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Nonalcoholic fatty liver disease in a group of Iraqi obese children attending children welfare teaching hospital

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Abstract

Background: Background: Although liver biopsy is the gold standard method for diagnosing and staging non-alcoholic fatty liver disease (NAFLD), the majority of patients can be effectively diagnosed non-invasively with tests that are routinely available in the clinic today as abdominal ultrasound.

Aim of the study: to study the prevalence of NAFLD as a complication among obese children and some of its related variables.

Patients and methods: A cross-sectional case-control study was conducted on 71 obese cases with an age range of 2-15 years in the medical city of Baghdad from the 1st of September 2014 to the 1st of September 2015. Obese children were selected according to their Body Mass Index which should be 97th centile according to the Center for Disease Control and Prevention growth charts. We depended on abdominal ultrasound to look for FLD.

Results; Most of the cases are school-age. Of these cases 17 (23.9%) were pre-hypertensive and 10 (14.1%) were hypertensive so obesity was significantly correlated with increased blood pressure. Bone age was advanced in 38 (53.5%) meaning that it had an obvious correlation with obesity. Formula-fed cases 20 (28.2%). Family history of obesity was 51 (71.8%). FLD among obese children; in the obese group; the prevalence of FLDr was 25 (35.2%). Males were 19 (76%). In obese with FLD 8 (32%) of them were hypertensive. Bone age was advanced in 18 (72%) of them. Ten (40%) were formula fed. Total serum bilirubin 3 (12%). Alanine aminotransferase 18 (72%) and Aspartate aminotransferase 13 (52%)were elevated. 13 (52%) had elevated Fasting blood glucose. Four (16%) had elevated Triglyceride levels. All of these values are more in obese with fatty liver than in obese without FLD.

Conclusions; Non-alcoholic fatty liver disease is associated with significant comorbid conditions as they have more prevalence of hypertension and increased lipid profile. There is a significant correlation between early feeding type and the growing problem which is excessive TV watching and digital games playing using mobile phones by most of them.

Keywords: Overweight, Obese children; Non-alcoholic fatty liver disease; Abdominal ultrasound; Pediatric

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1. Introduction

1.1. Nonalcoholic fatty liver disease (NAFLD)

Is part of the spectrum of liver disease strongly associated with obesity and is the most common chronic liver disease in children. NAFLD can range from fatty liver alone to a triad of fatty infiltration, inflammation, and fibrosis, termed nonalcoholic steatohepatitis (NASH), which resembles alcoholic liver disease but occurs with little or no exposure to ethanol. Unlike adults, NASH in children has 2 distinct histologic types. Type 1 NASH resembles adult histologic findings with steatosis and balloon degeneration of hepatocytes and/or periportal fibrosis. Type 2 NASH includes steatosis and portal inflammation. Many patients are asymptomatic [1].

Liver histology from autopsy data suggests that 10% of children and 38% of obese children ages 2-19 yr have NAFLD. The risk is lower in African-American children. Elevated serum aminotransferase levels are not sensitive or specific markers for NAFLD. A normal serum alanine aminotransferase level is present in 21-23% of pediatric patients with NAFLD[1].

No biomarkers are currently a reliable alternative to biopsy. Although ultrasonography detects NAFLD, no current imaging modalities distinguish between steatosis and NASH. A liver biopsy may be required for a delimiting diagnosis. The estimated prevalence in adults is thought to be as high as 15-20% for NAFLD overall and 2-4% for NASH. Risk factors in pediatric cohorts include obesity, male gender, white or Hispanic ethnicity, hypertriglyceridemia, and insulin resistance [1].

Hepatic steatosis alone may be benign, but up to a quarter of patients with NASH can develop progressive fibrosis with resultant cirrhosis. The long-term prognosis of NASH that has developed in childhood is unknown. Children diagnosed with NAFLD should be screened for comorbid conditions associated with the metabolic syndrome, including diabetes, hypertension, dyslipidemia, and obstructive sleep apnea. Obese children and overweight children with other risk factors who are older than 3 yr of age should be screened for NAFLD by checking aminotransferase levels and liver ultrasound, even though neither is highly sensitive or specific [1].

NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis [1].

The definition of nonalcoholic fatty liver disease (NAFLD) requires that (a) there is evidence of hepatic steatosis, either by imaging or by histology and (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders [2].

Factors associated with hepatic steatosis differ between obese children and adolescents. Oxidative stress is seen to be the main process in children, whereas in adolescents oxidative stress and insulin resistance are significant factors for steatosis [3].

NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) [3].

Non-alcoholic fatty liver disease is the most common cause of elevated liver enzymes. Within the NAFLD spectrum, only NASH progresses to cirrhosis and hepatocellular carcinoma. With the growing epidemic of obesity, the prevalence and impact of NAFLD continues to increase, making NASH potentially the most common cause of advanced liver disease in coming decades [3].

Obesity is a common and well-documented risk factor for NAFLD. Both excessive body mass index (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 [4].

The natural history of NAFLD and the optimal strategy to identify subjects with progressive liver disease are unclear. Objectives. To assess the evidence in: (1) natural history of NAFLD; and (2) non-invasive methods to differentiate NAFLD histological subtypes [2].

One component of abnormal body fat deposition involves the deposition of adipose tissue, so-called ectopic fat, around organs and the vasculature. Perivascular fat is one such ectopic fat depot that has been postulated to have a local pathogenic effect on blood vessels. Periaortic fat is a subtype of perivascular fat and can now be quantified using multidetector computed tomography, but only in adults [5].

This disease has a range of conditions involving the liver; the mildest type is simple fatty liver (hepatic steatosis), but there is a potentially serious type of non-alcoholic steatohepatitis (NASH), which is accompanied by liver-damaging inflammation and, sometimes, the formation of fibrosis. The more serious one is progressive fibrosis and cirrhosis. Investigators have used various methods to detect the prevalence rate of NAFLD in childhood [2].

The presence, the degree or pattern of aminotransferase elevation are non-specific and cannot help us in etiological differentiation when used as a single method. Sonography of the liver has been found to be a good screening method in the evaluation of the degree of fat in the liver, having a sensitivity of 89% and specificity of 93% in detecting steatosis in the liver and a sensitivity of 77% and specifity of 89% in detecting increased fibrosis in the liver. CT scan is more specific in detecting hepatic fibrosis, but it is costlier and not feasible at the moment for use in routine screening of suspected NAFLD [2].

Although there is no definitive treatment for NAFLD, gradual weight loss is effective in normalizing serum alanine aminotransferase and improving NAFLD. Low glycemic index foods, avoiding fructose, and substituting polyunsaturated fatty acids for saturated fats may help. Vitamins E and C provide no additional benefit to the efficacy of lifestyle intervention (diet and exercise) in improving steatosis or biochemical abnormalities in pediatric NAFLD. However, vitamin E does improve balloon degeneration in pediatric NASH [2].

A preliminary study using ω-3 docosahexanoic acid in children showed improved insulin sensitivity, alanine aminotransferase, triglycerides, body mass index, and histology in children with NAFLD. Cysteamine bitartrate (slow release), a potential precursor of glutathione, an antioxidant, may reduce liver enzyme levels, as well as serum leptin and adiponectin levels, and is also a potential candidate for the treatment of NAFLD [6]. This study aimed to study risk factors and causes obesity as a major and out growing health problem in Iraqi children. Also, to study some of associated factors and complications of obesity which can be obtained by history, physical examination and investigations of significant relevance? in addition to study the prevalence NAFLD as a complication among obese children and some of its related variables.

2. Material and methods

2.1. Patients and methods

Cross-sectional case control study, included 71 obese case; done in Baghdad medical city; children welfare teaching hospital, from 1st of September 2014 to the 1st of September 2015.

The obese cases included in the study have a BMI >97th centile for age and gender on CDC charts. Their ages are between 2 years and 15 years were collected from outpatient clinic.

Patients with diseases or taking medications known to be causes of obesity were excluded. Obese patients who had features and/or laboratory investigations causing liver disease or another abnormality not related to obesity where excluded.

Clinical informations were collected through direct interview with patients' families that included; age and sex of the cases, family history of obesity (first degree relatives), we took the history of early infancy feeding whether breast formula or mixed feeding, and history of excessive TV watching and digital games playing**.**

Their weight was taken in kilograms, and their height in centimeter. If the height was >95th centile it was considered tall stature and short stature if it was < 3rd centile. Measurements are plotted on CDC growth charts.

Single blood pressure reading was taken for all obese cases. If blood pressure was >95th centile it was considered hypertensive and pre-hypertensive if it was between 90th and 95th centile. All cases were examined for hepatomegaly.

BMI was calculated for all cases by dividing the weight in kg by the height in meter square.

All the cases were sent for fasting blood sugar; normal range (>60 to <105mg/dl), total serum cholesterol; normal range (150-250mg/dl), serum triglyceride; normal range (65-180mg/dl), and total serum bilirubin; normal range (0.3-1.0mg/dl) with fractionation to direct and indirect. Liver enzymes; alanine aminotransferase; normal range (15-25IU/L, and aspartate aminotransferase (6-40 IU/l). but our lab. Standards put the normal range<20 IU/l.

Abdominal ultrasound was taken focusing on liver for fatty changes [7].

Cases were also sent for left wrist x-ray for bone age assessment on RUS (radius, ulna and short bones) method [8-11].

The history taken, examination done, and investigations sent after informing the relatives that they were for research purposes and getting an oral consent from all cases and control group.

3. Results

There are significant findings correlated with presence or absence of fatty liver among obese cases.

Table 1 Relation between obese patients groups (fatty liver and normal) and their age and gender, n=71

Variables	Fatty liver		Total (n=71) No. (%)	p-value
	Yes (n=25) No. (%)	No (n=46) No. (%)		
Age groups				
Toddler	0 (0)	1 (2.2)	1 (1.4)	0.117
Preschool	1 (4)	10 (21.7)	11 (15.5)	
School	16 (64)	27 (58.7)	43 (60.6)	
Teenage and adolescents	8 (32)	8 (17.4)	16 (22.5)	
Gender				
Males	19 (76)	24 (52.2)	43 (60.6)	0.05*
Females	6 (24)	22 (47.8)	28 (39.4)	

Pearson's chi-square test, * significant at 0.05 level

Table 2 Relation between obese patients groups (fatty liver and normal) and their height and blood pressure centiles, n=71

Variables	Fatty liver		Total (n=71) No. (%)	p-value
	Yes (n=25) No. (%)	No (n=46) No. (%)		
Height (according to centiles)				
Short stature	1 (4)	0 (0)	1 (1.4)	0.362
Normal	20 (80)	40 (87)	60 (84.5)	
Tall stature	4 (16)	6 (13)	10 (14.1)	
Blood pressure (according to centiles)				
Normotensive	11 (44)	33 (71.7)	44 (62.0)	**0.005***
Pre-hypertensive	6 (24)	11 (23.9)	17 (23.9)	
Hypertensive	8 (32)	2 (4.3)	10 (14.1)	

Pearson's chi-square test, * significant at 0.05 level

The age groups of the obese patients (n=71) in correlation with presence or absence of fatty liver; no one of the toddlers had fatty liver, 1 (4%) Preschool age case had fatty liver while 10 (21.7%) did not have fatty liver , 16 (64%) School age had fatty liver while27 (58.7%) did not have fatty liver , 8 (32%) Teenage and adolescents had fatty liver while 8 (17.4%) did not have fatty liver. p-value 0.117. (table1). The mean age in years for obese with fatty liver and obese with non-fatty liver was (10±2.5) and (10±1.5) respectively. The no. of school age obese children was more than in the control group so it was not considered as risk factor. In the 25 cases with fatty liver; 19 (76%) were males, while females with fatty liver were 6 (24%); p-value 0.05. (table1). So mal sex was a risk factor to develop fatty liver in obese children**.**

Bone age was advanced in 18 (72%) in obese with fatty liver. While in obese without fatty liver were 20 (43.5%). p-value = 0.021. (table3). Bone age was more advanced in obese children with fatty liver.

Table 3 Relation between fatty liver in obese child and bone age, n=71

Bone age	Fatty liver		Total No. (%)
	Yes No. (%)	No No. (%)	
Normal	7 (28)	26 (56.5)	33 (46.5)
Advanced	18 (72)	20 (43.5)	38 (53.5)
Total	25 (100)	46 (100)	71 (100)

X^2= 5.297, df=1, p-value = 0.021* (significant at 0.05 level)

Family history of obesity; in obese cases with fatty liver there was 17 (68%) had family history of obesity, and in obese with non-fatty liver 34 (73.9%) had family history of obesity. P-value 0.597.

Table 4 Relation between obese patients groups (fatty liver and normal) and their early feeding, family history of obesity and excessive TV watching, n=71

Variables	Fatty liver		Total (n=71) No. (%)	p-value
	Yes (n=25) No. (%)	No (n=46) No. (%)		
Family history of obesity				
Positive	17 (68)	34 (73.9)	51 (71.8)	0.597
Negative	8 (32)	12 (26.1)	20 (28.2)	
Excessive TV Watching and Digital games play				
Yes	19 (76)	34 (73.9)	53 (74.6)	0.847
No	6 (24)	12 (26.1)	18 (25.4)	
Early feeding				
Breast feeding	1 (4)	25 (54.3)	26 (36.6)	**<0.001***
Formula	10 (40)	10 (21.7)	20 (28.2)	
Mixed	14 (56)	11 (23.9)	25 (35.2)	

Pearson's chi-square test, * significant at 0.05 level

Excessive TV Watching and Digital games play; in obese cases with fatty liver there was 19 (76%) had Excessive TV Watching and Digital games playing. And in obese with non-fatty liver 34 (73.9%) had Excessive TV Watching and Digital games playing. P-value 0.847.

Early feeding; in obese cases with fatty liver there was 1 (4%) was breast fed, 10 (40%) were formula fed, and 14 (56%) had mixed formula and breast feeding. While in obese with non-fatty liver; 25 (54.3%) were breast fed, 10 (21.7%) were

formula fed, and 11 (23.9%) had mixed formula and breast feeding. P-value **<**0.001. So breast feeding was protective against fatty liver. Feeding history showed that obese cases with fatty liver had formula and mixed feeding more than obese without fatty liver. While there was no difference regarding family history of obesity or excessive TV watching and digital games playing**.** (table 4).

Disturbed liver function was related to fatty liver. Regarding TSB it is elevated in obese cases with fatty liver 3 (12%), while no one of the obese cases without fatty liver has elevated TSB p-value; 0.016.

ALT was elevated in obese cases with fatty liver 18 (72%), more that obese without fatty liver 5 (10.9%), p-value; <0.001.

AST was elevated in obese cases with fatty liver 13 (52%), while no obese cases without fatty liver have elevated AST, p-value; <0.001. (table5).

Table 5 Relation between obese patients groups (fatty liver and normal) and their TSB, ALT and AST levels, n=71

Variables	**Fatty liver**		**Total (n=71) No. (%)**	**p-value**
	Yes (n=25) No. (%)	No (n=46) No. (%)		
Total serum bilirubin				
Elevated	3 (12)	0 (0)	3 (4.2)	**0.016***
Normal	22 (88)	46 (100)	68 (95.8)	
Alanine Aminotransferase				
Elevated	18 (72)	5 (10.9)	23 (32.4)	**<0.001***
Normal	7 (28)	41 (89.1)	48 (67.6)	
Aspartate Aminotransferase				
Elevated	13 (52)	0 (0)	13 (18.3)	**<0.001*F**
Normal	12 (48)	46 (100)	58 (81.7)	

Pearson's chi-square test, F Fisher's exact test,* significant at 0.05 level

Fasting blood sugar and serum triglyceride are more in obese cases with fatty liver, than in obese cases without fatty liver while there was no significant difference in the level of total serum cholesterol. (table11).

Fasting blood glucose; in obese cases with fatty liver; 13 (52%) had elevated Fasting blood glucose, and no one of the obese cases without fatty liver had elevated Fasting blood glucose. P-value **<**0.001.

Total serum cholesterol; in obese cases with fatty liver; 5 (20%) had elevated total serum cholesterol and in obese cases without fatty liver 2 (4.3%) had elevated total serum cholesterol. P-value 0.09.

In obese cases with fatty liver 4 (16%) had elevated Triglyceride level and no one of the obese cases without fatty liver had elevated Triglyceride level p-value 0.024 (Table6).

Table 6 Relation between fatty liver (by U/S) in obese child and FBS, total serum cholesterol and TG levels, n=71

Variables		**Fatty liver**		**p-value**
		Yes (n=25) No. (%)	No (n=46) No. (%)	
Fasting blood glucose	Elevated	13 (52)	0 (0)	**<0.001***
	Normal	12 (48)	46 (100)	

Total serum cholesterol	Elevated	5 (20)	2 (4.3)	0.09
	Normal	20 (80)	44 (95.7)	
Triglyceride level	Elevated	4 (16)	0 (0)	**0.024***
	Normal	21 (84)	46 (100)	

Yates continuity correction test for chi-square, * significant at 0.05 level

All those with increased FBS had fatty liver. And all those with increased serum triglyceride also had fatty liver.

4. Discussion

Obesity is an important health-care problem in developed countries. It is considered a multisystemic disease, but it may also affect the liver, thus provoking non-alcoholic fatty liver disease. This disease has been less extensively studied among children than among adults.

This study shows that most common age of fatty liver in obese patients was school age group 16 (64%) and it was statistically not significant p-value 0.117.

Mean age for obese with fatty liver and obese with non-fatty liver cases was (10 ± 2.9) and (9 ± 2.6) respectively. So the age difference between obese with fatty liver and obese without fatty liver was not significant. This result agree with the study by Jose Maria Navarro et al.[11]. who found that the age for obese cases with fatty liver and non-fatty liver were (10.54 ± 2.17) and (10.68 ± 2.30) respectively with p-value 0.722. Which was also not statistically significant.

In the 25 cases with fatty liver 19 (76%) where males, while females with fatty liver where 6 (24%); p-value 0.05. higher rate for NAFLD in males was recorded by Chen ZW, Chen et al. [12] the prevalence of NAFLD was 31% in men and 16 % in women.

The height in obese with fatty liver; 1 (4%) was Short stature, 20 (80%) were Normal, and 4 (16%) were tall stature. While in obese without fatty liver; no one was short stature, 40 (87%) were Normal, and 6 (13%) were tall stature. p-value 0.362. It was statistically not significant. This agree with the result of the study by Jose Maria Navarro, et al.[11] Who used the mean to assess height difference between obese with fatty liver and obese with non-fatty liver and there was no statistically significant difference.

Blood pressure was higher in obese with fatty liver 8 (32%) cases were hypertensive. While only 2 (4.3%) of the obese without fatty liver were hypertensive. p-value0.005. This result agrees with a study by University of California, San Diego Clinical Research Network who found that 21 percent of obese with fatty liver had persistently high blood pressure. In comparison, high blood pressure was present in two to five percent of all children and 10 percent of obese children [13]. The higher the BMI and the more fatty liver are associated with more cardiovascular risk factors including hypertension and hyperlipidemia [14].

Bone age was advanced in 18 (72%) in obese with fatty liver. While in obese without fatty liver were 20 (43.5%). p-value = 0.021.

Of those who had fatty liver 24 cases were school age and preadolescent, so the advancement might be due to premature adrenarche. As discussed by Aviva B. Sopher, Amy M. Jean, et al.[15] who concluded that obesity and premature adrenarche (PA) are both associated with bone age (BA) advancement of unclear etiology, which may lead to earlier puberty, suboptimal final height and obesity in adulthood.

Family history of obesity; in obese cases with fatty liver there was 17 (68%) had family history of obesity, and in obese with non-fatty liver 34 (73.9%) had family history of obesity. P-value 0.597. So it was not a significant difference.

Excessive TV Watching and Digital games play; in obese cases with fatty liver there was 19 (76%) had Excessive TV Watching and Digital games playing. And in obese with non-fatty liver 34 (73.9%) had Excessive TV Watching and Digital games playing. P-value 0.847. Also, it wasn't a significant difference.

Early feeding; in obese cases with fatty liver there was 1 (4%) was breast fed, 10 (40%) were formula fed, and 14 (56%) had mixed formula and breast feeding. While in obese with non-fatty liver; 25 (54.3%) were breast fed, 10 (21.7%) were formula fed, and 11 (23.9%) had mixed formula and breast feeding. P-value <0.001.

Feeding history showed that obese cases with fatty liver had formula and mixed feeding more than obese without fatty liver. So breast feeding may give some protective effect against development of fatty liver in obese children according to this result.

Regarding TSB it is elevated in obese cases with fatty liver 3 (12%), While no one of the obese cases without fatty liver has elevated TSB p-value; 0.016.

This result agree with the study done by Kang [16] who mentioned that abnormal liver biochemistry is expected in any obese child. But disagree with results obtained by Kwak et al. [17] which concluded a protective effect of elevated TSB against NAFLD [Serum bilirubin levels are inversely associated with nonalcoholic fatty liver disease].

ALT was elevated in obese cases with fatty liver 18 (72%), more that obese without fatty liver 5 (10.9%), p-value; <0.001. This result agree with the study by Jose Maria Navarro, et al. [11] Which linked the elevation of ALT to the severity of fatty liver. AST was elevated in obese cases with fatty liver 13 (52%), while no obese cases without fatty liver have elevated AST, p-value; <0.001. This may be a result of liver inflammatory response to fatty infiltration [16].

Fasting blood sugar and total serum cholesterol and serum triglyceride are more in obese cases with fatty liver than obese cases without fatty liver. This agrees with the study of Maria Navarro et al [11].

5. Conclusion

- Fatty liver was present in 35.2% of obese children.
- More prevalence of fatty liver in obese males.
- Higher blood pressure and advanced bone age are highly correlated with fatty liver.
- Breast feeding gives protective effect against both obesity and fatty liver.
- Abnormal LFT, IFG, and increased triglyceride are strongly correlated with fatty liver.

Recommendations

- We should measure the height, blood pressure, and examine for hepatomegaly for all obese children to look for possible complications.
- All obese cases should be sent for lipid profile, fasting blood sugar, liver function test and abdominal U/S.
- We need a larger study in multiple centers in Iraq that should include a liver biopsy in cases of fatty liver.
- Picking out obese children.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declared no conflict of interest.

Statement of informed consent

Adequate and appropriate information about research and researchers were provided.

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