

Non-Alcoholic Fatty Liver Disease in Africa and Middle East: An Attempt to Predict the Present and Future Implications on the Healthcare System

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Abstract

Non-alcoholic fatty liver disease (NAFLD) encompasses a group of hepatic diseases that range in severity. NAFLD is increasingly recognized as an epidemic among different populations, including those in Africa and the Middle East. The objective of this narrative review is to document the prevalence of and risk factors for NAFLD in Africa and the Middle East and the potential implications on the healthcare systems. An in-depth search on Google Scholar, Medline and PubMed was conducted using the terms “non-alcoholic fatty liver disease” and “non-alcoholic steatohepatitis”, in addition to “prevalence and risk factors for NAFLD”, with special emphasis on Africa and the Middle East countries. There were three types of epidemiological studies that included prevalence, risk factors and management/complications of NAFLD. There was noticeable variation in the prevalence of NAFLD among different countries, based on the variation in the prevalence of risk factors (type 2 diabetes, obesity, metabolic syndrome and dyslipidemia) and the diagnostic tool used in the study. However, the highest prevalence rate was reported in some Middle East countries. In Africa, there were few studies about NAFLD and most reported variable prevalence rates. There is

an increasing prevalence of NAFLD as a result of the increasing risk factors, particularly in the Middle East, while in Africa, the situation is still unclear. Health providers in these regions are faced with many challenges that need urgent plans.

Keywords: Fatty liver; Africa; Lipid profile

Introduction

Non-alcoholic fatty liver disease (NAFLD) is regarded as a common and fast growing liver disease across the globe with an increase in both mortality and morbidity [1]. The estimated prevalence of NAFLD is thought to be around 25-35% across the globe and affect large different proportions of men and women. NAFLD refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis [2]. An in-depth search on Google Scholar, Medline and PubMed was conducted using the terms “non-alcoholic fatty liver disease” and “non-alcoholic steatohepatitis”, in addition to “prevalence and risk factors for NAFLD”, with special emphasis on “Africa” and the “Middle East” countries in names.

Definition of the Terms

NAFLD encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis [3, 4].

Non-alcoholic fatty liver (NAFL) is the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal. The definition of NAFLD requires that 1) there is evidence of hepatic steatosis, either by imaging or histology and 2) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders [4-9].

Non-alcoholic steatohepatitis (NASH) is the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cir-

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rhosis, liver failure and rarely lead to liver cancer [4-9]. It is a more severe form of NAFLD, and is regarded as a major cause of liver cirrhosis [4-9].

NASH cirrhosis is the presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis [4-9].

Cryptogenic cirrhosis is the presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are likely to have two or more of the metabolic risk factors such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia and metabolic syndrome (MS).

NAFLD activity score (NAS) is an unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials [4-9].

MS is defined by the presence of several risk factors associated with an increased risk of cardiovascular disease (CVD); these include insulin resistance, T2DM, high blood pressure, high triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C) and an increased waist circumference (WC) (above 102 cm in men and 88 cm in women) [3, 9].

Symptoms and Signs of NAFLD

Most people with NAFLD have few or no symptoms. Patients may complain of fatigue, malaise, and dull right-upper-quadrant abdominal discomfort. Mild jaundice may be noticed although this is rare. More commonly NAFLD is diagnosed following abnormal liver function tests during routine blood tests. By definition, alcohol consumption of over 20 g/day (about 25 mL/day of net ethanol) excludes the condition [3, 7].

Investigations and Diagnostic Grades

Common findings are elevated liver enzymes and a liver ultrasound showing steatosis. An ultrasound may also be used to exclude gallstone problems (cholelithiasis). A liver biopsy is the only test widely accepted as definitively distinguishing NASH from other forms of liver disease and can be used to assess the severity of the inflammation and establish grades of liver fibrosis [3-9].

Epidemiology of NAFLD

The estimated prevalence of NAFLD is approximately 30-40% in men and 15-20% in women [7]. The prevalence of NAFLD in Italy is about 25%, while the prevalence in USA is estimated to be around 33.6% and 34% [6, 8]. The association of NAFLD with obesity and insulin resistance is well established. The majority of individuals with NAFLD have insulin resistance and the prevalence of type 2 diabetes among individuals with NAFLD was estimated to be around 39% [3]. NAFLD is associated with T2DM, obesity and hyperlipidemia [4]. There is now general agreement in the literature that NAFLD is the hepatic component of the MS [5, 6]. Importantly, diabetes is

an independent risk factor for the development of NAFLD and progression to advanced liver disease, fibrosis, cirrhosis and hepatocellular carcinoma. Importantly, higher prevalence of NAFLD was recorded with diabetes. For instance, the estimated prevalence of NAFLD in people with T2DM is thought to be around 70% [7]. In UK, the estimated prevalence of NAFLD among type 2 diabetic individuals was found to be around 42.6%, while in Italy the prevalence of NAFLD among type 2 diabetic individuals was around 70% [9, 10]. The prevalence of NAFLD among type 2 diabetic individuals in Brazil, Malaysia and China was estimated to be 42%, 49.6% and 61%, respectively [11-13].

Natural Course of NAFLD

Once liver fibrosis develops, it carries with it ominous prognosis. For instance, in follow-up study for around three decades duration, hepatic fibrosis was regarded the strongest predictor for all-cause and disease-specific mortality in patients with histologically confirmed NAFLD [14-16]. Furthermore, in a meta-analysis, it was shown that the degree of liver fibrosis in individuals with NASH is associated with an increase in risk of liver-related mortality by almost 10 folds [15]. It was noted that there was alarming increase in the prevalence of hepatocellular carcinoma (HCC) within the last two decades. This was likely to be attributed to the increase in well-known risk factors for HCC like diabetes and obesity [17-20]. And, it is well documented in the literature that NASH is a risk factor for HCC, even in people without cirrhosis [21-23]. Basaranoglu et al showed a proportionally greater elevation in liver transplant candidacy in patients with NAFLD and portal vein thrombosis. Their data showed that older patients were more prone to develop liver cirrhosis, HCC and a high mortality rate. While younger patients exhibited more portal vein thrombosis and gastric varices [24]. One of the difficult burdens of NAFLD on health authorities in Africa and Middle East in the near future will be the demand for liver transplant due to NAFLD. Importantly, NASH is the second leading etiology of liver disease among adults awaiting liver transplantation in the USA in the year 2013 [25]. However, NASH was the third most common indication for liver transplantation in the USA in the year 2009 [25, 26]. Different studies showed that the frequency of NASH as the primary indication for liver transplant in USA increased from 0% or 3% to 19% or 26% within the last 13 - 15 years [27, 28].

In the view of the increase in prevalence of epidemic of obesity and diabetes, it is plausible to suggest that NAFLD is on a trajectory to become the most common indication for liver transplantation. Liver transplant due to NAFLD is associated with high rates of complications due to diabetes and obesity. Furthermore, the rate of recurrence of NASH was estimated to be around 20-40% [29]. NAFLD does not only cause chronic liver disease but also is regarded as multisystem disorder. For instance, NAFLD is associated with an increase in CVD mortality and twofold increase in risk of incident T2DM. Furthermore, a meta-analysis showed that NAFLD was associated with an increased risk of chronic kidney disease (CKD) [30,

31]. Several studies showed an association between NAFLD and osteoporosis, cholesterol gallstones, colorectal cancers, sleep apnea and polycystic ovary syndrome [2, 32, 34]. Given the rising incidence and prevalence of T2DM, obesity and MS among populations in Africa and Middle East regions, it is highly recommended that policy makers should make an accurate estimate of the prevalence of NAFLD in order to predict the number of those who will develop advanced liver disease or NAFLD-related morbidities and to develop strategies for interventions to treat this condition.

This narrative review will discuss: 1) prevalence of NAFLD in adult and pediatric population in the middle East and Africa, 2) the increase in prevalence of obesity, MS and diabetes in these regions as these conditions are associated with high prevalence of NAFLD, and 3) the burden of the disease and future implications for medical forces working in these regions.

Prevalence of NAFLD in Adult and Pediatric Populations in Africa and Middle East

Adult population

The prevalence of NAFLD varies widely in different populations ranging from 4% to 47%. In USA and industrialized countries, NAFLD represents the most common hepatic disorder in the current time. It affects 18% of the general adult population and 90% of markedly obese individuals with overall prevalence of 35% [35].

It is estimated that the burden of non-communicable disease will exceed that of communicable disease in the regions. For instance, it was estimated that by the year 2020 the rate of communicable disease will be 20% and non-communicable disease will increase to 60% [36]. Being the most prevalent non-communicable chronic liver disease in Western countries, NAFLD has not yet been studied in most countries in Africa and Middle East countries [37]. Furthermore, it is not easy to determine the prevalence of any health problem in areas that still lack reliable, regularly updated, population-based data. Even where data exist, poor reporting regulations and practices affect their quality and reduce the usefulness of national registries [38]. In spite of that there are some published data from some countries, but they are mostly not population-based surveys, rather they were done in certain categories of patients. In the view of the increase in the epidemic of obesity and diabetes in these regions, it is possible to predict that there will be a parallel increase in the epidemic of NAFLD.

Onyekwere et al determined the prevalence of NAFLD among patients with diabetes mellitus (DM) attending an endocrine clinic in Nigeria and compared it with non-diabetic subjects. They found that the overall prevalence of NAFLD amongst all study subjects was 8.7% and the prevalence rate of NAFLD was higher in the DM cases than in the control subjects but the difference was not statistically significant (9.5% vs. 4.5%, $P = 0.2$) [39]. The prevalence of NAFLD in Kuwait, Saudi Arabia, South of Iran and North of Iran was 33.3%, 16.6%, 21.5% and 43.8%, respectively [40, 41]. Almobarak

et al studied the prevalence of NAFLD and risk factors among asymptomatic co-patients accompanying patients admitted to Gastroenterology Wards at the National Centre for GI and Liver Diseases, Ibn Sina Hospital (Khartoum, Sudan). Their study revealed 20% prevalence among the studied group with equal gender distribution and increased prevalence with age and body mass index (BMI) [42]. The prevalence of NAFLD appeared to be higher in individuals with T2DM. For instance, Almobarak et al have shown the prevalence of NAFLD among Sudanese individuals with T2DM was around 50% [43].

Kruger et al found NAFLD in 111 out of 233 patients (47.6%) in the Western Cape population. This high percent could be attributed to the study methods. They screened only overweight/obese subjects by ultrasound and those with fatty liver/hepatomegaly were included [37]. Zatu et al found that NAFLD in South Africa is more in women with high BMI, WC, high TG and high cholesterol [44]. Interestingly, Matsha et al showed that gamma-glutamyltransferase (GGT) is an independent risk factor for insulin resistance in African population with NAFLD [45]. Mahmoud et al have shown that serum transforming growth factor $\beta 1$ (TGF- $\beta 1$), MMP-1, and homeostatic model assessment insulin resistance (HOMA-IR) proved to be potentially useful non-invasive markers in predicting fibrosis in Egyptian patients with NASH [46]. Ahmed et al showed that steatosis is a histopathologic feature in > 50% of Egyptian patients with chronic HCV infection. Insulin resistance has an important role in the pathogenesis of steatosis, which represents a significant risk factor of fibrosis together with high serum AST level and older age [47].

Pediatric population

NAFLD was reported in children and adolescent. In a cross-sectional, nested case-control study, Alkassabany et al selected cases and controls randomly from outpatient schoolchildren aged 6 - 18 years attending the Radiology Clinic in Alexandria, Egypt. Their study revealed that fatty liver was prevalent in schoolchildren (15.8%) and increased significantly with age ($P = 0.004$) [48]. They found that positive family history of DM, hypertension (HTN), obesity, and liver disease were all statistically significant risk factors for fatty liver. WC and BMI were considered the best predictors of pediatric NAFLD. Furthermore, NAFLD in children was significantly associated with high TGs, low HDL-C, homeostatic model assessment (HOMA) percentile, and the number of MS components [49]. El-Koofy et al showed that in Egyptian children polymorphisms in the promoter of microsomal triglyceride transfer protein (MTP) do exist in obese children with NASH [50]. This polymorphism leads to decreased MTP transcription, less export of TG from hepatocytes, and greater intracellular TG accumulation in liver and ultimately leads to NAFLD. Interestingly, El-Karaksy et al showed that dyslipidemia *per se* is a strong predictor of NAFLD among obese Egyptian children [51]. In large population study, it was estimated that the upper normal value for alanine amino transaminase (ALT) and aspartate amino transaminase (AST) was 40 U/L for the pediatric age group (10 - 18 years old). Importantly, the association with BMI was significant for ALT in both females and

Table 1. The Prevalence of NAFLD in Some African and Middle East Countries [37, 39-43, 48]

Country	Prevalence rate (%)	Comment(s)	Authors
South Africa	47.6	Among overweight/obese subjects	Kruger et al [37]
Nigeria	8.7	Population-based	Onyekwere et al [39]
Kuwait	33.3		Ramezani et al [40]
Iran	33.9	Meta-analysis	Sohrabpour et al [41]
Sudan	20	Among non-diabetic	Almobarak et al [42]
Sudan	50	Among diabetic patients	Almobarak et al [43]
Egypt	15.8	Among school children	Alkassabany et al [48]

males [52]. However, El-Koofy et al showed that in Egyptian children, there was a close association between obesity, MS, insulin resistance and NAFLD [53]. They have also concluded that ultrasound is a useful method for screening of NAFLD in children.

This review of literature is not without limitations. The search terms may have not encompassed all available literature that was published in highly visible journals and this may show why there are limited studies about NAFLD in Africa and the Middle East. Another problem is about what defines NAFLD and the use of liver biopsy to define NASH, as the diagnosis of NAFLD is not by the same tools in all studies included. A third limitation is the effect of ethnicity and economic status between different countries cannot be easily identified. It is clear that it is difficult to realize the precise prevalence of NAFLD in African and Middle East countries. This could be partially attributed to limited research work carried out concerning NAFLD prevalence, lack of population-based data and method-based diagnostic differences (Table 1) [37, 39-43, 48]. In spite of that there are some published data from some countries, but they are mostly not population-based surveys, rather they were done in certain categories of patients. However, this review is the first to shed some light on this epidemic, hopefully paving the way for further and more comprehensive work to be done in the near future.

Diabetes, Obesity and MS in Africa and Middle East

There is a very high prevalence of NAFLD in individuals with T2DM [1, 9]. An ultrasonographic study of patients with T2DM showed a 42.6% prevalence of NAFLD [9]. In another study, 127 of 204 diabetic patients displayed fatty infiltration on ultrasound, and 87% of the patients with fatty infiltration who consented to biopsy had histologic confirmation of NAFLD [54]. High serum TG levels and low serum HDL levels are very common in patients with NAFLD. The prevalence of NAFLD in individuals with dyslipidemia attending lipid clinics was estimated to be 50% [55]. Basaranoglu et al showed that high carbohydrate and fructose intake may be a risk factor for development of NAFLD and progress to NASH [56, 57]. Furthermore, Neuschwander-Tetri et al showed that dietary trans-fatty acid may also play a role in pathogenesis of NASH [58].

Up to 80% of obese people have NAFLD [59]. Obesity is a common and well-documented risk factor for NAFLD. Both excessive BMI and visceral obesity are recognized risk factors for NAFLD. In patients with severe obesity undergoing bariatric surgery, the prevalence of NAFLD can exceed 90% and up to 5% of patients may have unsuspected cirrhosis [1, 60-64]. NAFLD is associated with insulin resistance and MS (obesity, combined hyperlipidemia, T2DM, and high blood pressure) [59].

DM is a current challenge for most health authorities in Africa and Middle East. For instance, the prevalence of DM in Iraq was estimated to be around 9.33% while in Kuwait it was estimated to be around 21.1% [65, 66]. We have shown that the prevalence of undiagnosed diabetes in rural communities of north Sudan was 2.6% and the prevalence of impaired glucose tolerance was 1.6%. We identified increasing age and obesity as important risk factors [67]. Furthermore, we have also shown that in urban community in Sudan, the prevalence of diabetes is estimated to be around 19.1% [68]. This prevalence is almost similar to prevalence of diabetes in Iran (18%) but higher than Ethiopia where the prevalence was 5.1% [69, 70].

The Middle East and North African countries are regarded as highly prevalent countries with diabetes. For instance, in epidemiological study in 4,378 individuals in Africa and Middle East (AfME-14 countries) region, the prevalence of diabetes was shown to be 25% [71]. Importantly, several countries in these regions have diabetes prevalence of more than 18%, like Kuwait (21.1%), Lebanon (20.2%), Qatar (20.2%), Saudi Arabia (20.0), Bahrain (19.9%) UAE (19.2%) and Sudan (19.1%) [65]. The increase in DM prevalence has been attributed to increasing urbanization, aging, obesity, reduced physical activity and unhealthy diet [65].

Type 2 diabetes accounts for over 90% of diabetes cases in Sub-Saharan Africa, whilst the other 10% are represented by type 1 diabetes, gestational diabetes, and malnutrition-related diabetes [71]. There is strong association between type 2 diabetes and NAFLD. Therefore, it is plausible to suggest that epidemiological studies about NAFLD in these regions may reveal important outcomes for health policy makers in these regions. The other reason for the increase in NAFLD and diabetes is obesity and MS. Importantly, there is an increase in prevalence in obesity and MS in Africa and Middle East regions. Table 2 [72-115] presents studies about diabetes, MS and obesity in some African and Middle Eastern

Table 2. The Prevalence of Diabetes, Obesity and Metabolic Syndrome in Different Countries of Middle East and Africa [72-115]

No.	Country	Diabetes	Obesity	Metabolic syndrome	References
1	South Africa	7%	29.9%	23.3%	[72-74]
2	Ethiopia	8.9%	20%	12.5%	[75-77]
3	Egypt	14.9%	70%	7.4%	[78-80]
4	Ghana	1.9%	58%	35.9%	[81-83]
5	Saudi	17.6%	23.6%	28%	[84-86]
6	Iran	8.7%	14.2%	30.1%	[87-89]
7	Yemen	9.75%	8.8%	46%	[90-92]
8	Pakistan	16.68%	22.2%	46%	[93-95]
9	Jordan	17.1%	34.8%	37.4%	[96-98]
10	Kuwait	21.1%	78.4	32.8%	[94, 99, 100]
11	Nigeria	1.9%	15%	12.1%	[101-103]
12	Uganda	2.5%	2.3%	58%	[104-106]
13	Kenya	3.3%	8.9%	34.6%	[107-109]
14	Botswana	3.9%	12.7%	11%	[110-112]
15	United Republic of Tanzania	3.5%	19.2%	30%	[113-115]

countries.

Future Perspectives and Implications

In the light of the increasing prevalence of NAFLD, necessary steps for prevention need to be taken before the epidemic of NAFLD becomes uncontrollable. Given the rising incidence and prevalence of T2DM, obesity and MS among populations in Africa and Middle East regions, it is highly recommended that policy makers should make an accurate estimate of the prevalence of NAFLD in order to predict the number of those who will develop an advanced liver disease or NAFLD-related morbidities and to develop strategies for interventions to treat this condition. Liver transplant will come with huge financial cost and most countries in particular in Africa will find themselves struggling to survive such metabolic epidemic of NAFLD. The following are examples of challenges that urgently need to be addressed by the healthcare systems and healthcare workers in Africa and Middle East. 1) Despite the fact that there is a steady increase in prevalence of NAFLD, there is no cheap specific, reliable and sensitive biochemical marker to help establish diagnosis. 2) The gold standard diagnosis is through liver biopsy which is not routinely performed. However, clinical diagnosis may be based on liver ultrasound and biochemical liver function test. Still mass population screening in low-resource setting countries may not be feasible. 3) In the view of the increase in epidemic of obesity and NAFLD, financial cost may be higher for some African countries. 4) NAFLD is associated with an increased risk of developing diabetes. This may already add to the high prevalence of epidemic of diabetes and associated diabetes complications. 5) NAFLD is a multisystem disorder (CKD, CVD and chronic liver disease) and this may increase the burden of non-communicable diseases. 6) NAFLD will increase the burden on the,

already limited number of, hepatologists in the region in dealing with increased numbers of individuals with liver disease such as NASH, cirrhosis and HCC. 7) NAFLD is one of the leading causes of liver transplantation. This may represent current and future challenges for most of the healthcare systems in resource-poor countries. 8) Health education for all health professions is needed, including public health specialists. This is important, as the only treatment of NAFLD is weight reduction. 9) Epidemiological studies may reveal the accurate status of the prevalence in these regions. 10) Training of more diabetologists, hepatologists and other health care professions, e.g. dieticians, lab specialists and imaging technologists on issues related to NAFLD is needed so as to increase the number of manpower to deal with this epidemic. 11) The need for scientific studies to explore the various disease aspects may add further burden to the cost of NAFLD. 12) NAFLD can be associated with HIV/AIDS. The high prevalence of HIV in Africa may raise the concern about an increase in prevalence of MS, diabetes, NAFLD and dyslipidemia. Ahmed et al suggested that the Metabolic Clinic in Milton Keynes University Hospital, UK for individuals living with HIV is currently one of the option for prevention of NAFLD [116]. Therefore, metabolic clinic in HIV centers in Africa may decrease the burden of non-communicable diseases among HIV population.

Conclusion

NAFLD will be a challenge for healthcare systems, diabetologists and hepatologists in Africa and the Middle East. This is attributable to the remarkable increase in the epidemic of obesity and T2DM. The lack of biochemical markers and the high financial cost associated with the burden of NAFLD will be beyond the capacity of most African and Middle East countries. One particular problem extremely difficult to manage in

the region is the need for liver transplantation. Therefore, a concentrated global initiative by all health authorities in the region is urgently needed. Furthermore, health education and public health awareness are the essence to stop the increasing prevalence of NAFLD in Africa and Middle East.

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