Original Article

# The Association of Metabolic Syndrome, Insulin Resistance and Non-alcoholic Fatty Liver Disease in Overweight/Obese Children

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## ABSTRACT

**Background/Aim:** To study the prevalence of metabolic syndrome (MS), insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD) in overweight/obese children with clinical hepatomegaly and/or raised alanine aminotransferase (ALT). **Patients and Methods:** Thirty-three overweight and obese children, aged 2–13 years, presenting with hepatomegaly and/or raised ALT, were studied for the prevalence of MS, IR and NAFLD. Laboratory 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 biochemical profile, in addition to liver ultrasound and liver biopsy. **Results:** Twenty patients (60.6%) were labeled with MS. IR was present in 16 (48.4%). Fifteen (44%) patients had biopsy-proven NAFLD. Patients with MS were more likely to have NAFLD by biopsy ($P$=0.001). 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 histology ($P$< 0.05) and fitted more with the criteria of MS (80% vs. 44%). IR was significantly more common among NAFLD patients (73% vs. 28%). **Conclusion:** There is a close association between obesity, MS, IR and NAFLD. Obese children with clinical or biochemical hepatic abnormalities are prone to suffer from MS, IR and NAFLD.

**Key Words:** Children, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, obesity, overweight

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As the number of obese children has increased worldwide, risks for obesity-related metabolic and endocrine derangements, including hyperinsulinemia, hypertriglyceridemia, and hypercholesterolemia, have led to early development and increased incidence of type 2 diabetes, cardiovascular disease, hypertension, and non-alcoholic fatty liver disease (NAFLD).[1]

The metabolic syndrome (MS) encompasses a group of factors that together confers an increased risk of cardiovascular disease and is associated with insulin resistance (IR) and type 2 diabetes mellitus. The most commonly used definition for pediatric MS was modified from the National Cholesterol Education Program (NCEP), Adult Treatment Panel III,[2] in which individuals must have at least three of the following criteria: Elevated blood pressure, low high-density lipoprotein cholesterol (HDL-c), high triglycerides (TG), high fasting glucose level, and abdominal obesity.

The risk factors for MS appear to track from childhood into adulthood.[3,4] Thus, prevention of MS during childhood might not only decrease chronic disease burden early in life but also lower the proportion of adults who will develop the disease.[5]

NAFLD is a clinicopathologic condition characterized by abnormal lipid deposition in hepatocytes (steatosis) in the absence of excess alcohol intake. NAFLD comprises a

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spectrum of diseases, ranging from simple hepatic steatosis to steatosis in association with necroinflammation and fibrosis (non-alcoholic steatohepatitis or NASH) to cirrhosis.[6] Although NAFLD is not traditionally part of the MS definition, it is widely considered the hepatic manifestation of the MS.[7]

Our aim was to study the prevalence of MS, IR and NAFLD in overweight/obese children with clinical hepatomegaly and/or raised alanine aminotransferase (ALT).

## PATIENTS AND METHODS

This study included overweight/obese children referred to the Pediatric Hepatology Unit, Cairo University Children's Hospital, Egypt, because of clinical hepatomegaly and/or elevated ALT. The following inclusion criteria were applied: Simple overweight/obesity, both sexes, age range 2–15 years and those consenting to perform a liver biopsy. The exclusion criteria applied were: 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], long-term use of drugs known to cause steatosis (e.g. glucocorticoids, aspirin) and any cause with syndromatic obesity. Informed consent was obtained from parents/guardians of all enrolled patients.

The total number of enrolled patients was 33 (19 males and 14 females); 8 were overweight and 25 obese. Their ages ranged between 2 and 13 years and the mean age was 8.4 ± 3 years. All the patients were subjected to the following.

### Anthropometric assessment

This includes weight (Wt) and height (Ht). Body mass index (BMI) was calculated as body weight (in kilogram) divided by height square (in meters). All were plotted on Egyptian growth charts.[8] Children were defined as overweight if their BMI was equal to or above 85$^{th}$ percentile and as obese if BMI was equal to or above 95$^{th}$ percentile. Abdominal obesity was assessed by comparing children's waist circumference (WC) measurements to the age- and gender-specific population distribution. Children were considered as having abdominal obesity if they met or exceeded the 90$^{th}$ percentile for age and gender.[9]

### Blood pressure

Blood pressure was assessed. Hypertension was considered when an average systolic or diastolic blood pressure was >90$^{th}$ percentile by age, gender and ethnic group (National High Blood Pressure).[10]

### Abdominal ultrasound examination

This was performed for all the enrolled patients, following not less than 8 hours fasting, by a single sonographer using an FFsonic UF-4100. Liver echo pattern was graded as follows:[11]

*Grade I (mild)*: A slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders.

*Grade II (moderate)*: A moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm.

*Grade III (marked)*: A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver.

### Biochemical tests

All patients underwent the following tests (following not less than 12 hours fasting period): Total cholesterol (normal range 100–200 mg/dl), high-density lipoprotein cholesterol (HDL-c) (normal range 30–70 mg/dl), low-density lipoprotein cholesterol (LDL-c) (normal value less than 130 mg/dl), TG (normal range 35–160 mg/dl) and fasting blood sugar (FBS) (normal range 65–100 mg/dl). Measurement was carried out using an auto-analyzer (Synchron-clinical system-CX5). Fasting serum insulin measurement was done by an auto-analyzer (DDC/immulite). IR was calculated using the following equation:

The homeostasis model assessment method

HOMA-IR = fasting insulin ($\mu$U/ml) × fasting glucose (mmol/l)/22.5.

IR was defined as HOMA-IR ≥ 3.5.[12]

### Liver biochemical profile

The following tests were conducted using an auto-analyzer (Abbott AXSYM system, UK): Total serum bilirubin (normal range: 0.2–1 mg/dl), direct serum bilirubin (normal range 0.1–0.3 mg/dl), ALT (normal range 5–41 U/l), aspartate aminotransferase (AST) (normal range 5–37 U/l), alkaline phosphatase (AP) (normal range 180–1200 U/l) and gamma glutamyl transpeptidase (GGT) (normal range 0–50 U/l). Prothrombin time (PT) and concentration (PC) (normal range 75–100%) were determined.

### Liver biopsy

Liver biopsy was performed for all patients. It was obtained with the Menghini technique using a secure cut biopsy needle of 1.6-mm diameter [Hospital Service S.p.A.Via Naro, Pomezia (RM), Italia].

The main histological features commonly described in NAFLD/NASH, including steatosis, inflammation (portal and lobular), hepatocyte ballooning, and fibrosis, were graded

according to the scoring system for NAFLD.[13]

### Metabolic syndrome

Patients were labeled as having MS by the presence of three or more of the following modified criteria: (1) TG levels ≥ 110 mg/dl, (2) HDL-c ≤ 40 mg/dl, (3) fasting blood glucose levels ≥ 100 mg/dl, (4) WC ≥ 90$^{th}$ percentile for age and gender, and (5) blood pressure ≥ 90$^{th}$ percentile.[2]

### Statistical methods

Statistical Package for Social Science (SPSS) program version 11.0 was used. Data were summarized as mean and standard deviation (SD). Differences in clinical and biochemical characteristics were tested by Student's *t* test for continuous variables and by Chi-square test for categorical data. A two-sided *P* value <0.05 was considered statistically significant.

## RESULTS

Demographic, physical and biochemical characteristics of the 33 patients are shown in Table 1. WC was ≥90$^{th}$ percentile in all but one patient. Systolic and diastolic blood pressures were normal in all the patients. Seven patients (21%) had elevated ALT and 3 (9%) had elevated AST; otherwise, GGT, AP, serum albumin and total serum bilirubin were within normal limits.

**Table 1: Demographic, physical and biochemical characteristics of the 33 overweight/obese patients**

| Characteristics | Subjects (*N* = 33) | Number of patients with abnormal results (%) |
|---|---|---|
| Demographic | | |
| Sex (male/female) | 19/14 | 33 (100) |
| Age (years) (mean ± SD) | 8.4 ± 3 | |
| Overweight/obese | 8/25 | |
| Physical characteristics | | |
| Waist circumference (cm) | 90.95 ± 12.36 | 32 (97) |
| Body mass index (kg/m$^2$) (mean ± SD) | 33.16 ± 5.42 | 33 (100) |
| Biochemical characteristics (mean ± SD) | | |
| ALT (U/l) | 35 ± 9.8 | 7 (21) |
| AST (U/l) | 30 ± 9.7 | 3 (9) |
| AP (U/l) | 348 ± 64.76 | 0 (0) |
| GTT (U/l) | 32 ± 10.7 | 0 (0) |
| Total serum bilirubin (mg/dl) | 0.53 ± 0.17 | 0 (0) |
| Serum albumin (g/dl) | 4.35 ± 0.23 | 0 (0) |
| Total cholesterol (mg/dl) | 181 ± 20 | 0 (0) |
| LDL-c (mg/dl) | 90 ± 20 | 0 (0) |
| HDL-c (mg/dl) | 40 ± 8.5 | 22 (66.7) |
| Triglyceride (mg/dl) | 150 ± 47 | 27 (81.8) |
| Fasting blood glucose (mg/dl) | 92 ± 8.7 | 8 (24.2) |
| Fasting insulin level (μU/l) | | |
| HOMA-IR | 15.7 ± 6.8 | 29 (87.8) |
| | 3.8 ± 0.9 | 16 (48.5) |
| | | 16 (87.8) |

Twenty patients (60.6%) had three or more criteria of MS. More specifically, 100% had hypertriglyceridemia, 95% low HDL-c and 30% high fasting blood glucose [Table 2]. IR was present in 16 children (48.4%).

The abnormal sonographic findings were echogenic liver in 32 patients (96.9%): 11 patients (33.3%) showed grade I echogenicity, 12 patients (36.3%) grade II echogenicity and 9 patients (27.2%) grade III echogenicity.

A percutaneous liver biopsy was obtained in all the patients: 18 cases (54.5%) had normal liver histology and 15 (45.5%) had NAFLD; 8 (24.2%) had simple steatosis and 7 (21.2%) had NASH. Patients with NASH were histologically graded. Four patients had moderate macrovesicular fatty changes and grade 1 (mild) necroinflammatory activity. Three patients had moderate macrovesicular fatty changes, grade 1 (mild) necroinflammatory activity [Figure 1] and stage 1 fibrosis.

Patients labeled as having MS had significantly higher incidence of histological NAFLD (70% vs. 7.7%; *P*=0.001), but no significantly higher ALT or echogenic liver by ultrasound [Table 3].

Children with NAFLD had significantly higher BMI, WC, ALT, total cholesterol, LDL-c, TG, fasting insulin, and lower

**Table 2: Frequency of criteria of MS (*N* = 20)**

| Variable | Criterion *n* (%) |
|---|---|
| Waist circumference ≥ 90$^{th}$ percentile | 20 (100) |
| Blood triglycerides ≥ 110 mg/dl | 20 (100) |
| HDL-c ≤ 40mg/d | 19 (95) |
| Fasting glucose ≥ 100 mg/dl | 6 (30) |
| Blood pressure ≥ 90$^{th}$ percentile | 0 (0) |

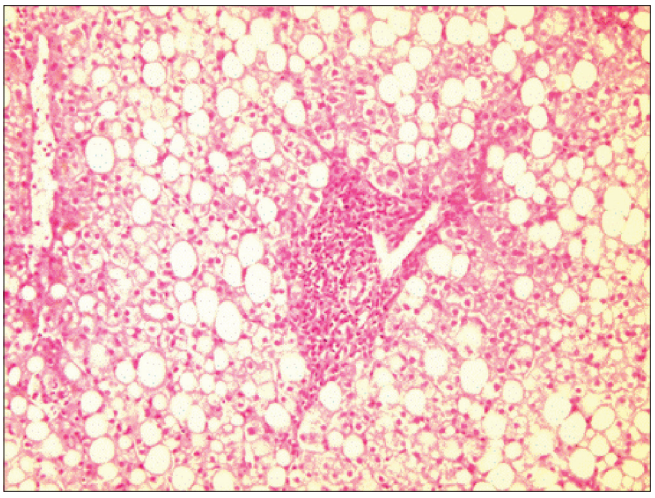

**Figure 1:** Liver biopsy of case 7 showing macrovesicular steatosis associated with mild mononuclear inflammatory cellular infiltrate in the portal area (H and E, original magnification ×200)

**Table 3: Comparison of hepatic abnormalities between patients with and without MS**

| Variable | Not meeting MS criteria (*N* = 13) *n* (%) | MS (*N* = 20) *n* (%) | *P* value |
|---|---|---|---|
| ALT ≥ 40 (IU/l) | 1 (7.7) | 6 (30) | NS |
| Bright liver by US | 12 (92.3) | 20 (100) | NS |
| NAFLD by biopsy | 1 (7.7) | 14 (70) | 0.001* |

**P* value <0.05 significant

HDL-c compared to patients with normal liver histology ($P<0.05$) and fitted more with the criteria of MS (80% vs. 44%). IR was significantly more common among NAFLD patients (73% vs. 28%). Sex, age and fasting glucose were not significantly different between the two groups [Table 4].

## DISCUSSION

Among our overweight/obese children presenting with hepatomegaly and/or raised ALT, 60% met three or more criteria for MS; 76% of them were obese. Many authors reported the prevalence of MS among obese adolescents to be between 12.4 and 54.2%,[5,14-22] reaching approximately 50% in some populations.[23] The higher prevalence of MS among our studied group may be explained by the fact that our obese/overweight patients were presenting with at least one hepatic abnormality (clinical hepatomegaly and/or raised ALT). This fact also accounts for the higher percentage of hypertriglyceridemia (81%) seen in our studied patients, in comparison to 26% in obese children as reported by Cruz *et al*.[21] Our selection criteria necessitated the presence of at least one hepatic abnormality to justify performing a liver biopsy for the patients.

In the present study, we graded according to the scoring system for NAFLD.[13] No special criteria were used that distinguish children from adults. The prevalence of MS in children with biopsy-proven NAFLD in the present study was 80%. A high prevalence of risk factors for the MS in patients with NAFLD has been previously described.[24-27] Goessling *et al*.[28] found that increased ALT was associated with developing MS over 20 years of follow-up. In the present study, almost half of children with NAFLD had increased ALT levels. Our patients with NAFLD had significantly higher ALT as compared to those with normal liver histology (mean ALT 43 ± 6 vs. 28 ± 7; $P=0.001$).

Obesity is strictly related to the development of NAFLD. In the present study, 45% of obese/overweight patients had biopsy-proven NAFLD which is similar to values observed by other authors,[29,30] but lower than Chan and colleagues who found it in 77% of their studied population.[31] This difference may be explained by genetic and/or environmental factors, similar to what has been hypothesized for adults.[32,33] Moreover, it is to be noted

**Table 4: Characteristics of patients with normal liver histology and NAFLD**

| Variable | Normal liver histology (*N* = 18) | NAFLD (*N* = 15) | *P* value |
|---|---|---|---|
| Sex (M/F) | 12/6 | 7/8 | NS |
| Age (years) (mean ± SD) | 8.6 ± 2.3 | 8.2 ± 3.9 | NS |
| Overweight/obese | 8/10 | 15/0 | 0.003* |
| BMI (kg/m$^2$) (mean ± SD) | 29.8 ± 2.3 | 37.4 ± 5.25 | 0.001* |
| WC (cm) (mean ± SD) | 86 ± 10 | 97 ± 13 | 0.001* |
| Waist circumference ≥ 90$^{th}$ percentile [n (%)] | 17 (94.4) | 15 (100) | NS |
| ALT (U/l) (mean ± SD) | 28 ± 7 | 43 ± 6 | 0.001* |
| Total cholesterol (mg/dl) (mean ± SD) | 171 ± 21 | 192.7 ± 9.9 | 0.001* |
| LDL-c (mg/dl) (mean ± SD) | 79 ± 14 | 103.6 ± 18.3 | 0.001* |
| HDL-c (mg/dl) (mean ± SD) | 44 ± 8 | 35 ± 7 | 0.001* |
| HDL-c ≤ 40 mg/dl [n (%)] | 8 (44.4) | 14 (93.3) | 0.01* |
| Serum triglyceride (mg/dl) (mean ± SD) | 125 ± 42 | 182 ± 35 | 0.001* |
| Serum triglycerides ≥ 110 mg/dl [n (%)] | 12 (63.2) | 15 (100) | 0.05* |
| Fasting blood glucose (mg/dl) (mean ± SD) | 90 ± 9 | 94 ± 8 | NS |
| Fasting glucose ≥ 100 mg/dl [n (%)] | 3 (15.8) | 5 (33.3) | NS |
| Fasting insulin level (μU/l) (mean ± SD) | 12.7 ± 6 | 19.35 ± 5.9 | 0.001* |
| HOMA-IR (mean ± SD) | 2.98 ± 0.8 | 4.77 ± 0.9 | 0.001* |
| Insulin resistance (HOMA-IR > 3.5) [n (%)] | 5 (27.7) | 11 (73.3) | 0.001* |
| Blood pressure ≥ 90$^{th}$ percentile [n (%)] | 0 (0) | 0 (0) | NA |
| Metabolic syndrome [n (%)] | 8 (44.4) | 12 (80) | 0.05* |

**P*<0.05 is statistically significant, NA = Not applicable, NS = Not significant

that 100% of our patients with NAFLD were obese. Thus, NAFLD is invariably associated with obesity and not simply overweight, although these results need to be verified and reproduced on a larger number of studied children.

In the present study, 100% of children with NAFLD had an elevated WC. WC is a surrogate marker for visceral fat, and visceral fat appears tightly correlated with hepatic TG content, elevated ALT, liver inflammation, and fibrosis.[34-36]

In a pediatric study,[37] every 1 cm increase in WC was associated with a 1.97-fold increased risk of NAFLD in boys and a 2.08-fold increased risk in girls.

In the present study, fasting serum insulin was significantly higher in patients with NAFLD in the present study. IR leads to increased lipolysis and free fatty acid output. The influx of free fatty acid into the liver combined with alternations of the fat metabolism in the liver result in accumulation of TG within the hepatocytes.[38,39] Hepatic steatosis alone can have a benign course without histological progression to fibrosis. IR is involved in the development of not only steatosis but also fibrosis by increasing fatty acid β-oxidation and oxidative stress.[40]

In the present study, 73% of our NAFLD patients had IR. The high rates of obese, insulin-resistant children with NAFLD meeting the criteria for MS suggest that a large number of these children will go on to develop diabetes.[41] This belief is supported by a cohort study from Sweden of adults with biopsy-proven NAFLD who had a 9% prevalence of diabetes at baseline. After nearly 14 years of follow-up, the majority (78%) of these patients developed impaired glucose tolerance or diabetes.[42]

The study limitation is the lack of data about liver histology from obese/overweight children who do not have hepatic abnormalities (lacking hepatomegaly and having normal ALT). The authors considered obtaining liver biopsy in obese children with no evidence of hepatic abnormalities unjustifiable.

Another limitation is the choice of raised ALT as an inclusion criterion. Among the seven cases with raised ALT, six had histologically proven NAFLD. However, raised ALT in one patient with normal liver biopsy may point to a patchy distribution of fatty infiltration in early NAFLD.

Abdominal ultrasonography showed an increased echogenicity: Grade I in 11 cases with normal liver histology and grade II in another 6 cases with normal liver histology. This may point to the lack of specificity of grades I and II echogenicity of abdominal ultrasound in detecting hepatic steatosis.

## CONCLUSION

In conclusion, there is a close association between obesity, MS, IR and NAFLD. Biopsy-proven NAFLD is invariably associated with obesity. Obese children with clinical or biochemical hepatic abnormalities are prone to suffer from MS, IR and NAFLD. Prevention of obesity and early intervention might be needed to reverse these abnormalities to reduce morbidity among obese children and adolescents.

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