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Research Article

**NONALCOHOLIC FATTY LIVER DISEASE IN OBESE AND
OVERWEIGHT CHILDREN**¹Dr Ayesha Akhtar, ²Dr Iqra Aslam, ³Dr Hafiza Maham Shafiq^{1,2}MBBS, Nawaz Sharif Medical College, Gujrat., ³WMO, BHU 59/5-L, Sahiwal.**Article Received:** August 2019**Accepted:** September 2019**Published:** October 2019**Abstract:**

Childhood obesity is a worldwide health problem associated with an increase in the prevalence and severity of nonalcoholic fatty liver disease (NAFLD). Non-alcoholic fatty liver disease (NAFLD) is probably the most common cause of liver disease in the pediatric community. It is closely associated with obesity and insulin resistance. NAFLD may lead to non-alcoholic steatohepatitis (NASH). Confirmation of the diagnosis of NAFLD can usually be achieved by imaging studies; however, staging the disease requires a liver biopsy. Current treatment relies on weight loss and exercise, although various insulin-sensitizing agents, antioxidants and medications appear promising. The aim of this review is to summarize what is known about pediatric NAFLD in terms of prevalence, pathogenesis, diagnosis, histology and treatment.

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INTRODUCTION:

Introduction Nonalcoholic fatty liver disease (NAFLD), characterized by accumulation of macrovesicular fat in the hepatocytes, is the most common form of chronic liver disease in the pediatric population. The term nonalcoholic steatohepatitis (NASH) was introduced in 1980 to describe alcoholic hepatitis-like histology in adults who did not consume alcohol. In 1983, NASH was first reported in children. With the rapid rise in childhood obesity, there has been an increase in the prevalence, recognition, and severity of pediatric NAFLD.

This review focuses on recent advancements in the understanding of the epidemiology, histology, pathogenesis, and treatment of pediatric NAFLD. Epidemic of Childhood Obesity According to data from the National Health Examination Survey (NHES) and the National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity in adolescents was stable in the United States (at 5%) from 1966 to 1980. The prevalence doubled to 10.5% between 1994 and 1998, and continued to

increase, reaching 17.4% in 2003 and 2004. The prevalence of obesity in preschool and school-age children followed a similar trend [1].

The obesity epidemic is not restricted to the United States—it is a global problem. In a survey across 34 countries, the prevalence of overweight youths was more than 15% in North America, Great Britain, and Western Europe [2]. A population survey in Korea demonstrated that 17.1% and 14.7% of adolescent boys and girls, respectively, were overweight [3]. The rise in the prevalence of obesity was accompanied by an increase in obesity-related conditions such as hypertension [4], impaired glucose tolerance [5], and NAFLD.

The available data suggest a prevalence that ranges from 2.6% to 9.6% for suspected NAFLD among children and adolescences in United States [6] and Asia. [7] However, a limitation of these studies was the different method was used to determine the definition of NAFLD (Table 1).

Table 1 Prevalence of NAFLD in children.

Country	Overall total children	Ages	Fatty liver definition
USA	2450	12 – 18	3 % ^a
USA	742	2 – 19	9.6 % ^b
Korean	1594	10 – 19	3.2 % ^a
Japan	810	4 – 12	2.6 % ^c

^a Based on elevated Alanine aminotransferase levels (ALT).

^b Based on χ 5 % of hepatocytes containing macrovesicular fat.

^c Based on ultrasonography.

Moreover, several studies in Europe, [12] Asia, [13-18] South and North America [3,4,19-21] have been conducted in cohorts of children selected for overweight and obesity and found that the prevalence of NAFLD in these groups may range from 12% to

80%. Again, different techniques were used in these studies for the diagnosis of NAFLD making unavailable to determine percentage of simple steatosis versus NASH or cirrhosis (Table 2).

Table 2 Prevalence of NAFLD in overweight and obese children.

Country	Total overweight and obese children ^a	Fatty liver definition	Ref.
Italy	268	44 % ^b	7
Italy	375	38.7 % ^c	8
Italy	288	10 % ^b	9
Italy	72	53 % and 25 % ^{b,c}	10
Italy	175	55 % and 15 % ^{b,c}	11
China	84	77 % and 24 % ^{b,c}	13
China	123	80 % and 44 % ^{b,c}	14
China	113	55.7 % ^b	15
Japan	310	25 % ^b	16
Japan	299	12 % ^b	17
Japan	228	24.2 % ^b	18
USA	181	8 % ^b	19
USA	127	23 % ^b	20
USA	315	16 % ^b	3
USA	320	81 % ^d	4
Mexico	80	42 % ^b	21
Greece	43	41.8 % ^c	12

^a Based on 4 85 th and 95 th percentile for age and sex and IOTF criteria.

^b Based on elevated alanine aminotransferase levels (ALT).

^c Based on ultrasonography.

^d Based on x 5 % of hepatocytes containing macrovesicular fat.

Pathophysiology of NAFLD:

The pathophysiology of NAFLD has been directly linked to the pediatric obesity problem and is caused by excessive lipid accumulation in the liver. The normal liver contains approximately 5% of lipids. When the amount of lipids surrounding the liver becomes excessive, the hepatocytes absorb the excess lipids and cause cell lysis. This lysis releases the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) into the bloodstream, which, in turn, forces the absorption of a higher percentage of lipids into the hepatocytes. Because the hepatocytes are now overburdened with lipids, the liver's ability to appropriately process fat is diminished. A layer of lipids has now enveloped the liver, causing decreased mitochondrial oxidation, hepatocyte irritation, and suffocation. This persistent proinflammatory cycling of cell irritation and destruction ultimately leads to the development of the initial stage of liver disease, fibrosis, which is scarring of the liver. If the inflammation is not halted, over time the scarring worsens, and the liver stiffens

and develops cirrhosis. Cirrhosis is a nonreversible condition that can progress to end-stage liver disease and failure, leaving transplantation as the only treatment option to prevent mortality.

Assessment of Obesity Related Liver Involvement in NAFLD

Investigators have used various methods (either singly or in combination) to determine the prevalence of NAFLD in childhood. The presence, degree and pattern of aminotransferase elevation are non-specific and do not provide etiological differentiation when used in isolation. Ultrasound of the liver has been found to be a good screening tool for assessment of the degree of fat in the liver, but it does not correlate well with the degree of fibrosis. Joseph et al reported a sensitivity of 89% and specificity of 93% in detecting steatosis in the liver, and a sensitivity of 77% and specificity of 89% in detecting increased fibrosis in the liver. The sensitivity of CT scans varied from 54% to 93% and specificity among 87% to 97%, depending on the protocol followed.

Fishbein et al evaluated 22 obese (BMI>95th percentile) children with hepatomegaly by estimating their hepatic fat fraction (FF) by a modified Dixon method using fast MRI scanning, and have reported a sensitivity of 92% and specificity of 100% in detecting NAFLD when combined with serum ALT estimation. Ultrasound screening for presence of fatty liver in high risk individuals seems to be a reasonable tool, while CT scans and MRI are very costly and not feasible at the moment for use in routine work up of suspected NAFLD. Liver biopsy remains the gold standard for diagnosis of steatosis and various degrees of fibrosis, and for comparison of various other diagnostic modalities.

Fatty Liver on Imaging Ultrasonography:

CT and MRI imaging are valid and reliable for diagnosing moderate to severe fatty changes in the liver. Hepatic fat gives hyperechogenic feature on ultrasound compared to spleen, while it gives hypodense shadows on CT scan. accurate diagnosis can be made by Sonologically when there is moderate or severe (>33%) fatty infiltration of liver.

MRI is the only noninvasive modality with ability to quantify the fat content of liver. No imaging method is able to distinguish between simple steatosis and NASH and/or indicate the stage of fibrosis. Ultrasonography has a sensitivity of 82 to 90% for detecting a fatty liver, and the sensitivity approaches 100% when steatosis involves more than 10% of the liver on biopsy. When it shows an echogenic pattern of the liver, its specificity for detecting steatosis is 93%. Hepatic inflammation, fibrosis and cirrhosis are most accurately diagnosed by liver biopsy results. Routine CT scanning does not add more information on fatty liver disease that what is known from ultrasonography.

Elevated Serum Aminotransferases:

Studies have estimated alanine aminotransferases (ALT) and aspartate aminotransferases (AST), either in isolation or in combination to estimate the prevalence of fatty liver in childhood. In NAFLD the ALT and AST levels are elevated to up to 5 times the upper limit of normal. The ratio of ALT: AST in obese individuals is reported to be greater than 1.

LIVER BIOPSY:

The gold standard for diagnosing NAFLD in children is liver biopsy because the degree of steatosis, inflammation, and fibrosis can be directly identified on the liver tissue sample. However, it is expensive and not without risks. Liver biopsy is typically performed in an acute care setting by a pediatric hepatologist or surgeon. It requires sedation, which can be dangerous for those who are obese or have

pulmonary issues. There is also a potential for postbiopsy bleeding caused by mild liver disease. Additionally, liver biopsy is prone to sampling error because of the small amount of tissue removed from a selected site, which may not have areas of steatosis or fibrosis needed to definitively diagnose NAFLD.

Risk Factors and Predictors for Obesity Related Liver Involvement (NAFLD):

The occurrence of fatty liver has been described from early childhood and it increases with advancing age. Overweight and obese children older than 16 years were significantly likely to have abnormal ALT levels. 12 With advancing age the sequelae of hepatic steatosis becomes more apparent; steatosis, steatohepatitis, cirrhosis, liver cancer. Obesity (BMI based) was present in 88% children, fasting hyperinsulinemia was present in 75% and insulin resistance (assessed by either HOMA-IR or QUICKI methods) was present in 95% of the subjects. Using multivariate modeling method, hepatic steatosis was significantly ($p > 0.0001$) predicted by a combination of quantitative insulin sensitivity check index, age and ethnicity; portal inflammation was predicted by combination of elevated ALT and fasting insulin ($p=0.0009$); perisinusoidal fibrosis was predicted by a combination of elevated ALT, fasting insulin and BMI Z score ($p > 0.0001$); and portal fibrosis was predicted by a combinations of right upper quadrant pain and homeostasis model assessment of insulin resistance ($p=0.0028$). Thus, children with NAFLD should be screened for insulin resistance which is nearly universal, and correlates well with liver histology. Rashid et al conducted the study with 36 children who had non-alcoholic steatohepatitis (NASH), and they did not find any statistically significant difference for the mean age, degree of obesity, and mean ALT and AST levels in children with no fibrosis or severe fibrosis. Franzese et al found 5 that the age at diagnosis of obesity was significantly more advanced in patients with shorter duration of obesity ($p < 0.0002$).

Treatment:

Lifestyle intervention Because NAFLD is associated with obesity, it is widely promoted that lifestyle interventions designed to produce weight loss may be a treatment for NAFLD. This hypothesis was explored in three studies during the 2005 to 2007 review period. The inclusion criteria, case ascertainment, and duration and intensity of the treatment differed among the three studies. Two studies used liver ultrasonography to subcategorize obese children, whereas one study was performed in children with a biopsy-proven diagnosis of NAFLD. All three studies used liver ultrasonography as an

assessment of response to treatment. These studies highlight the importance of accounting for subject retention when designing clinical trials in pediatric NAFLD.

Pharmacological treatment in the only pediatric treatment trial restricted to subjects with biopsy-proven steatohepatitis, metformin was used because of the association of insulin resistance with NAFLD. Metformin reduces hepatic glucose production and increases insulin sensitivity in adolescents with type 2 diabetes mellitus. Ten non-diabetic children with NASH received open-label treatment with metformin at a dose of 500 mg twice daily for a period of 24 weeks. Mean ALT and AST improved significantly from baseline to end of treatment. ALT normalized in 40%, and AST normalized in 50% of subjects.

CONCLUSION:

Pediatric NAFLD has become the more common form of liver disease in children. NAFLD in children will continue to increase especially where the incidence of obesity is rising. Liver biopsy remains the criterion for the diagnosis and staging of NAFLD. Histologically, there is a difference between adults and children that needs more study. Diet and exercise will most likely reduce NAFLD and obesity rates. The condition is potentially reversible and preventable. If unchecked, it is likely to progress to steatohepatitis and cirrhosis. Understanding the role the liver plays in the development and expression of the metabolic program will provide important insight into the pathogenesis and treatment of this increasingly common disease. There is an urgent need to undertake large population based studies in children (from pre-school age till adolescents) from various ethnic and regional areas, to document the epidemic of obesity using valid and internationally comparable definitions and measuring techniques.

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