

Non-alcoholic fatty liver disease: A real threat in Pakistan

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Abstract

The rise in obesity, along with its association with unhealthy lifestyles and poor health awareness, has led to an increasing prevalence of non-alcoholic fatty liver disease (NAFLD). Only a few studies have addressed the changing trends in obesity and have tried to estimate the frequency of NAFLD in Pakistan. Fatty liver is seen in about 15% of the general population. Insulin resistance, diabetes, dyslipidaemia, high body mass index (BMI) and waist circumference, and increasing age are associated with NAFLD. In patients without insulin resistance, dyslipidaemia is usually present. Lean NAFLD is not common. In facilities where elastography is unavailable, NAFLD fibrosis score may be used to predict NAFLD in such patients. There is a need to conduct population-based studies to understand the risks and to design initiatives to increase public awareness regarding this disease. NAFLD screening is advisable in overweight individuals, diabetic patients, and persons at high cardiovascular disease risk.

Keywords: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Diabetes; Obesity; Insulin resistance

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The spectrum of non-alcoholic fatty liver disease (NAFLD) comprises of non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). The increasing fibrosis can lead to cirrhosis and hepatocellular carcinoma (HCC). The global prevalence of NAFLD is 25.2%, with the highest in South America and the Middle East and the lowest is reported in Africa.¹ The prevalence also tends to rise with increasing age. Based on surveys using ultrasonography, the prevalence of NAFLD in Asia varies from 5-30% depending on different regions.² Various metabolic comorbidities such as obesity, type 2 diabetes, hyperlipidaemia, hypertension, and metabolic syndrome have been associated with NAFLD.[1] Liver-specific mortality is estimated to be 0.77 per 1,000 person-years and 11.77 per 1,000 person-years for patients with NAFLD and NASH respectively.^{3,4}

Rising trends of obesity in Pakistan

The problem of obesity has been escalating and is transforming into an epidemic. As in the Western countries, obesity and lack of physical activity are on the rising trend in Pakistan as well. WHO classifies overweight as body mass index (BMI) between 23-25 kg/m², and obesity as BMI greater than 25 kg/m² for the Asian population.⁵ The Asia Pacific Working Party for NAFLD has also included the waist-hip ratio (WHR) in the regional criteria, emphasising on visceral fat and central obesity, based on various Asian studies.⁶ Compared with Caucasians, healthy Asians with comparable BMI and age have insulin resistance, dyslipidaemia, and increased cardiovascular risk. These differences are contributed by increased abdominal and visceral fat.⁷

The adult prevalence rate of obesity is estimated to be 8% (6% in males and 10% in females), and the adolescent prevalence rate is 3% in Pakistan according to WHO.⁸ This is not a recent development, as a National Health Survey conducted between 1990-94 reported the rising trend of obesity according to class and location; it was 9%, 15% and 27% for rural areas and 21%, 27% and 42% for urban areas according to low, middle and high socioeconomic status respectively.⁹ This reflects the effect of socio-economic status, industrialisation, and urbanisation on BMI. The Pakistan STEPS survey conducted from 2013-2014 noted that the prevalence of obesity was 14.9% (95% CI: 13.4–16.5%), while 26.3% (95% CI: 24.8–27.8%) of the participants were overweight.¹⁰

A rise in childhood obesity has been noted in spite of persistently high rates of under-nutrition. A study conducted at private and public schools in Hyderabad noted a high prevalence of being overweight (8%) and obesity (12%) among the study sample.¹¹ Similarly, another study performed in many schools of Karachi, Pakistan, demonstrated that 29.8% of children were obese and overweight. Comparing school-children with normal weight and those who were obese/over-weight, the study demonstrated sedentary lifestyles and increased duration of sleep as risk factors for obesity.¹²

Prevalence of NAFLD in Pakistan

There is a change in the prevalence of NAFLD due to the rise of obesity, with this changing trend reflected in the rest of South Asia and the Asia Pacific region as well. This

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problem is aggravated further with an unhealthy lifestyle and poor health awareness. To help formulate plans to manage strategies for tackling this potential issue in Pakistan, the burden of the disease has to be estimated first. Studies were conducted on the visitors of hospitals around the country to estimate the frequency of NAFLD. A small hospital-based study in Peshawar estimated NAFLD prevalence of 47% in its visiting patient population,¹³ whereas other studies report it to be around 14%.¹⁴⁻¹⁶ There appears to be a male predominance with earlier age of onset in this population compared to its Western counterpart.¹⁷ This increasing prevalence of NAFLD can lead to a rise in the incidence of HCC in the future. There is a need to conduct population-based studies to understand the risks and to design initiatives to increase public awareness regarding this disease.

In one study, 1000 visitors came for a medical check-up in a tertiary care hospital. After excluding other causes of chronic liver disease, 13.5% of the individuals had fatty liver and elevated ALT.¹⁴ In another study of 164 visitors, overall NAFLD prevalence was 47% while NASH was established in 20 patients (12.3%).¹³ Ghani et al evaluated the risk factors of NAFLD in the Pakistani cohort, which included obesity, hyperglycaemia, hypertension, dyslipidaemia, advanced age, male gender, and a raised BMI.¹⁶ Hypertriglyceridaemia has been noted to be independently associated with histological features of NASH.¹⁸ NASH is common in patients with male gender, high BMI, diffuse fatty liver on liver ultrasound, and raised ALT.¹⁹

Diabetes and NAFLD

According to the second National Diabetes Survey of Pakistan (NDSP), 2016–2017, the overall age-adjusted weighted prevalence of diabetes was 26.3%, with a higher prevalence in urban areas compared to rural ones (28.3% and 25.3%, respectively).²⁰ Age (≥ 43 years), family history of diabetes, hypertension, obesity and dyslipidaemia were noted to be significant risk factors for diabetes ($p \leq 0.0001$). Type 2 diabetes and insulin resistance have been associated with NAFLD. Seetlani et al have reported that patients with type 2 diabetes longer than 5 years and elevated ALT had a biopsy-proven prevalence of NASH to be 56.49%.²¹ In another study, the frequency of NAFLD was 75% and NASH was 22.5% among 26 diabetic patients.¹³ Various other studies have reported a prevalence of NAFLD to be 35–72% in patients with type 2 diabetes.²²⁻²⁴

To screen or not to screen for NAFLD?

NAFLD is a common diagnosis in patients with incidental abnormal liver enzymes such as ALT and AST.²⁵ However, liver enzymes may be within the normal range in

approximately 80% of such cases.²⁶ ALT typically decreases with advanced fibrosis, and as NASH progresses, AST/ALT ratio may increase. Furthermore, there is a poor correlation of ALT levels with histological findings; the severity is similar in patients with normal versus abnormal liver enzyme profiles.²⁷⁻²⁹ A new approach is therefore required to identify subjects with this phenomenon.

Screening for NAFLD in the population at risk should keep in mind the available resources, the drain on the local healthcare systems, and the limited effectiveness of most treatments. Routine screening for NAFLD may not be currently advisable in high-risk groups because of reservations with diagnostic tests and treatment options, along with unawareness regarding long-term benefits and cost-effectiveness of screening. There should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. NAFLD fibrosis score (NFS), fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE) and other such aids may be used to classify risk for advanced fibrosis.³⁰ NAFLD screening is advisable in persons at high cardiovascular disease risk.³¹

NAFLD in the local population of Karachi

As the presence of NAFLD is common in the local population, its evaluation should be part of screening programmes for liver disease along with viral serology. Hepatitis awareness campaign is one method which allows evaluation of the disease. One study was done on 928 visitors to the hepatitis awareness programme. Individuals who were non-reactive to hepatitis B or C, with no liver disease, and without a history of excess alcohol intake ($n=806$) were further analysed. The fatty liver based on ultrasound findings was present in 15.3% of individuals and elevated ALT in 22% cases with fatty liver.³² BMI was noted to be an independent risk factor for NAFLD based on regression analysis. Fatty liver was found in 32 individuals with body BMI $\leq 25 \text{ kg/m}^2$, nine of them had elevated ALT. It was noted that lean NAFLD was not common.

In another study done on NAFLD patients, 82.5% of the attendees with NAFLD had a BMI $> 23 \text{ kg/m}^2$.³³ Triglyceride and cholesterol levels correlated poorly with insulin resistance. A significant increase in elasticity (F2-F4) suggested by transient elastography was seen in 32% cases of elevated controlled attenuation parameter (the parameter which suggests fatty liver on transient elastography). Dyslipidaemia was seen in patients without insulin resistance. NFS might be used in predicting significant fibrosis in NAFLD patients where elastography facility is unavailable, as demonstrated by a study comparing serological values of fibrosis with transient elastography.³⁴ A study done by Asim et al on patients with

chronic hepatitis B observed that a significant number of patients with positive Hepatitis B surface antigen (HBsAg) with mildly elevated ALT levels were overweight, had significant steatosis and fibrosis, but low HBV DNA levels of less than 2000 IU/ml. This aspect is important while making any decision regarding the initiation of hepatitis B treatment.³⁵

Approach to manage NAFLD

Lifestyle intervention can be an effective way for the management of patients with NAFLD.³⁶ These recommendations include weight reduction, exercise, and dietary changes. Weight reduction has a clear dose-response association for the treatment of NAFLD and NASH. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, weight loss promotes a reduction in hepatic steatosis, with at least 3-5% required to show a reduction.³⁰ To improve the histopathological features of NASH, including fibrosis, greater weight loss of 7-10% is needed. Exercise too may prevent or reduce steatosis, but its ability to improve other aspects of liver histology is unknown. Due to the cardiovascular benefits of exercise, it should be an adjunct to weight loss and dietary regimen. An interventional study done by Wolf et al noted that a low-calorie diet 2 weeks prior to bariatric surgery improved steatosis, lobular inflammation, and hepatic ballooning.³⁷ Furthermore, the weight loss on this diet prior to bariatric surgery was predictive of weight loss 6 months after surgery. It is premature to consider bariatric surgery in itself as an established option to treat NASH, but it may be considered in the eligible obese patients.³⁰ There is still no approved pharmacological therapy for NAFLD. Current therapies target insulin resistance, dyslipidaemia and free radical injury.

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