Clinical and Biochemical Predictors of Non-Alcoholic Fatty Liver Disease in Obese Children and Adolescents

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Abstract

Background

Obesity and associated co-morbidities are growing worldwide, including non-alcoholic fatty liver disease (NAFLD), which become one of the leading causes of chronic liver diseases in both children and adults. The aim of this study is to investigate the clinical and biochemical predictors associated with NAFLD among obese children.

Materials and Methods

Ninety obese children and adolescents, aged 12–18 years, were enrolled in this study. All were subjected to anthropometric measurement; biochemical analysis included fasting blood glucose, serum insulin, serum triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and liver function tests. Ultrasonography was used to diagnose NAFLD.

Results

The frequency of NAFLD was 38.9% among obese children 68.6% of them met the criteria of metabolic syndrome. Children with NAFLD had significantly higher body mass index, waist circumference, ALT, total cholesterol, LDL-c, TG, fasting insulin, and lower HDL-c compared to patients with normal liver ultrasound ($p < 0.05$). Insulin resistance was significantly more common among NAFLD group (88.6% vs. 18.2%) ($p <$ 001). Logistic regression analysis revealed that BMI and HOMA-IR are the independent predictors for NAFLD with (P 0.034 and 0.022) respectively

Conclusion

More than one third of obese children have NAFLD, which is closely linked to metabolic syndrome and insulin resistance.

Background

Recently there has been a rise in childhood obesity globally, affecting both developed and developing countries. Excess adiposity at a young age is related to acute and long-term health hazards, including an elevated risk of hypertension, type 2 diabetes and cardiovascular diseases, and a resulting probability of premature death and middle-age morbidity independent of adult weight status]1[.

One of the main causes of both adults and children chronic liver disorders are non-alcoholic fatty liver diseases (NAFLD). This condition has a wide variety of continuum affecting the liver; the mildest type is simple fatty liver (hepatic steatosis), however there is a potentially severe type of non-alcoholic

steatohepatitis (NASH), which is characterized by liver-damaging inflammation and, occasionally, the development of advance fibrosis and cirrhosis]2[

Pediatric NAFLD has a significant association with obesity, and patients with nonalcoholic fatty liver disease have an elevated rate of related Type II diabetes mellitus, dyslipidemia, hypertension, insulin resistance (IR), metabolic syndrome (MetS), and the occurrence of cardiovascular disease in adulthood. Children in these groups are also at an elevated risk of experiencing chronic liver disease and secondary liver failure]3[

Patients of NAFLD present with non-specific signs or most often asymptomatic, so early diagnosis can be very challenging. In adults, liver biopsy is the gold standard. But, due to the invasive nature of the procedure, it is not practical for children and is typically not performed]4[. In 2012, the European Society of Pediatric Gastroenterology, Herpetology and Nutrition (ESPGHAN) has advised that all obese children aged 10 years and older should be screened for liver disorders by liver function tests and liver Ultrasonography as a first diagnostic step]5[

This research aims to assess the clinical predictors and biochemical profile of NAFLD among obese children and identifying the high-risk groups.

Material And Methods

Study design and population

A total of 90 obese children aging 12–18 years old were recruited from pediatric endocrinology unit, Suez Canal University Hospital, Egypt. The study subjects were divided into the two groups: obese children with NAFLD (n = 35) and obese children without NAFLD (n = 55), based on the ultrasonographic evidence of fatty liver.

Inclusion and exclusion criteria

Inclusion criteria: Children and adolescents with BMI (Body Mass Index) ≥ 95th percentile and from 12–18 years of age.

Exclusion criteria included Patients with known disorders to cause fatty liver [e.g.
hepatitis B virus (HBV), hepatitis C virus (HCV), Wilson's disease, glycogen storage disease, type 1 diabetes]. Children have long-term use of drugs known to cause steatosis, (e.g. glucocorticoids, aspirin) and those with syndromic obesity. Patients have renal failure, recent trauma, or acute illness.

Methods

All subjects were subjected to the following:

Anthropometric measurements:

Weight, height, waist circumference (WC) and Tanner stage were recorded in all children. Body mass index (BMI) was calculated as body weight (in kilogram) divided by height square (in meters). All records were plotted on the Egyptian growth charts. Obesity was defined if BMI was equal to or above 95th percentile for age and sex according to the criteria from International Obesity Task Force (IOTF)]6[. Waist circumference was measured at the level of the umbilicus and abdominal obesity was considered if the WC equal or above the 90th percentile for age and gender]7[

Blood pressure:

Using the clinical learning guide for calculating blood pressure then placed the blood pressure reading on the percentile]8[. Hypertension was considered based on systolic or diastolic pressure of ≥ 90th percentile for age and sex]9[

Biochemical tests:

All patients were subjected to the following tests (following not less than 10 hours fasting period): Triglyceride (TG), Total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein cholesterol (HDL-c), fasting blood sugar (FBS), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), measurement was carried out using automated chemistry analyzer (COBAS e411 Roche diagnostics, Germany). TG was considered high if > 150 mg/dl, TC and LDL were considered elevated if > 200 and 130 mg/dl respectively, low HDL-c diagnosed if value < 40 mg/dl, high fasting blood sugar value > 100 mg/dl and upper cutoff points of both ALT and AST were 41 and 37 U/l respectively]10[

Fasting serum Insulin hormone level was measured by ELISA (Immunospec Corporation, CA, USA) and insulin sensitivity index: HOMA-IR (homeostasis model assessment) calculated according to the following formula: HOMA-IR= [fasting insulin (μU/mL) x Fasting glucose (mg/dL)]/405. HOMA-IR ≥ 3.16 was interpreted as impaired insulin sensitivity or insulin resistance]11[

Liver ultrasound:

Ultrasonography (US) was used to diagnose NAFLD by the one experience radiologist who is blinded to the clinical and biochemical data of the patients using Philips ClearVue 650 ultrasound system. Liver steatosis was classified as follows: Absent steatosis was identified as normal liver echotexture; mild steatosis (grade I) as diffuse increase in hepatic echogenicity; moderate steatosis (grade II) as moderate and diffuse increase in parenchymal echoes with moderately impaired visualization of vessels walls and diaphragm; and sever steatosis (grade III) as small echoes with absent visualization of hepatic vessels, diaphragm, and posterior part of the right lobe]12[.

Metabolic syndrome:

Metabolic syndrome (MetS) was diagnosed if patients had three or more of the following modified criteria according to the International Diabetes Federation (IDF) consensus report

1. Fasting blood glucose levels ≥ 100 mg/dl
2. blood pressure ≥ 90th percentile
3. WC ≥ 90th percentile or adult cutoff if lower
4. TG levels ≥ 150 mg/dl
5. HDL-c ≤ 40 mg/dl]13[

Statistical analysis

Statistical evaluation was carried out by using SPSS program version 21.0 (SPSS Inc., Chicago, IL, USA). Data were summarized as mean and standard deviation (SD). Comparison between different groups in the present study was done using Student t test for comparing continuous data when normally distributed. P values < 0.05 were considered statistically significant. Multiple regression analysis was used to evaluate the independent predictor of NAFLD in obese children. Receiver operating characteristic (ROC) curves were generated to identify the cut-off values, sensitivity, and specificity for significant parameters for association with NAFLD.

Results

A total of 90 obese children were enrolled in this study, of those 29 (32.2%) were males and 61 (67.8%) were females, the mean age was 15.1 ± 2.9. Mean BMI was 29 ± 4.2. Thirty-two (35.5%) children fulfill the criteria of metabolic syndrome, furthermore 35 (38.9%) diagnosed NAFLD according to the Ultrasonography features, most of them were grade I or II 32 (91.4%).

Clinical Parameters:

In NAFLD group (13 males, 22 females), the mean age was 15.1 ± 2.2 compared to 15.2 ± 2.1 in the non-NAFLD group (16 males, 39 females). There was no statistically significant difference regarding age and sex (p = 0.24, p = 0.46) respectively.

The mean BMI is significantly higher in patients with NAFLD (31.2 ± 2.6) compared to patients without NAFLD (27 ± 2.2) p = 0.003. Furthermore, WC was 86.2 ± 6.89 for the NAFLD group while non-NAFLD group the mean was 71.60 ± 3.67. The difference was statistically significant between the two groups with p value for BMI p = 0.0027 and p = < 0.001 for WC.

Although the mean B.P was within normal range, it was significantly (P < 0.05) higher in obese group with NAFLD than obese group without Acanthosis Nigricans was present in 60% of NAFLD patients (Table 1)

Table 1
(Clinical and biochemical characteristics in obese children with and without NAFLD)

Parameter	Obese with NAFLD "n = 35" Mean ± SD or n (%)	Obese without NAFLD "n = 55" Mean ± SD or n (%)	P value
Age	15.1 ± 2.2	15.2 ± 2.1	0.2442
Sex (M/F)	13/22	16/39	0.4641
BMI (kg/m2)	31.2 ± 2.6	27 ± 2.2	0.0027*
WC	86.20 ± 6.89	71.60 ± 3.67	0.001*
Systolic BP (mm Hg)	121.8 ± 9.6	106 ± 8.7	0.031
Diastolic BP (mm Hg)	74.4 ± 6.2	68.6 ± 5.6	0.042
Acanthosis Nigricans	21 (60)	32 (58.2)	0.6246
AST (U/l)	39.86 ± 9.2	31.4 ± 7.4	0.0901
ALT (U/l)	46.3 ± 8.9	33.1 ± 10.2	0.007*
Total cholesterol (mg/dl)	198.1 ± 24	187.6 ± 20.3	0.0291*
Triglyceride (mg/dl)	126.2 ± 28.7	104.9 ± 33	0.0021*
LDL cholesterol (mg/dl)	131.6 ± 25	125.4 ± 23	0.2361
HDL cholesterol (mg/dl)	39 ± 8.3	51.2 ± 7	0.001*
Fasting blood sugar (mg/dl)	99.3 ± 19.2	89.2 ± 10.7	0.002*
Fasting serum insulin (µU/ml)	36.4 ± 18.6	10.8 ± 5.2	0.001*
HOMA-IR	6.4 ± 2.6	3.6 ± 1.8	0.001*
Insulin resistance HOMA-IR > 3.16	31 (88.6)	10 (18.2)	0.001*
MetS	24 (68.6)	8 (14.5)	0.001*

∗P < 0 05 (statistically significant).BMI, body mass index; WC, waist circumference; BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; MetS, metabolic syndrome

Biochemical parameters:

Children with NAFLD had significant higher total cholesterol, triglyceride, fasting blood sugar, fasting serum insulin and lower HDL-c compared to patients with normal liver ultrasound (P < 0.05) (Table 1)

The calculated HOMA-IR was 6.4 ± 2.6 and 3.6 ± 1.8 for the NAFLD and non-NAFLD groups respectively. This finding suggestive that insulin resistance is significantly higher in patients with NAFLD 31 (88.6%) compared to patients without NAFLD 10 (18.2%) (p = < 0.001). Receiver operating characteristic (ROC) analysis was performed to obtain the cut-offs of HOMA-IR for predicting a higher risk for NAFLD, with area under the curve (AUC) of 0.865 (95% CI 0.784–0.946), and the cut-off being 3.15 sensitivity 88.6% and specificity 72.7% (Fig. 1).

Metabolic syndrome diagnosed in 24 (68.6%) of patients with NAFLD compared to 8 (14.5%) in patients without NAFLD and the difference was significant (p = < 0.001)

Obese children with NAFLD had a mean ALT 46.3 ± 8.9. For the non-NAFLD group, the mean ALT was 33.1 ± 10.2. The difference between the two groups was found to be significant (p = 0.007)

Logistic regression analysis for NAFLD predictors:

Regression analysis was conducted to assess predictors of NAFLD. Variables that had been found in a previous analysis to be significant, including the BMI, WC, total cholesterol, triglyceride, HDL-c, ALT, FBS, HOMA-IR as well as the metabolic syndrome, were entered as independent variables for analysis. As shown in Table 2, the best predictors of NAFLD were BMI (B = 0.761, P = 0.034) and HOMA-IR (B = 0.553, P = 0.022).

Table 2
(logistic regression analysis for predictors of NAFLD in obese children)

predictors	B	S.E.	P value	OR	95% C.I	
					Lower	Upper
BMI	0.761	0.828	0.034*	2.172	0.034	0.872
WC	0.236	0.543	0.092	1.452	0.523	1.239
Total cholesterol	1.012	0.764	0.231	1.023	0.645	1.254
Triglyceride	0.465	0.032	0.674	1.213	0.854	2.543
HDL cholesterol	0.524	0.795	0.392	1.964	0.423	3.765
ALT	0.188	0.156	0.230	1.829	0.610	1.126
Fasting blood sugar	0.083	0.087	0.342	0.920	0.776	1.092
HOMA-IR	0.553	0.045	0.022*	3.981	0.287	2.311
MetS	0.602	0.067	0.092	2.134	1.076	1.123

∗P < 0 05 (statistically significant).BMI, body mass index; WC, waist circumference; HDL, high-density lipoprotein; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance; MetS, metabolic syndrome

Discussion

In the current study the prevalence of fatty liver was 38.9 % (n = 35) out of 90 obese children and adolescents and most of them having mild degree of fatty liver infiltration. This prevalence is lower in comparable to that reported in Jain et al. (62.5%)]14[but it agreed with a pediatric autopsy study conducted in 2006 by Schwimmer and colleagues found that the NALFD prevalence range from 9.6% in normal weight subjects to 38% in obese children and adolescents]15[. However, it remains difficult to compare the prevalence in various populations as the published data differ regarding their study design, sample selection, diagnostic modality used to define fatty liver and the age, sex, and ethnicity of the study population.

Both BMI and WC noted to be higher in NAFLD group; moreover, elevation in BMI was a significant predictor of fatty liver disease. A study by Hagström and colleagues showed that high BMI in adolescents is a risk factor of severe liver disease later in life with 5% increased risk per 1 kg/m2 increase in BMI]16[, in addition it was demonstrated that increased abdominal obesity lead to higher risk of fatty liver due to accumulation of lipid in hepatocytes]17[, furthermore Dâmaso et al. showed that every 1 cm increase in WC is associated with two-folds greater risk of NAFLD in obese children and adolescents]18[

In the present study significant dyslipidemia (lower HDL-c, Higher triglyceride, and total cholesterol levels) occurs in NAFLD obese children. In multiethnic study on children with NAFLD and according to pediatric cutoff values, the prevalence of elevated triglyceride, non-HDL cholesterol and low HDL-c was 77, 58 and 88% respectively]19[, in contrast to our findings Gupta et al. showed that lipid levels were not statistically significantly different in the children with and without NAFLD]3[

In our study, we found that the calculated HOMA-IR score is significantly higher in NAFLD group (6.4 ± 2.6) and it was a good predictor for NAFLD in multivariate logistic regression analysis, also 88.6% of our NAFLD patients had insulin resistance. Significant elevation of HOMA-IR in obese children with fatty liver disease has been reported in several studies]20, 21[. Furthermore, in a study by Schwimmer et al. on 43 children with biopsy-proven NAFLD, concluded that IR markers (HOMA-IR and Quantitative Insulin Sensitivity Check Index QUICKI) were correlated with severity of liver pathology]22[. These findings explained by the fact that IR result in increased lipolysis and free fatty acid influx with accumulation of TG within the hepatocyte]23[. Moreover, it leads to hepatic fibrosis by increasing oxidative stress and fatty acid β-oxidation]22[. In our study ROC analysis of HOMA-IR cutoff value 3.15 showed sensitivity 88.6% and specificity 72.7% in predicting NAFLD. This was concordant with Salgado et al., who stated that HOMA-IR values above or equal to 2.0 or 2.5 show enhanced diagnostic value in distinguishing non-alcoholic fatty liver disease carriers from control group individuals with sensitivity 85%, specificity 83% and Sensitivity 72%, specificity 94% respectively]24[. A recent joint European practice guideline for NAFLD]25[concluded: 'HOMA-IR provides a surrogate estimate of insulin resistance in persons without diabetes and can therefore be recommended'.

Metabolic syndrome has been diagnosed in 68.6% of NAFLD patients compared with 14.5% of NAFLD-free patients and this is due to the fact that although NAFLD is not traditionally part of the MetS

definition, it is widely considered to be the hepatic manifestation Metabolic syndrome. In a case-control study of 150 obese children with biopsy-proven NAFLD and 150 without, children with MetS had five times the risk of developing NAFLD as obese children without MetS]26[. In addition, Fu et al. found that the incidence of NAFLD reached 84.61% among 221 obese children with MetS, and this suggests that NAFLD may be an early stage mediator for the prediction of MetS]27[. Another study on 254 biopsy-confirmed NAFLD showed that the diagnosis of MetS is a good predictor not only of the severity of hepatic steatosis but also of the degree of fibrosis]28[.

The main and inexpensive screening test for NAFLD is alanine amino transferase. Mild elevation of serum aminotransferase levels is seen in patients with NAFLD, but liver enzymes may be normal in up to 78% of patients]29[. This is concordant with our results which demonstrated that only 14.2% of children with NAFLD had abnormal ALT. however we found that the mean ALT was significantly elevated in NAFLD group 46.3 ± 8.9. Kim et al. stated that the high ALT level was identified as the most critical factor in NAFLD risk. But high ALT is not a definite NAFLD indicator, nor is high ALT frequently seen in NAFLD patients. A serum ALT of more than 40 IU/L is corresponding to a NAFLD probability of < 0.6. This result shows that high ALT alone does not accurately predict the existence of NAFLL. In addition to serum aminotransferases, additional markers are therefore necessary for accurate evaluation of NAFLD]30[

One of the limitation of this study is the diagnosis of NAFLD is based on ultrasound imaging which although approved as a safe, inexpensive and non-invasive test with sensitivity y ranging from 60–96% and a specificity ranging from 84–100%]5[, however it cannot replace liver biopsy as a gold standard for diagnosis which unfortunately carries risk of complications and often not accepted by the parents

Conclusion

Based on our findings, more than one third of obese children had substantial incidence of non-alcoholic fatty liver, which linked tightly with metabolic syndrome parameters and insulin resistance. HOMA-IR is a valuable predictor to determine hepatic steatosis in children with obesity. Screening for NAFLD should be a part of the evaluation for all obese children since this disorder can be prevented with dietary intervention and proper exercise.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AUC: Area under the curve; BMI: Body mass index; BP: Blood pressure; CI: Confidence interval; ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology and Nutrition; FBS: Fasting blood sugar; HBV: Hepatitis B virus; HCV: Hepatitis C virus, HDL-c: high-density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment-insulin resistance; IDF: International diabetes federation; IOTF: International obesity task force; IR: Insulin resistance; LDL-c: Low-density lipoprotein cholesterol; MetS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; ROC: Receiver operating characteristics; TG: Triglyceride; US: Ultrasonography; WC: Waist circumference

Declarations

Acknowledgments

Not applicable.

Authors' contributions

HA and AI-study design and preparation of the manuscript; HA, AI, and JL- Data collection and analysis from participants and review of literature; HA-perform liver ultrasonography with radiological interpretation and analysis; HA-revision of the manuscript; All the authors read and approved the final manuscript

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Medical Research Ethics Committee of the Suez Canal University Faculty of Medicine (Ismailia, Egypt). Written informed consents were obtained from parents/guardians of the participants.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Figures

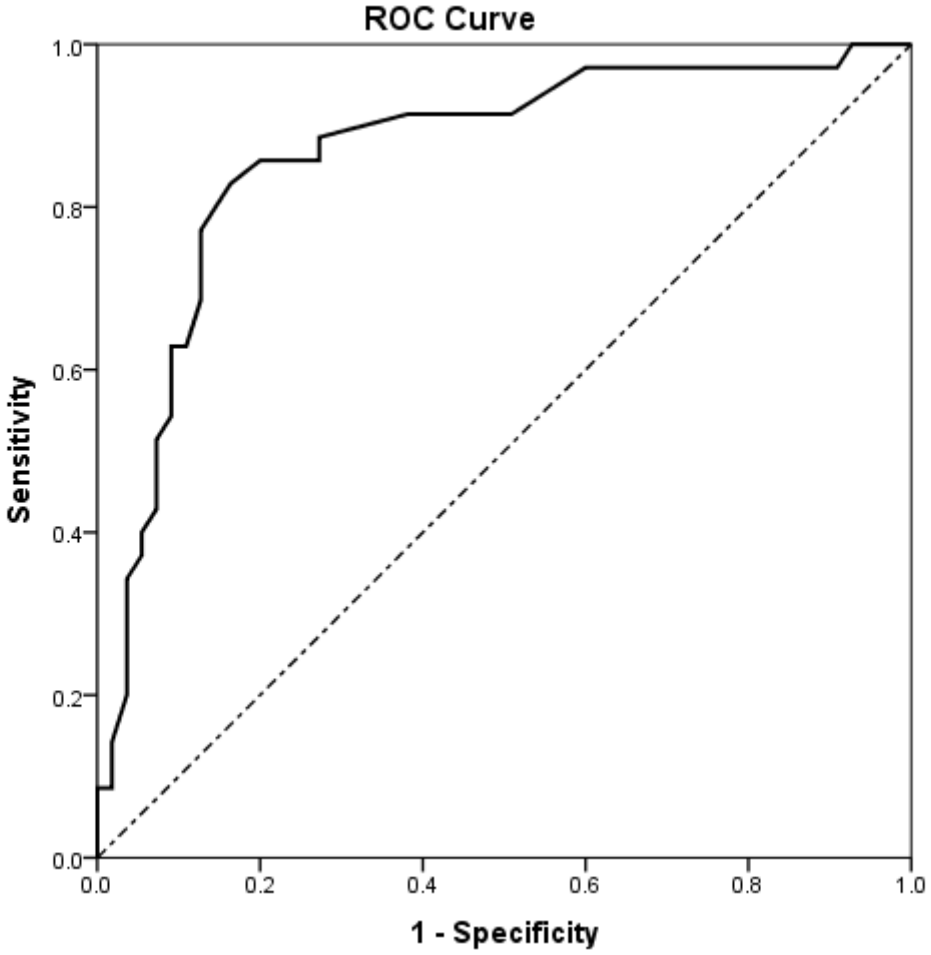

Figure 1

Receiver operating characteristic (ROC) curves to identify the cut-off value of homeostatic model assessment of insulin resistance HOMA-IR for association with non-alcoholic fatty liver disease in obese children