Non-alcoholic fatty liver disease in sub-Saharan Africa 1

Epidemiology, risk factors, social determinants of health, and current management for non-alcoholic fatty liver disease in sub-Saharan Africa

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Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease globally and is estimated to affect approximately 25% of the world's population. Data about the prevalence and incidence of NAFLD in Africa are scarce, but the prevalence is estimated to be 13·5% for the general population. This is likely to be an underestimate considering the increasing burden of non-communicable diseases, particularly the rising prevalence of obesity and type 2 diabetes, driven by the overlapping challenges of food insecurity, nutritional transition, and associated increased consumption of calorie-dense foods. Establishing the true prevalence of NAFLD, raising public awareness around the risk factors behind the increase in NAFLD, and proactively addressing all components of metabolic syndrome will be important to combat this silent epidemic, which will have long-term health-care costs and economic consequences for the region.

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This is the first in a Series of two papers on non-alcoholic fatty liver disease in sub-Saharan Africa

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the leading global cause of chronic liver disease, estimated to affect approximately 25% of the world's population.[1] Data for the prevalence and incidence of NAFLD in Africa are scarce. A meta-analysis reported a NAFLD prevalence of 13·5% (95% CI 5·67–28·7), ranging from 9% in Nigeria to 20% in Sudan.[1–3]

NAFLD, defined as the presence of more than 5% hepatic steatosis without causative factors such as alcohol, certain drugs, or other defined liver disorders, encompasses the histological spectrum of simple steatosis, non-alcoholic steatohepatitis (NASH), and advanced fibrosis. Overall, 3–5% of patients with NAFLD develop NASH, with 1–2% developing advanced fibrosis.[1,2]

Extrahepatic manifestations of NAFLD include cardiovascular disease, cerebrovascular disease, chronic kidney disease, extrahepatic malignancies, polycystic ovary syndrome, and sleep apnoea.[4] NASH with advanced hepatic fibrosis can rapidly progress to cirrhosis and decompensate with hepatic encephalopathy, ascites, variceal bleeding, and death.[5] Although liver-related mortality is increased, cardiovascular disease remains the leading cause of death in patients with NAFLD and liver fibrosis stages F3 or F4.[6]

NAFLD is seldom considered as a complication of metabolic syndrome, despite its increasing prevalence and associated morbidity and mortality with long-term health-care costs and consequent economic burden.[4,7,8] NAFLD is more likely to be diagnosed incidentally, as specific screening is seldom recommended in clinical management guidelines for obesity, diabetes, dyslipidaemia, and hypertension. The risk of hepatocellular carcinoma, which can occur in the absence of cirrhosis, is underestimated. Determining a more precise prevalence of NAFLD and associated disorders, and in turn addressing the disease burden in sub-Saharan Africa, will require increased awareness and access to affordable, reliable diagnostic tests.

The burden of non-communicable diseases associated with NAFLD in sub-Saharan Africa

A transition from the infectious diseases of tuberculosis, malaria, and HIV to an increasing burden of non-communicable diseases (NCDs) is occurring in sub-Saharan Africa.[9] According to the 2017 Global Burden of Disease (GBD) study, the all-age total disability-adjusted life-years (DALYs) due to NCDs increased by 67% between 1990 (90·6 million; 95% uncertainty interval 81·0–101·9) and 2017 (151·3 million; 133·4–171·8). This increase reflected a rise in the proportion of total DALYs attributable to NCDs, from 18·6% (17·1–20·4) to 29·8% (27·6–32·0). Cardiovascular diseases were the second leading cause of NCD burden in 2017, resulting in 22·9 million DALYs (21·5–24·3), which is 15·1% of the total NCD burden.[9] In southern sub-Saharan Africa, diabetes and kidney disease were particularly onerous, with the crude rate of 1927·2 DALYs per 100 000 population (1693·8–2191·9) being almost twice that of other sub-Saharan African regions (1233·3 DALYs per 100 000 population [1047·6–1432·8] in central, 887·4 [771·0–1016·7] in western, and 915·2 [811·3–1029·2] in eastern sub-Saharan Africa).[9] Africans with NCDs are younger by 10 years or more compared with people in other world regions.[10] Thus, it is anticipated that sub-Saharan Africa will experience the largest global increase in NCD-related mortality.[11]

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Metabolic syndrome

Metabolic syndrome is core to NCDs and the development of NAFLD. An individual with metabolic syndrome is three times more likely to have a cardiovascular or cerebrovascular event and twice as likely to die from that event as an individual without metabolic syndrome.[12] A systematic review and meta-analysis[12] of 65 studies in 14 different countries, including 34 324 healthy participants aged 16 years or older, reported a pooled prevalence of metabolic syndrome in sub-Saharan Africa ranging from 11·1% to 23·9% depending on various diagnostic criteria used. The prevalence of metabolic syndrome in sub-Saharan Africa was higher in women than in men and tended towards being greater in semi-urban and urban areas than in rural areas. Prevalence of metabolic syndrome was highest in southern Africa, consistent with the higher rates of obesity there, followed by eastern, western, and central Africa.[12,13]

Obesity

WHO defines overweight as BMI 25 kg/m² or higher, and obesity as BMI 30 kg/m² or higher.[14] A 2017 study revealed that between 1980 and 2014, the age-standardised body-mass index (BMI) in sub-Saharan Africa increased from 21·0 kg/m² (95% credible interval [CrI] 20·3–21·7) to 23·0 kg/m² (22·7–23·3) in men, and from 21·9 kg/m² (21·3–22·5) to 24·9 kg/m² (24·6–25·1) in women.[13] Particularly concerning is the increasing prevalence of overweight and obesity in children, with a systematic review showing a transition towards overweight and obesity among school-aged children and youth in sub-Saharan Africa. In children, the weighted average of overweight and obesity was 10·6% and that of obesity alone was 2·5%, being higher in girls, individuals living in urban areas, and individuals of higher socioeconomic status.[13,15]

Diabetes

Between 2017 and 2045, Africa is projected to experience the highest relative increase worldwide in diabetes: the number of adults with all types of diabetes is predicted to increase from 16 million to 41 million people, a 156% increase.[16] Between 1980 and 2014, the age-standardised prevalence of diabetes increased from 3·4% (95% CrI 1·5–6·3) to 8·5% (6·5–10·8) in men and from 4·1% (2·0–7·5) to 8·9% (6·9–11·2) in women. A positive association (correlation coefficient approximately 0·9) was observed between mean BMI and diabetes prevalence in 1980 and 2014.[13] A 2020 meta-analysis reported an average pooled prevalence of undiagnosed diabetes among adults in Africa of 3·85% (95% CI 3·10–4·60) and in the different regions: 4·72% (2·64–6·80) in western, 4·43% (3·12–5·74) in eastern, 4·27% (1·77–6·76) in northern, and 1·46% (0·57–2·34) in southern Africa.[17] NAFLD prevalence in patients with type 2 diabetes in Africa, based on four studies, was 30·39% (11·64–67·09).[18]

Hypertension

A systematic review and meta-analysis of 33 studies done in sub-Saharan Africa (110 414 participants, mean age 40 years) assessing the burden of hypertension between 2000 and 2013 confirmed a pooled prevalence of 30% (95% CI 27–34). 18% (14–22) were receiving treatment and blood pressure control was attained in 7% (5–8).[19]

Dyslipidaemia

In a 2018 systematic review of 177 population-based studies with 294 063 participants, the pooled prevalence of dyslipidaemia, a leading contributor to cardiovascular disease, was 25·5% (95% CI 20·0–31·4) in the general African population.[20] Detection and effective treatment of dyslipidaemia is important to reduce the risk of NAFLD and reduce cardiovascular diseases in Africa.

Chronic kidney disease

A meta-analysis of 98 studies involving 98 432 individuals reported an overall prevalence of 15·8% (95% CI 12·1–19·9) of chronic kidney disease stages 1 to 5 and a 4·6% (3·3–6·1) prevalence of chronic kidney disease stages 3 to 5 for the general population in Africa.[21] A cross-sectional population-based study suggested that the increasing incidence of hypertension, HIV, and diabetes in Africa were all independently associated with chronic kidney disease.[22]

Risk factors and prognostic indicators for NAFLD

NAFLD is the liver manifestation of metabolic syndrome and is part of a multisystem disease.[4] The relationship between NAFLD and metabolic syndrome has been consolidated by the proposal to amend the nomenclature for NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). The definition of MAFLD is based on the presence of hepatic steatosis with at least one of the following: overweight, obesity, type 2 diabetes, or metabolic disease. MAFLD is not a diagnosis of exclusion.[23] Nevertheless, the pathogenesis of NAFLD involves a complex interplay between genetics, epigenetics (gut microbiome), and environmental triggers, with obesity and type 2 diabetes being the predominant modulators of NAFLD and NASH.[2,6,24,25]

Clinical predictors of NASH and fibrosis include male sex, elevated aminotransferases, type 2 diabetes, age older than 50 years, Hispanic ethnicity, and having a first-degree relative with advanced NAFLD fibrosis.[26,27] The risk of advanced fibrosis was 12-times higher in first-degree relatives of individuals with NAFLD cirrhosis, after adjusting for age, sex, BMI, type 2 diabetes, and Hispanic ethnicity.[28] An increasing number of metabolic diseases are associated with increased risk of progressive liver disease and reduced survival.[26,27] The odds ratios for the development of moderate-to-severe fibrosis for metabolic risk factors are 1·61 (95% CI 1·21–2·01; p=0·0374) for hypertension, 1·64 (1·13–2·17; p=0·0258) for type 2

diabetes, 1·69 (1·11–2·28; p=0·0246) for type 2 diabetes and hypertension, and 1·72 (1·13–2·31; p=0·0205) for type 2 diabetes, hypertension, and visceral obesity.[27]

Obesity

Obesity is associated with a 3·5-times increased risk of NAFLD.[29] There is a dose-dependent relationship between BMI and NAFLD risk (per one-unit increment in BMI, relative risk 1·20, 95% CI 1·14–1·26, p<0·001).[30] Visceral adiposity and its surrogate marker, waist circumference, is a key risk factor for many complications of metabolic syndrome and has a stronger association with NAFLD than does BMI alone, predisposing to a greater risk of NASH and fibrosis.[31] Both BMI and waist circumference should be measured to assess the risk and progression of NAFLD. Increased visceral adiposity is a risk factor in the development of NAFLD in lean individuals (ie, BMI <25 kg/m²), especially in Asian populations (in whom lean BMI is <23 kg/m²),[2,32] with the *PNPLA3* I148M allele playing a contributing role.[33]

Type 2 diabetes

The relationship between NAFLD and type 2 diabetes is bidirectional. The global prevalence of NAFLD in patients with type 2 diabetes, based on ultrasound or proton magnetic resonance spectroscopy, is 55·48% (95% CI 47·26–63·67).[18] NAFLD is associated with a roughly 2·2-fold increased risk of incident diabetes, with risk paralleling the underlying NAFLD severity.[34] Type 2 diabetes accelerates the progression of liver disease in NAFLD and is a predictor of advanced fibrosis and mortality.[2,34] The global prevalence of NASH among individuals with type 2 diabetes is 37·3% (95% CI 24·7–50·0), with advanced fibrosis occurring in 17·0% (7·2–34·8) of patients with NAFLD and type 2 diabetes.[35]

Dyslipidaemia

The global pooled dyslipidaemia prevalence estimates are 69·2% (95% CI 49·9–83·5) in patients with NAFLD and 72·1% (54·6–84·8) in patients with NASH.[1] The pooled overall prevalence estimates for hypertriglyceridaemia are 40·7% (30·8–51·5) in patients with NAFLD and 83·3% (36·87–97·72) in patients with NASH.[1] Ratios of high total cholesterol to HDL cholesterol and high triglyceride to HDL cholesterol are associated with increased risk of advanced NAFLD.[36]

Polycystic ovary syndrome

Polycystic ovary syndrome is associated with insulin resistance and metabolic syndrome, and affects about 10% of the female population. This is a high-risk group for the development of NAFLD and NASH.[37]

Gut microbiome

The gastrointestinal tract and the gut microbiome composition play a role in the development of NAFLD. Clinical studies have shown that NAFLD is associated with dysbiosis, characterised by increased growth of bacteria such as Enterobacteriaceae and *Escherichia coli*, and a decrease in *Faecalibacterium prausnitzii*. Intestinal dysbiosis and microbiome instability influenced by the consumption of saturated fatty acids, fructose, and advanced glycated end-products contribute to development of liver disease. Dysbiosis is associated with altered production of short-chain fatty acids; altered choline and bile acid metabolism; increased lipopolysaccharide-containing bacteria and bacteria-derived ethanol; increased intestinal permeability; and promotion of chronic low-grade inflammation with induction of pro-inflammatory cytokines (IL-1, IL-6, and TNFα), activation of hepatic TLR4, and generation of reactive oxygen species. All of these are contributing factors to the development of NAFLD.[4,38]

Epidemiology of NAFLD in sub-Saharan Africa

Sub-Saharan Africa, a middle-to-lower-income region, has varied evolving economies and increasing urbanisation. The effect is pro-NAFLD dietary and behavioural changes, including a move towards a more sedentary, urban lifestyle. In food-insecure countries (ie, countries in which individuals lack regular access to enough safe and nutritious food for normal growth and development and an active and healthy life), transition to an increased use of inexpensive, low nutritional value, higher calorie options drives obesity and metabolic syndrome. Given this issue, WHO and the UN General Assembly have identified food insecurity as a global health risk because it promotes poor metabolic health.[39,40] A meta-analysis focusing on the relationship between food insecurity and metabolic risk factors in sub-Saharan Africa corroborates a high pooled prevalence estimate of key metabolic risk factors among food-insecure participants (41·8% [95% CI 33·2–50·8, I^2=99·5%]).[41] The most prevalent risk factors were dyslipidaemia (27·6% [6·5–54·9]), hypertension (24·7% [15·6–35·1]), and overweight (15·8% [10·6–21·7]).[41] Reliable data about prevalence and incidence of NAFLD in sub-Saharan Africa are lacking.[6] Estimates based on GBD data (1990–2017) suggested that the age-standardised prevalence of NAFLD in sub-Saharan Africa ranged from 5·0–7·5% to 10·1–12·5%, with 20·1–25·0% in Mauritius. Ghana and Benin had the highest estimated annual percentage change of 1·26–1·5.[42]

Western sub-Saharan Africa

Regional data about the incidence of NAFLD in western sub-Saharan Africa are scant. Using data derived from the GBD study, NAFLD cases have increased from 8·4 per million in 1990 to 23·2 per million in 2017, with the age-standardised prevalence increasing from 6·5% to 8·0%.[42] This yields an estimated annual percentage change in age-standardised prevalence from 1990 to 2017 of 0·69 (95% CI 0·63–0·75).[42] NAFLD risk factors, including obesity and type 2

diabetes, are increasing in the region.[43–46] In Nigeria, NAFLD prevalence has been reported as 9·5–16·7% in people with type 2 diabetes and 1·2–4·5% in people without diabetes.[45,47] NAFLD was associated with central obesity (waist circumference >88 cm in women and >102 cm in men) and dyslipidaemia.[45]

In Ghana, obesity prevalence has increased from 5·5% to 25·4% in the past decade, with a rising NAFLD incidence being a potential consequence of this.[48,49] A Ghanaian cross-sectional study of 88 premenopausal and 97 postmenopausal women[50] revealed an overall prevalence of metabolic syndrome of 25% (46 of 185 women) and NAFLD prevalence of 40% (74 of 185 women). Among postmenopausal women, metabolic syndrome prevalence was 33% (32 of 97 women) and NAFLD prevalence was 49% (48 of 97 women), higher than the 16% prevalence of metabolic syndrome (14 of 88) and 30% prevalence of NAFLD (26 of 88) observed in premenopausal women.[50] Coronary artery disease and comorbidities of metabolic syndrome and NAFLD, were significantly correlated (odds ratio 5·2, 95% CI 2·2–12·4; p<0·001).[50] An ultrasound-based study of 97 patients undergoing elective general and gynaecological procedures found that 54 (56%) had features of NAFLD, with associated prolonged hospital stay.[51]

Central sub-Saharan Africa

In central sub-Saharan Africa, GBD estimates noted NAFLD cases increasing from 2·3 per million in 1990 to 6·2 per million in 2017, with age-standardised prevalence increasing from 6·5% to 7·5%.[42] The estimated annual percentage change in age-standardised prevalence from 1990 to 2017 was 0·58 (0·50–0·67).[42] In urban-based individuals with metabolic syndrome, high NAFLD prevalences have been documented: 37·2% in Burundi and 38·7% in Congo (Brazzaville).[52,53]

Obesity is less prevalent in the central African region than in other regions. For example, the proportion of individuals with BMI 30 kg/m² or higher in Equatorial Guinea is 17·5% (world ranking 119); in Cameroon, 11·4% (135); in Congo (Brazzaville), 11·0% (136); in DR Congo, 6·7% (177); in Chad, 6·1% (178); in Rwanda, 5·8% (180); and in Burundi, 5·4% (186).[53] However, obesity prevalence has increased progressively over the past two decades. For example, in Burundi it has increased from 2·6% to 5·4% and in DR Congo it has increased from 4·4 to 6·7%.[54] This trend relates to lifestyle changes mostly in the urban middle classes.[55] Notably, the traditional local diet appears to be protective, with foresters (more vegetarian diet) and the Sahelians (more meat-based diet) having a lower prevalence of obesity.[55]

NAFLD risk factors such as diabetes are increasing in prevalence in central Africa; for example, in Cameroon, age-standardised prevalence of diabetes increased from 2% in 1999 to 5·8% in 2018.[13] This finding could suggest an epidemiological transition, with NAFLD emerging at greater rates over time.

Southern sub-Saharan Africa

Estimates using GBD data show that NAFLD cases have increased from 3·7 per million in 1990 to 8·1 per million in 2017, with the age-standardised prevalence increasing from 9·3% to 11·4%.[42] This gives an estimated annual percentage change in age-standardised prevalence of 0·73 (95% CI 0·69–0·77) during this period.[42] Risk factors such as diabetes and obesity are invariably surrogate markers of the potential NAFLD burden. Across all countries in southern sub-Saharan Africa, the age-standardised prevalence of diabetes increased between 1980 and 2014.[56] For example, in Botswana in 1980, diabetes prevalence was 2% in men and 3·8% in women, increasing to 7·6% in men and 9·5% in women in 2014. Similarly, in South Africa, the prevalence increased from 4·8% in men and 7·7% in women in 1980, to 9·7% in men and 12·6% in women in 2014.[56]

Obesity rates in southern sub-Saharan Africa are the highest in sub-Saharan Africa. Age-standardised obesity estimates are 11·7% in men and 37·0% in women, and combined estimates of obesity and overweight are 34·2% in men and 63·7% in women.[57] Botswana and South Africa are most affected, with 26·5–38·6% of men and 50·7–64·0% of women being overweight, and 7·0–14·5% of men and 25·5–38·5% of women being obese, in 2016.[58] Malawi and Madagascar are only marginally affected, probably reflecting differing socioeconomic levels.[58] A South African NAFLD study among overweight or obese adults attending a liver clinic evaluated liver biopsies of 127 patients.[59] The prevalence of NAFLD was 87% (n=111), simple steatosis was 51% (n=65), NASH was 36% (n=46), and advanced liver fibrosis was 17% (n=20). All patients with NAFLD had insulin resistance, but only 5% of patients were Black, the majority being either of mixed ancestry or White.[59]

Of note, HIV infection and its therapies and metabolic consequences are potential additive factors that might affect NAFLD prevalence in southern sub-Saharan Africa, the region with the highest HIV prevalence globally.[60] Retrospective data of liver biopsies in a South African study showed liver steatosis was more frequent in HIV-positive patients (23 [21%] of 108) compared with HIV-negative patients (three [12%] of 25).[61] A prospective study of 301 HIV-positive patients undergoing a liver biopsy reported NAFLD in 58 (19%) patients, of whom 16 (28%) had steatohepatitis.[62]

Eastern sub-Saharan Africa

Using GBD data, estimates for NAFLD cases increased from 7·1 per million in 1990 to 18·0 per million in 2017, with age-standardised prevalence increasing from 6·0% to 7·0%.[42] The estimated annual percentage change in age-standardised prevalence in this time period was 0·58 (95% CI 0·55–0·60).[42] Data from the GBD study showed rising diabetes trends, with incident cases of 314 000 in 1990 increasing to 726 000 in 2017, with an estimated annual percentage change in incident cases of 0·25.[63]

Ethiopia was estimated to have 2·6 million people (95% CI 1·1–3·8) with diabetes in 2017.[15,64] Prevalence of diabetes in adults aged 35 years or older in a cross-sectional population-based survey in northwest Ethiopia was 5·1% (95% CI 3·8–6·4) for urban dwellers and 2·1% (1·2–2·9) for rural dwellers.[65] In a 2020 systematic review and meta-analysis of 16 studies and 19 527 participants, the estimated pooled prevalence of overweight in adult Ethiopians was 19% and that of obesity was 5·4%.[66] There is regional variation in Ethiopia; the prevalence of overweight varied from 16·1% to 25·3%, and that of obesity from 5·6% to 16·2%.[67–70] A cross-sectional study from southeast Ethiopia found a prevalence of NAFLD of 73% (70 of 96 people) in those with type 2 diabetes.[71] In an unmatched case-control study among patients attending a hepatology and gastroenterology clinic in Addis Ababa, 163 (20%) of 812 patients with chronic liver disease had NAFLD and 192 (24%) of 798 without chronic liver disease had NAFLD.[72] NCDs in Ethiopia were the leading contributors to age-standardised death rates in 2015, with 711 deaths per 100 000 people (95% uncertainty interval 468·8–1036·2). Metabolic risk factors included high rates of hypertension (16%), hyperglycaemia (5·9%), hypercholesterolaemia (5·6%), overweight (5·2%), and obesity (1·2%).[73]

A 2014 population-based NAFLD study suggested a prevalence of 20% in the Sudanese population.[74] A subsequent cross-sectional hospital-based study revealed an overall NAFLD prevalence of 50% (84 of 167) in individuals with diabetes, with overweight, obesity, visceral obesity, and dyslipidaemia being significantly associated with NAFLD; having two to three metabolic syndrome components was associated with a higher prevalence of NAFLD (12% NAFLD prevalence among patients with two components and 21% among those with three components).[75] In a population-based urban study in north Sudan, the overall prevalence of diabetes was 19·1% (182 of 954 people) and impaired glucose tolerance 9·5% (91 of 954 people).[76] A study among rural communities of north Sudan has shown that the prevalence of undiagnosed diabetes was 2·6% (29 of 1111 people) and impaired glucose tolerance 1·3% (14 of 1111 people).[77]

An analysis of healthy Black Africans from a global study to determine reference intervals found a metabolic syndrome prevalence of 25·6% (95% CI 22·0–29·5) in urban Kenyans.[78]

Overall, the reported NAFLD prevalence is probably an underestimate, as the burden of NCDs and rising prevalence of overweight and obesity and diabetes in eastern sub-Saharan Africa suggest NAFLD is likely to be more prevalent.

Social and other determinants of NAFLD in sub-Saharan Africa

A complete understanding of the drivers of NAFLD in sub-Saharan Africa is required to enable an appropriate response to the growing problem. Many factors, including variability in dietary composition, exercise and lifestyle habits, environmental factors, and genetics, can influence the burden of NAFLD in the region. Many sub-Saharan African countries are undergoing rapid but variable epidemiological transitions driven by fast urbanisation; 41·3% of the population were living in urban areas in 2020 compared with 27·4% in 1990.[79] The importance of changes in nutrient intake and their effect on the development of obesity and type 2 diabetes are known. Factors influencing nutrition transition in Africa include food insecurity, urbanisation, and economic growth with increases in income and globalisation.[41,80,81] Gross domestic product in many sub-Saharan African countries has progressively increased, while the UN Food and Agriculture Organisation has shown a steady increase in daily caloric intake in Africa as a consequence of the nutritional transition.[82] Traditional diets, which are high in fibre and low in fat, are being substituted by more calorie-dense diets with increased intake of sugar-sweetened beverages and fast foods and increased fat and protein consumption.[38,80,81]

Obesity and type 2 diabetes have been associated with soft drink consumption, and soft drink intake is often higher in patients with NAFLD than in those without NAFLD.[83–85] Globally, consumption of sugar-sweetened beverages is increasing, especially in low-income and middle-income countries, including in sub-Saharan Africa.[84] People in some sub-Saharan African countries, such as South Africa, have considerably higher intake of sugar-sweetened beverages, correlating with the highest obesity prevalence in sub-Saharan Africa.[85,86] The addition of fructose or sucrose to beverages and foods contributes to NAFLD development through increasing liver triglyceride synthesis. Data from mouse models suggest that fructose might promote hepatic triglyceride synthesis and NAFLD by damaging the intestinal barrier and promoting endotoxaemia; the endotoxin interacts with TLR4, triggering TNFα production by liver macrophages and thereby inducing lipogenic enzymes.[87]

Small observational studies show an association between physical inactivity and NAFLD, suggesting that sedentary behaviour increases susceptibility to NAFLD and might be causative.[88] Moreover, reduced physical activity can increase the risk of NASH and fibrosis among patients with proven NAFLD.[89] Reduced physical activity, poor aerobic fitness, and overweight and obesity all contribute to hepatic insulin resistance, reduced mitochondrial function and triglyceride export, and increased de-novo lipogenesis and fatty acid uptake, leading collectively to increased hepatic lipid accumulation.[88] A meta-analysis including 28 randomised controlled trials showed that exercise, independent of diet, significantly reduces alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic triglyceride content.[90]

In an individual participant data meta-analysis across ten sub-Saharan Africa countries (26 022 participants),

18·9% (95% CI 14·3–24·1; I^2=99·0%) of adults (≥18 years) participated in leisure-time physical activity. Men were more likely to participate in leisure-time physical activity than women (risk ratio [RR] for women 0·43, 95% CI 0·32–0·60; p<0·001; I^2=97·5%), with age inversely associated with participation. Higher levels of education were associated with increased participation in leisure-time physical activity (RR 1·30, 95% CI 1·09–1·55; p=0·004; I^2=98·1%), with people living in rural areas or self-employed being less likely to participate. These associations remained after adjusting for time spent physically active at work or through active travel.[91]

It is increasingly recognised that genetic factors might account for the high NAFLD prevalence in some populations. Ethnic variation in NAFLD has been described, with a lower prevalence reported in people of African descent.[92] Although the lower prevalence might be accounted for to some extent by under-recognition, genetic factors also play a role.[93] A number of candidate genes have been linked with NAFLD, including *PNPLA3*, *MBOAT7*, and *TM6SF2*.[94] The *PNPLA3* rs738409 C→G single nucleotide polymorphism has been shown to be independently associated with NAFLD and an increased risk of hepatocellular carcinoma in patients with cirrhosis.[95] The prevalence of this mutation differs among ethnic groups, with the lowest expression among African Americans, in whom a protective *PNPLA3* allele, rs6006460 G→T, was found to be common.[96]

Subcutaneous fat stores might in fact be protective. In a South African study of 106 female volunteers, Black African women had a lower hepatic fat content on liver CT scan than their Indian and White counterparts, despite having a higher level of total body fat, subcutaneous body fat, BMI, and waist circumference. Subcutaneous fat was found to be a significant negative determinant of hepatic fat content.[97]

There are no genetic studies of NAFLD from sub-Saharan Africa and a crucial need exists to better understand the risk of NAFLD in the region, as well as highlighting the risk factors for disease progression.

Management of NAFLD

In sub-Saharan Africa, the management of NAFLD must be centred on prevention. Irrespective of the scarce data available, specifically about NASH in sub-Saharan Africa, metabolic factors promoting NAFLD are abundantly present, with an increasing incidence on the continent. Sub-Saharan Africa is in a unique position to potentially offset the emerging NAFLD burden through aggressively pursuing prevention and primary care strategies. Management requires a diagnosis in the first instance and screening for NAFLD. Using a simple, non-invasive, cost-effective test such as the Fibrosis-4 (FIB-4) index would be of value in resource-constrained countries in targeted populations, such as people with obesity or type 2 diabetes.[43] Coupling FIB-4 with transient elastography for the diagnosis of fibrosis, and with the controlled attenuation parameter of FibroScan for steatosis, can optimise performance, with cost being a limiting factor to access and availability.[6,43]

General management strategies for NAFLD

Alcohol consumption

For a NAFLD diagnosis, alcohol consumption greater than 20 g/day for women and 30 g/day for men requires exclusion.[98] However, the effect of moderate amounts of alcohol use (<30 g/day) in the general population is conflicting. There are cardiovascular and metabolic benefits of moderate alcohol consumption that might be offset by the risks of cancer-related mortality and all-cause mortality.[99] Long-term moderate alcohol consumption data for people with metabolic cofactors suggested that alcohol was a major factor in promoting liver disease, even when average alcohol consumption was within the limits currently defined for NAFLD.[100] Overall, moderate alcohol consumption has been associated with a reduction in overall mortality, mostly accounted for by cardiovascular mortality benefits. However, no protective benefit has yet been conclusively shown in people with NAFLD.[101] Another aspect of alcohol consumption relevant to NAFLD is the negative caloric effects of alcohol on diet and weight loss. Thus, alcohol abstinence remains the recommended advice for patients with NAFLD.

Lifestyle changes, dietary intervention, weight loss, and physical activity

Diet, as part of lifestyle changes, is key in NAFLD treatment. It has the strongest association with improved outcomes of all interventions and improves histology in NASH. A decreased caloric intake and reductions of at least 5% of bodyweight achieve a significant reduction in intrahepatic lipid content with a reduction in NAFLD activity scores.[102] A meta-analysis of eight studies showed that weight loss of 7% or more was associated with improved NAFLD activity scores, while a prospective paired liver biopsy study of 261 patients found that 10% bodyweight reduction produced complete resolution of NASH in 26 (90%) of 29 patients.[103,104] In essence, a 7–10% or greater reduction in bodyweight is associated with improvement in all NASH histological parameters, with at least one stage reduction in fibrosis; furthermore, cardiovascular and type 2 diabetes risks also decrease.[105]

This weight reduction can only be achieved with a calorically restricted diet of 500–1000 kcal/day or a total intake of 1200–1800 kcal/day, low in fat and carbohydrates and rich in fibre, to effect 500 g to 1 kg weight loss per week. Data from analysis of the PIVENS and FLINT trials[105] of adults with NASH, in which paired liver biopsies were done, clearly showed that weight loss was associated with beneficial changes in both liver enzymes and NASH histology scores. Each kilogram of weight loss was associated with a 7% increase in odds of NASH resolution (95% CI 3–10; p<0·001), with no deterioration

in fibrosis. There was a 5% (95% CI 1–8; p=0·01) increase in likelihood of fibrosis improvement.[105] Dietary intervention and weight loss not only have clear benefits for NASH but also have cardiovascular, diabetes-related, and overall health advantages. With the rising obesity pandemic globally, it is self-evident that public health measures in sub-Saharan Africa need to target the prevention of weight gain while strongly supporting weight loss.

The role of sugar-sweetened beverages in promoting obesity, type 2 diabetes, and thus NAFLD risk is substantial, and it is advisable that population-wide interventions are introduced to reduce consumption of sugar-sweetened beverages in sub-Saharan Africa.

Exercise improves cardiovascular comorbidities, insulin-resistance, and hepatic triglyceride content. The general consensus is that exercise should be prescribed for 150–200 minutes per week in three to five sessions of moderate-intensity aerobic and resistance exercise.[102] A systematic review showed that resistance exercise improves NAFLD with lower energy consumption. This is a useful intervention in patients with NAFLD who have impaired cardiorespiratory fitness or are unable to do aerobic exercise.[106] Exercise at sustained levels is also beneficial in maintaining weight loss.[107]

Vitamin E

Vitamin E is an antioxidant that has been extensively studied for NAFLD, although there are few data from randomised controlled trials of vitamin E alone for NASH. The landmark PIVENS study showed that vitamin E reduced inflammation and steatosis but not fibrosis in patients with NASH without cirrhosis or diabetes.[108] In patients with diabetes, there was no improvement in inflammation or fibrosis. A 2021 systematic review and meta-analysis of eight studies concluded that vitamin E significantly reduced ALT and AST and improved liver pathology in all histological parameters, as well as lowering LDL cholesterol, fasting blood glucose, and serum leptin values.[109] Other data have indicated a benefit of vitamin E in patients with advanced fibrosis or cirrhosis (in both those with diabetes and those without diabetes) and improved transplant-free survival.[110] Concerns have been raised regarding long-term vitamin E treatment and higher all-cause mortality, risk of haemorrhagic stroke, and risk of prostate cancer in men aged 50 years or older, but were not noted in this study.[110]

Managing the comorbidities of NAFLD

Type 2 diabetes

Appropriate glycaemic control is associated with a reduction in steatosis, a decrease in serum amino-transferases, and improvement of liver inflammation and fibrosis. Achieving glycaemic control requires appropriate use of anti-diabetic therapies. In sub-Saharan Africa, choice of appropriate anti-diabetic therapies is incumbent upon patient requirements as well as drug availability, access to glycaemic monitoring, and laboratory or point-of-care HbA_{1c} testing. All of these factors are essential to achieving glycaemic control.

Specific anti-diabetic drugs might have potential effectiveness in NAFLD, beyond their glycaemic effect. Metformin, while improving HbA_{1c}, also has some modest weight loss benefits.[111] The data are not supportive with regard to histological improvement in NALFD, but metformin might have an effect on reducing the incidence of hepatocellular carcinoma.[112] Given the absence of supportive data showing significant histological improvement, metformin is not currently recommended for treatment of liver disease in patients with NAFLD. Metformin remains an important, cost-effective therapy in sub-Saharan Africa for type 2 diabetes, although lifestyle modifications are required for maximum benefit.[37,113]

The thiazolidinediones, including rosiglitazone and pioglitazone, have been extensively studied for the treatment of NASH. In a meta-analysis of eight randomised controlled trials, use of pioglitazone improved advanced fibrosis in NASH, including in individuals without diabetes.[114] However, these drugs cause weight gain, oedema, osteoporosis, and bone fractures, especially in post-menopausal women.[115] Additionally, these medications have been associated with an increased risk of cardiovascular events and possibly bladder cancer.[116]

Other anti-diabetic drugs have been associated with potentially beneficial effects in NAFLD. Liraglutide, a GLP-1 agonist, has shown significant improvement in glycaemic control and a reduction in cardiovascular events and deaths in people with diabetes.[117] In a small study, liraglutide was associated with a significant improvement in NASH histology (reduced progression of fibrosis), ALT improvement, and weight loss.[118] Semaglutide administered subcutaneously daily in a phase 2 placebo-controlled trial resulted in a significantly greater resolution of NASH than placebo, with no benefit on fibrosis observed.[119] Weight loss was another observation, and was corroborated in a once-weekly dosing regimen of 2·4 mg yielding significant, sustained, and clinically relevant reduction in weight in over-weight or obese participants, in both individuals without diabetes and those with diabetes.[120,121]

Data about the effects of DPP-4 inhibitors in NAFLD are conflicting. Data from mouse models support these agents in preventing NASH-related liver fibrosis and development of hepatocellular carcinoma, independent of benefits for diabetes.[122] However, clinical data suggest that DPP-4 inhibitors do not improve histological features of NAFLD or NASH, despite clear improvements in HbA_{1c} and liver enzymes.[123] SGLT2 inhibitors have renoprotective and cardioprotective benefits. Similar to DPP-4 inhibitors, mouse data for SGLT2 inhibitors and NAFLD improvement are supportive, but data in patients with NAFLD are scant.[124] Liver aminotransferases improve, as does glycaemic control, but liver histological

Search strategy and selection criteria

References for this paper were identified through searches of PubMed with the search terms "non-alcoholic fatty liver disease", "NAFLD", "non-communicable diseases", "risk factors", "epidemiology", "social determinants of health", "current management", and "sub-Saharan Africa" from Jan 1, 2011, to June 15, 2021. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this paper.

improvement and long-term safety data in NAFLD are lacking.[125]

Lifestyle modification, physical activity, and weight loss remain the mainstay of NAFLD management. However, these changes are challenging to put into practice and even more so to sustain. Due to various shared pathogenic mechanisms leading to the development of NAFLD and type 2 diabetes, anti-diabetic therapies are potential treatment options for the management of both disease states. Current data support the use of thiazolidinediones and GLP-1 agonists as the only anti-hyperglycaemic agents showing histological improvement of NASH. To effectively address and perhaps offset the consequences of NAFLD in sub-Saharan Africa, urgent attention is needed to ensure equitable access to therapies of proven clinical benefit, in addition to promoting the public health benefits of lifestyle modification.

Hypertension

Hypertension is a major risk factor promoting the development of NAFLD, occasionally independent of other risk factors. Good blood pressure control protects against NAFLD and the absence of hypertension mitigates against liver fibrosis in NAFLD.[126] Additionally, blood pressure control is crucial to offsetting the cardiovascular risks associated with NAFLD.

Dyslipidaemia

Multiple studies have shown the efficacy of lipid-lowering drugs in patients with NAFLD and NASH. These drugs include statins, fibrates, and ezetimibe. Statins are the most widely used and have known efficacy in reducing cardiovascular mortality in patients with coronary artery disease and type 2 diabetes.[127] Statins are safe and effective in patients with NAFLD or NASH and have no excess hepatotoxicity.[128] Furthermore, short-term treatment with statins can have beneficial effects on hepatic portal vein pressure, suggesting additional benefits in patients with advanced chronic liver disease or cirrhosis.[129]

Bariatric surgery and obesity

Bariatric surgery is an effective treatment for obesity; with regard to NAFLD and NASH, it achieves histological resolution of NASH through both weight loss-dependent and weight loss-independent mechanisms.[130] Paired liver biopsy studies and NAFLD activity scores show substantial improvements.[131] In a prospective study of 109 patients with biopsy-proven NASH, 70 (85%) of 82 patients who had baseline and repeat liver biopsies had resolution 1 year after bariatric surgery, with a third of patients showing fibrosis regression according to Metavir scoring.[132] Bariatric surgery in patients with NASH cirrhosis requires careful consideration given the incident risk of complications. However, the risk of death from cardiovascular causes, the leading cause of mortality in NASH, is reduced after bariatric surgery.[133] Surgical options include Roux-en-Y gastric bypass or sleeve gastrectomy; jejunoileal bypass is not recommended given its risk of liver decompensation.

Conclusions

In Africa, the estimated NAFLD prevalence of 13·5% for the general population is likely to be an underestimate, given the rising prevalence of obesity and type 2 diabetes, driven by the overlapping social challenges of food insecurity, nutritional transition, and associated increasing consumption of calorie-dense foods. The HIV infection burden, increasing access to antiretroviral therapy, and an ageing population are all contributing factors. Upscaling awareness and well designed epidemiological studies that screen for NAFLD in the general population as well as in high-risk groups are needed to assess the true prevalence and to guide public health policy in addressing this silent epidemic, which has long-term health-care costs and economic consequences for the region. Sub-Saharan Africa is possibly uniquely poised to proactively address the impending disease burden of NAFLD. The opportunity should not be missed.

Contributors

CWS conceived of the manuscript and developed the preliminary outline. All authors contributed to and provided region-specific perspectives; reviewed the full draft of the manuscript and subsequent revisions; and approved the final version for submission. MWS provided additional technical expertise.

Declaration of interests

We declare no competing interests.

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