Europe, the prevalence of NAFLD is 24% [8, 9] with higher rates in the south than in the North of Europe [12] reaching 41% in Greece [8, 13]. In Spain it is 33% for men and 20% for women [14].

In Asia, the prevalence of NAFLD is 25% with 15% in China in adults and 2.1% in children affecting 68.2% of obese children. It is 32% in India [8, 10], 30% in Japan and 32.6% in urban Sri Lanka [8, 15, 16]. It is estimated at 20-30% in Australia [17] and 13% in New Zealand [8, 10].

In the Middle East, the prevalence of NAFLD is 20-32% and varies by country. It is estimated at 34% in Iran, 30% in Israel, 33.3% in Kuwait, 16.6% in Saudi Arabia and reaches the rate of 63.5% in Turkey [9, 18].

In Africa, data from studies on the prevalence of NAFLD are lacking or limited with small sample sizes. A rate of 13.5% is reported, which is the lowest in this continent. However, this rate is underestimated and hides the link of this disease with obesity and type 2 diabetes that are continuously increasing in Africa and the Middle East [11].

The reported prevalence of NAFLD in Africa varies by country, diagnostic method and different rates of comorbidity factors in patients such as obesity, type 2 diabetes and metabolic syndrome and increases with the age [5, 9, 18]. In Nigeria the prevalence is estimated at 16.7% in diabetics and 1.2-4.5% in non-diabetics [19, 20]. It is 36% in diabetics in South Africa [21] and more marked in women with body mass index (BMI), waist circumference (WC), and high levels of Triglycerides and cholesterol [22]. In Sudan it has been estimated at 20% in obese and 53% in diabetics [23]. Finally in Egypt, this prevalence is 15.8% in children aged 6 to 14 and increases with age [24].

2.2. The prevalence of NASH

NASH corresponds to an advanced stage of NAFLD and can progress to cirrhosis and a risk of hepatocellular carcinoma (HCC) [1, 2]. The prevalence of NASH in the world population is 3-5% [2, 8, 25]. It is 18% in South America [9, 26], 9% in Japan [10], 40% in Greece [13] and 17% in South Africa [21]. In Switzerland, the prevalence of NASH was estimated at 5.3% in 2018, and the projection in 2030 of the incidence of NAFLD, cirrhosis and HCC is estimated at 6.2%, 41% and 39% respectively. That said, the predictions are for an increase in liver-related mortality in the total NAFLD population, to 2.8% compared to 2.3% in 2018 of all deaths [5].

2.3. Age

Several studies confirm that the prevalence of NAFLD increases with age [8, 27] in both young people and adults with significant rates in people over 60 [5, 14, 28]. It can even start in utero in infants born to mothers with gestational diabetes [28, 29, 30]. It is more accentuated when these mothers are more obese [28, 31]. As in adults, childhood obesity is a considerable risk for the development of NAFLD estimated at one third in obese children [28, 32, 33]. In addition, an association between NAFLD, dyslipidemia and the number of components of metabolic syndrome has also been reported in Egyptian children [34, 35].

Age is a risk factor for advanced liver disease and progression to advanced stages of NASH [36-37-38]. The incidence of NASH and cirrhosis have been found to increase in patients 50 years of age or older [9] and an association of more severe fibrosis with increasing age has been reported in NASH patients reflecting the cumulative sum of metabolic
exposures [36, 37]. Indeed, in Africa and the Middle East NAFLD was prevalent in 50% of Sudanese patients with T2D [38] and in over 50% of Egyptian patients with chronic viral hepatitis C (VHC) infection. It is associated with insulin resistance, which is a significant risk factor for age-related fibrosis [39].

2.4. Sex

Evidence from the literature on the effect of gender in the development of NAFLD is divergent. Several studies provide data that suggests a higher prevalence in men. C’est le cas des études effectuées en Suisse, au Japon et en Espagne [5, 8, 14, 15, 16, 40, 41]. On the contrary, other studies in Sri Lanka and Thailand have concluded that women are associated with an increased risk of NAFLD [8, 24, 42]. Furthermore, the relationship between sex and fibrosis can be influenced by menopausal status. A study reports that the incidence of NAFLD increases in the woman after the age of 50 years with a peak at 60-69 years, and that NASH is more severe in women compared to men [43].

2.5. Ethnicity

The prevalence of NAFLD varies by ethnicity and ethnicity is an important predictor of chronic complications of liver disease. Indeed, NAFLD develops more in Hispanic patients [28, 44] with a higher prevalence in white Hispanic patients followed by non-Hispanic blacks and Caucasians. In the latter NAFLD is more common in men than women [8]. In the United States, a lower degree of steatosis is reported among African Americans compared to whites and higher among Asians and Hispanics [28, 45] with a development of NASH in the latter [28, 44, 45, 46].

3. Risk factors for NAFLD

3.1. Obesity

Overweight and obesity are defined as an abnormal or excessive accumulation of body fat that poses a health risk. Obesity increases the risk of NAFLD [47, 48]. The evaluation of this risk and its progression is done on the basis of the body mass index (BMI) and the waist measurement which measures visceral obesity linked to insulin resistance [42, 49].

The World Health Organization (WHO) estimated obesity at 13% and overweight in the global adult population in 2017 in 39%.

In Morocco, obesity is gaining ground. The latest epidemiological survey on the prevalence of risk factors for non-communicable diseases carried out by the Ministry of Health in collaboration with World Health Organization, reported that obesity affects 20% of the population. This prevalence was more marked in women (29%) with a rate three times higher than in men (11%) and in urban than in rural areas (22.8 vs 14.9% respectively). The obesity rate increased over the 2000-2017 period from 13.2 to 20% [50] and 29% in 2019. In Algeria a rate of 55.6% is recorded in 2019 [51].

This obesity and overweight problem also affect children. WHO estimated 41 million children under the age of 5 and more than 340 million children and adolescents aged 5-19 were overweight or obese in 2016. In addition, a study by the Imperial College London and the WHO reports that by 2022 there will be more obese children and adolescents than people with moderate or severe underweight. In addition, these obese people will develop more complications than non-obese people of the same age [8, 52].

NAFLD increases in parallel with obesity [2, 8]. Scientific studies show that the patients most at risk are those with massive obesity. The prevalence of NAFL reaches 90% and that of NASH 25% in these patients [12]. In addition, in developed countries, the prevalence of NAFLD is 34% in obese children [2].

3.2. Type 2 diabetes

Type 2 diabetes (T2D) is also on the rise worldwide. This is another risk factor for NAFLD and NASH [53]. The International Diabetes Federation reports that more than 400 million people will be living with diabetes as of 2015 [53]. WHO predicts that worldwide deaths from diabetes will double by 2030 [8, 52, 53]. Type 2 diabetes increasingly affects children and young people, especially overweight children [52]. This type of diabetes accelerates the onset of NAFLD and is a predictor of advanced fibrosis and mortality [18]. In T2D patients, the prevalence of NAFLD and NASH has been found to be 60% [12, 18].
3.3. Metabolic syndrome
Metabolic syndrome results in the concomitant presence of several physiological and metabolic disorders in an individual.

Several studies report that the incidence of NAFLD increases with increasing criteria for metabolic syndrome. Indeed, these studies show that around 90% of patients with NAFLD have more than one component of metabolic syndrome and around 33% have at least three components of metabolic syndrome [54, 55, 56, 57].

3.4. Malnutrition and the gut microbiota
Malnutrition characterized by an imbalanced supply of nutrients, alters the digestive barrier and changes the composition of the intestinal microbiota, inducing dysbiosis [58]. This modification increases the production of endotoxins from Gram-negative bacteria that can damage the intestinal barrier and promote obesity and NAFLD [59, 60]. In addition, dysbiosis of the intestinal microbiota leads to an increase in the secretion of inflammatory cytokines and promotes the progression of NAFLD to HCC [59, 60, 61, 62, 63]. In addition, endogenous alcohol is involved in NAFLD. In fact, the ethanol released by Gram-negative bacteria converts to acetaldehyde, and provides substrates for the synthesis of fatty acids and the production of reactive oxygen species [12]. In addition, the enzymes produced by the intestinal microbiota catalyze the conversion of dietary choline into toxic methylamines that when absorbed by the liver are capable of inducing NASH [12]. De même, le cholestérol accumulé dans le foie peut aussi activer les macrophages et les cellules étoilées hépatiques et favoriser ainsi l'évolution de la stéatose hépatique non alcoolique [59, 64]. Likewise, the cholesterol accumulated in the liver can also activate macrophages and hepatic star cells and thus promote the progression of non-alcoholic fatty liver disease [59, 64].

3.5. Diet and lifestyle
Lifestyle changes, including diet, smoking and physical activity are implicated in the pathophysiology of NAFLD. Interventions by modification of diet by an energy restriction from carbohydrates and lipids or by enrichment with monounsaturated fatty acids, have shown a reduction in NAFLD [65, 66, 67]. Other studies have shown that the risks of metabolic syndrome and NAFLD are increased by physical inactivity and that a calorie restriction associated with physical activity improves the management of NAFLD [68]. In addition, a ten-year retrospective study, which included 2,029 subjects, also showed the effect of smoking as an independent risk factor for the onset of NAFLD [69].

3.6. Genetic factors
Non-alcoholic fatty liver disease is partly a culprit in diet, lifestyle and obesity, but genetics are a determining factor in the existence of the disease. Indeed, a retrospective study on 669 NAFLD patients reports that 20% of these patients have NASH, and a fibrosis score equal to or greater than 2 even though they are thin [70]. Similarly, not all obese individuals develop NASH and a high caloric intake does not fully explain the pathogenesis of NASH that explains the existence of other risk factors including the genetic factor. Indeed, genetic predispositions such as polymorphisms of genes coding for PNPLA3, TM6SF2, MERTK and GCKR are factors contributing to hepatic inflammation, lipotoxicity and the high prevalence of NAFLD [48]. In addition, patients who wear these polymorphisms have a high fat content in the liver and high triglyceride reserves. This genetically determined accumulation of hepatic triglycerides is the first step in a liver injury that makes the liver more susceptible to lipotoxicity and oxidative stress [12].

3.7. Oxidative stress
Oxidative stress, characterized by an imbalance between pro and antioxidant mechanisms, followed by mitochondrial dysfunction, is a risk factor for the development and progression of NAFLD. Oxidative stress and inflammation are the main contributors to the progression of NAFLD [53, 71].

4. The diagnosis of NAFLD
The prevalence of NAFLD is increasing worldwide and varies according to ineffective screening tools in the entire population. Liver biopsy is the reliable reference method that differentiates NAFLD from NASH and assesses the severity of NASH, fibrosis and cirrhosis [72, 73, 74]. However, due to its invasive nature [75], its use poses ethical and feasibility problems in healthy populations or in children [65], in addition to potential risks, costs and sampling errors [73, 74].

Most often, the diagnosis of NAFLD is therefore based on useful indices such as BMI, waist circumference and metabolic syndrome, but in lean patients, the diagnosis is more difficult [65]. The severity of the disease is assessed with non-invasive tests by looking for blood markers such as levels of transaminases, bilirubin, growth factor (FGF21), alkaline
phosphatase [73, 74]. However, the problems of reliability and consensus on the normal values according to sex, age and ethnicity, concerning these tests, are still posed [65, 76, 77] and open up avenues of research to develop non-invasive and validated tools for quantifying NAFLD.

5. Treatment of NAFLD

NAFLD has become the first chronic liver disease. As a result, interventions aimed at modifying lifestyle, with a Mediterranean type diet and physical exercise, are promising. Indeed, several authors show that a weight loss of 3% to 5% reduces fatty liver and a greater loss of 10% is necessary to reduce inflammation [74, 78]. Pharmacological treatments are not currently validated in NAFLD, although many molecules are being evaluated in NASH [72].

6. Economic burden of NAFLD

Recent studies published by the World Economic Forum and the Harvard School of Public Health estimate that in the next fifteen years, non-communicable diseases (NCDs) would cost low- and middle-income countries more than $7 trillion in losses in national income [8].

Increasing the NAFLD alongside that of chronic diseases would represent a significant additional economic burden globally. In the United States, spending on these diseases is multiplied by a factor of 3.5. The significant increase in health care and economic burdens due to the development of NAFLD is aggravated by the rise in obesity [2, 9]. The same is true in Germany, France, Italy and the United Kingdom, where costs range from €345 to €1,115 per patient, increasing more at ages 45-65 years [8].

7. The epidemiological situation of NAFLD in Morocco

In Morocco, the resurgence of non-communicable diseases (NCDs), in particular metabolic disorders, is as alarming as it is at the global level. Indeed, 12.5% of children under 5 yrs are overweight and 2.6% are obese. In the adult population over 18, 53% are overweight and 20% are obese, 10.5% have high blood cholesterol, 29.3% are hypertensive, 10.6% are diabetic and 10.4% are pre-diabetic (Figure 1) [50]. Surveys carried out in regions of Morocco also show an increasing evolution of all these risk factors as well as that of the metabolic syndrome [79, 80, 81]. In addition, non-communicable diseases are responsible for 80% of all deaths [50].

Survey data on the prevalence of NAFLD are scarce if not non-existent in Morocco because of the cumbersome methods and equipment for diagnosing the disease. Thus, the information available is limited to the hospital environment and is obtained from patients with one of the cardiovascular risks mentioned above. The Figure 2 shows the results of a study carried out in 2009 on a sample of 117 patients with T2D. The data from this study show that 68.4% of these diabetic patients have NAFLD, 37.6% of whom had metabolic syndrome [82]. Another study carried out in 2012, on twenty cases of non-alcoholic fatty liver disease showed that the patients have metabolic syndrome (Figure 3) [83].

The evolution of all these diseases is linked to the global transition underway in Morocco. This includes a demographic and nutritional transition which is accompanied by an increase in the percentage of elderly people and NCDs. The continuous increase of these chronic diseases in this case, obesity, diabetes and Metabolic syndrome and their association with NAFLD will make the latter an additional challenge in the future for the Moroccan health system with considerable economic impact.

Indeed, the cost of treating NCDs is very high and the country has still not finished its fight against poverty, communicable diseases and diseases linked to under nutrition. In addition the cost generated by the methods in terms of equipment and human resources for diagnosis and treatment of NAFLD will be an additional burden for health care and care of the population. The situation is all the more worrying since medical coverage only covers 62% of the population. Indeed, studies of the impact of the burden linked to care have demonstrated the heaviness of the burden assumed by households and the gravity of the social and economic benefits [50].
Figure 1 Percentage of people by type of metabolic syndrome in Morocco [50]

Figure 2 Percentage of patients with or without metabolic syndrome (MS) in Morocco [82]

Figure 3 Metabolic syndrome components in the group with NAFLD [83]
8. Conclusion
Non-alcoholic fatty liver disease (NAFLD), usually asymptomatic, can be associated with obesity, type 2 diabetes and metabolic syndrome. This disease can progress and worsen, leading to a risk of morbidity and mortality worldwide. It is an important priority for health systems in terms of care and research. Knowing the prevalence of NAFLD in Morocco will help to put in place appropriate preventive measures to limit the management resources of NAFLD. Research studies on representative samples are necessary to determine the prevalence of the pathology, the associated metabolic problems as well as the determining factors of the disease in the country.

The search for non-invasive markers for the diagnosis and early detection of the disease to prevent and control NAFLD and its risk factors; and finally consolidate prospective studies on lifestyle, in particular nutritional interventions combined with physical activity.

Compliance with ethical standards

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Disclosure of conflict of interest
The authors declare that there is no conflict of interest.

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