Original Article

Ultrasonography and Functional Hepatic Alterations in Obese Children and Adolescents

Alteraciones ultrasonográficas y funcionales hepáticas en niños y adolescentes con obesidad

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Summary

Objective: To determine the ultrasonography and liver functional alterations in obese children and adolescents. **Methods:** non-experimental, analytical, cross-sectional study carried out in children and adolescents with obesity from five to seventeen years of age. The sample was divided into two groups, one with the presence of non-alcoholic fatty liver disease (NAFLD) (group 1) and the other with normal liver (group 2), determined by ultrasonography. Anthropometry, body composition and serum level measurements were performed to establish a biochemical and functional liver profile. Differences between groups were analyzed by Student's t-test, $p<0.05$. **Results:** a total of 59 participants were studied, of which 54.2% (n=32) were female and 45.8% (n=27) male. The average age of the population studied was 10.05 ± 2.5 years. Group 1 consisted of a total of 72.9% of patients (n=43), and group 2 consisted of 27.1% (n=16). The findings showed alterations in serum levels, biochemical profile and liver functionality. Fasting transaminases and insulin were significantly higher in group 1 patients than in group 2 ($p<0.05$). A higher insulin resistance ($p=0.000$) was also observed in group 1. **Conclusions:** there were alterations in serum levels, biochemical profile and hepatic functionality. Ultrasound and liver function tests should be part of the initial evaluation for early identification of this pathology in obese infants.

Keywords: Obesity; Children; Adolescent; Insulin Resistance; Non-alcoholic Fatty Liver Disease (NAFLD); Hepatomegaly; Fatty Liver; Liver Function Tests

Received: 30/09/2020
Accepted: 27/11/2020

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Quotation suggested: González-Pérez B, Salas-Flores R, Yáñez-Casados BM, Hernández-Carranco RG, Reséndiz-González E, Áspera-Campos T. Alteraciones ultrasonográficas y funcionales hepáticas en niños y adolescentes con obesidad. Aten Fam. 2021;28(2):75-81. http://dx.doi.org/10.22201/fm.14058871p.2021.2.78794

Resumen

Objetivo: determinar las alteraciones ultrasonográficas y funcionales hepáticas en niños y adolescentes con obesidad. **Métodos:** se realizó un estudio no experimental, analítico, de corte transversal en niños y adolescentes de cinco a diecisiete años con obesidad. La muestra se separó en dos grupos, uno con la presencia de enfermedad de hígado graso no alcohólico (grupo 1) y el otro con hígado normal (grupo 2), determinado mediante ultrasonografía. Se realizó antropometría, composición corporal y mediciones de niveles séricos para establecer un perfil bioquímico y funcional hepático. Las diferencias entre grupos se analizaron mediante la prueba t de Student, p<0.05. **Resultados:** se estudiaron un total de 59 participantes de los cuales 54.2% (n=32) fue de sexo femenino y 45.8% (n=27), masculino. La edad promedio de la población estudiada fue de 10.05 ± 2.5 años. El grupo 1 estuvo constituido por un total de 72.9% de pacientes (n=43), y el grupo 2 por 27.1% (n=16). Los hallazgos mostraron alteraciones en los niveles séricos, perfil bioquímico y funcionalidad hepática. Las transaminasas e insulina en ayuno fueron significativamente más elevados en los pacientes del grupo 1 que en los del grupo 2 (p<0.05). También se observó mayor resistencia a la insulina (p=0.000) en el grupo 1. **Conclusiones:** existieron alteraciones en los niveles séricos, perfil bioquímico y funcionalidad hepática. El ultrasonido y las pruebas de funcionamiento hepático deben formar parte de la valoración inicial para la identificación temprana de esta patología en infantes con obesidad.

Palabras clave: obesidad, niños, adolescentes, resistencia a la insulina, enfermedad del hígado graso no alcohólico, hepatomegalia, hígado graso, prueba de función hepática

Introduction

Childhood obesity is a global epidemic and in Latin America more than 20% of children and adolescents between zero and nineteen years of age are overweight or obese. In Mexico, the combined prevalence of overweight and obesity (OW-OB) in children between five and eleven years of age of both genders was 26.9% in 1999 and 34.8% in 2006. However, the results of the National Survey of Health and Nutrition (NSHN) in 2012 showed that the combined prevalence of OW-OB in that period decreased 0.4, from 34.8% to 34.4%.[1]

The mid-updated 2016 NSHN compared the national prevalence of OW-OB between 2012 and 2016 by gender for the different population groups and determined a national prevalence of OW-OB in preschool girls of 5.8%, which was lower than that observed in 2012 (9.7%); while in boys it was 6.5%, this is lower than that estimated in 2012 (9.9%). For schoolchildren, the prevalence of OW-OB was 32.8% for girls and 33.7% for boys in 2016; with respect to 2012, a slight increase was observed in girls and, in boys, a decrease of approximately three points. For adolescent females, the OW-OB went from 35.8% in 2012 to 39.2% in 2016 and for adolescent males it dropped from 34.1% to 33.5% from 2012 to 2016, respectively. Even though several efforts have been made to reverse the increase in childhood overweight and obesity in Mexico, high rates are still observed.[2]

As in other countries around the world, Mexico has been immersed in this epidemic that affects millions of infants and has become a public health problem, both because of its high prevalence and its association with diseases such as metabolic syndrome, diabetes, hypertension, heart disease, orthopedic problems, and non-alcoholic fatty liver disease (NAFLD).[3,4]

NAFLD is the most common cause of liver disease in infants and its increasing prevalence is associated with the concomitant rise in obesity. It is also considered the leading cause of liver disease in infants and adolescents in the United States (US) and probably in the Western world.[5] In the US the most reliable estimate of the pediatric prevalence of NAFLD is based on Schwimmer's analysis, a study of biopsies derived from autopsies of 742 infants in San Diego County, CA. In their research they found that the prevalence of NAFLD ranged from 0.7% in children aged two to four years to 17.3% in children aged 15 to 19 years. The prevalence was higher in infants with obesity (38%) regardless of age. Schwimmer also observed that the prevalence and severity of the disease varied among ethnicities, with the highest prevalence in Hispanic children, followed by Caucasians and then African Americans.[6] In Mexico, the prevalence of NAFLD was determined in 833 infants in an elementary school, aged 5.5 to 12 years, who presented OW-OB. It was concluded that 12.6% of those with OW-OB presented NAFLD and the metabolic parameters studied were similar regardless of their nutritional status.[7]

NAFLD is characterized by chronic elevation of aminotransferases and ultrasonography abnormalities (increased echogenicity); its prevalence and severity are related to variables such as body mass index (BMI), central fat distribution, dyslipidemia, glucose intolerance, hyperinsulinemia, and increased blood

pressure; it is also characterized histologically by triglyceride accumulation of hepatocytes in the cytoplasm.[8] The spectrum of NAFLD varies from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Likewise, bio-physiological data indicate that most infants will have simple steatosis. However, although there is little likelihood of complication, there are reported cases of liver cirrhosis in infancy.[9]

Children and adolescents are no exception to this medical condition and are likely to develop hepatocellular fibrosis and carcinoma, as well as high morbidity and mortality. The current annual medical and social costs of NAFLD are estimated at $292 billion in the US and the projected cost of patient care is expected to increase 18% by 2035.[10] This disease represents a high economic impact on the treatment of countries' healthcare systems; however, this disease and its complications can be prevented in time.[11]

NAFLD may not be easily recognized in obese infants because it usually produces no symptoms, only hepatomegaly. In most cases it is diagnosed incidentally when abnormal liver function tests are found in children and adults. The gold standard for definitive diagnosis is liver biopsy, which is an effective prognostic indicator of the disease, although it is not easy to perform in the pediatric population because it is an invasive and expensive method. An alternative is imaging studies such as ultrasound that help to diagnose it; on the other hand, computed tomography is not an appropriate diagnostic tool in children due to its radiation.[12,13]

The above gives relevance to the early identification of the disease and, in the case of children, to identify it in a non-invasive way to prevent progression to complications, by fully assessing infants with obesity. For this reason, the objective is to determine the ultrasonography (increased echogenicity) and functional hepatic alterations in children and adolescents with obesity.

Methods

The studied population consisted of children and adolescents aged five to seventeen years with obesity who were attended at the Pediatric Endocrinology Department of the "Clinica Hospital Cemain" in the city of Tampico, Tamaulipas, Mexico, who were included in a non-experimental, analytical, cross-sectional study during the period from March 2017 to December 2019. Informed consents were obtained from their parents or legal guardians and the letter of assent from all infants who agreed to participate in the study. The protocol was approved by the Ethics and Research Committee of the Clínica Hospital Cemain. Exclusion criteria were presence of diabetes, congenital or chromosomal anomalies, cardiovascular diseases, alcohol consumption, viral hepatitis, pathological states that may affect growth or body composition, or the use of orthopedic devices. Parents provided information related to the infant's disease background.

All measurements were performed by the same trained family physician. Participants were asked to remove their shoes and wear light clothing. Weight was measured to the nearest ±0.1 kg using a digital scale (Tanita Corporation, Japan). Height was obtained using a 225-cm portable stadiometer (SECA, Hamburg, Germany) with an accuracy of 0.1 cm. BMI was calculated as weight (kg) divided by height squared (m2).

The recommended tables by the National Center for Health Statistics (NCSH), created in 2000 and updated, were used, according to the BMI of each patient, which include centile registers of BMI for age and specific for each gender, available through the Center for Disease Control of the United States web page.[14] Patients with BMI above the 85th percentile for age were included in the study.

Body composition was determined by bioelectrical impedance analysis with a TANITA TBF310 model with a frequency of 50 kHz. Height, age and gender data were entered manually, while weight was automatically recorded using 0.5 kg as an adjustment for clothing weight in all patients. Measurements were taken during morning fasting, with bladder emptying, no liquids (prior four hours) and not having performed any vigorous physical exercise to reduce measurement bias. Blood pressure was measured with the appropriate cuff for the patient (at least surrounding 80% of the arm), in the sitting position with feet together, right arm supported at heart level, after the patient had been sitting quietly (without talking or performing any other activity) for at least ten minutes, a previously calibrated aneroid sphygmomanometer was used. The figures taken were classified according to the tables of blood pressure levels for boys and girls by age and weight percentile. Blood pressure figures were considered normotension when patients were below the 90th percentile; high normal pressure, between the 90th and 95th percentiles; and hypertension when they exceeded the 95th percentile.[15]

Blood samples were taken with twelve hours of fasting and the laboratory tests were performed in a Synchron CX systemized device, glucose was determined by the Glucose Oxidase

or UV-Hexokinase reaction, fasting insulin was evaluated by radioimmunoassay, hemoglobin A1c by immunoassay technique, Cholesterol profile by cholesterol oxidase/peroxidase enzymatic reaction, triglycerides by enzymatic colorimetric method, AST and ALT transaminases by Henry's technique, GGT was determined by Szasz technique, HOMA (Homeostatic Model Assessment) was calculated by the following formula to assess insulin resistance: HOMA= fasting insulin (μU/ml) x fasting glucose (mmol/L)/22.5 and QUICKI (Quantitative Insulin Sensitivity Check Index) to assess insulin sensitivity with the formula: 1 / log (fasting insulin) + log (fasting glucose).[16-18]

A Toshiba equipment was used for hepatic ultrasound, with a 3.5-5.0 MHz convex transducer. Longitudinal, subcostal, ascending and oblique measurements were always performed by the same radiologist, who was unaware of the clinical course and laboratory tests results of patients. The ultrasonography criteria to diagnose NAFLD were the increase of echogenicity (suggestive of hepatic steatosis) and the presence of hepatomegaly.[19]

Measures of central tendency and dispersion were used to describe quantitative variables, and frequencies and percentages for qualitative variables. Differences between groups were analyzed using Student's t test for independent samples and χ^2 in the SPSS statistical program (V.23; SPSS). A bilateral $p<0.05$ was considered statistically significant.

Results

A total of 65 patients were studied, five were excluded for not having completed the requested examinations, and one for having a BMI percentile of 75. The remaining 59 patients participated in the study, of which 54.2% (n=32) were female and 45.8% (n=27) were male. The average age of the studied sample was 10.05 ± 2.5 years; likewise, the average age of women was 10.5 ± 2.7 years,

Table 1. Distribution by gender with and without NAFLD*

Gender	With NAFLD		Without NAFLD		Total	
	n	%	n	%	n	%
Male	20	33.9	7	11.9	27	45.8
Female	23	39.0	9	15.3	32	54.2
Total	43	72.9	16	27.1	59	100

*χ^2 p value <0.22

Table 2. Somatometric characteristics in patients with and without NAFLD

Variable	With NAFLD		Without NAFLD		Student's t test
	$\overline{X}$	SD	$\overline{X}$	SD	p
BMI (kg/m2)	30.8	6.2	27.3	6.8	0.063
Fat Mass (kg)	23.6	12.8	15.8	10.6	0.035
Lean Mass (kg)	34.6	9.6	30.08	9.7	0.111
SBP (mmHg)	113.9	9.3	101.8	12.2	0.000
DBP (mmHg)	76.7	7.3	63.6	12.1	0.000

BMI= body mass index, $\overline{X}$= arithmetic average, SD= standard deviation, SBP=systolic blood pressure, DBP= diastolic blood pressure

Table 3. Classification of blood pressure in patients with and without NAFLD

Blood Pressure	With NAFLD		Without NAFLD		Total	
	n	%	n	%	n	%
Normal	1	2.3	10	62.5	11	18.6
Prehypertension	32	74.4	4	25	36	61
Hypertension	10	23.3	2	12.5	12	20.3
Total	43	72.9	16	27.1	59	100

while for men was 9.52 ± 2.2 years. The groups were defined as follows: group 1 with the presence of NAFLD 72.9% (n=43) and group 2 with normal liver 27.1% (n=16). It was observed that 39% (n=23) of the cases with NAFLD were female patients, see Table 1.

Somatometric characteristics

The average BMI in patients with NAFLD was higher, but without significant difference compared to patients without NAFLD (30.8 + 6.2 vs 27.3 + 6.8, p>0.063). Regarding fat mass values were also higher in patients with NAFLD presenting significant difference (23.6 + 12.8 vs 15.8 + 10.6; p<0.035). As for systolic and diastolic blood pressure, a significant difference was presented in both measurements, being higher in patients with NAFLD, see Table 2.

Blood pressure figures were classified according to the tables established for gender, age and height, with a greater number of cases with higher blood pressure figures in the group of patients with NAFLD, 23.3% (n=10) hypertension, 74.4% (n=32) prehypertension, and 2.3% (n=1) with normotension (Table 3).

Biochemical and Functional Liver Characteristics

The biochemical and functional liver profile was established, and the results were compared according to group 1 (NAFLD) and group 2 (normal liver). The average fasting glucose of group 1 patients was significantly higher than in group 2 (96.1 + 4.4 vs 87.1 + 7.4 mg/dl, p<0.001), as were the HbA1c averages (6.3 + 0.4 vs 4.8 + 0.6 %, p<0.001). Significant differences (p<0.001) were also found in all lipid tests, including triglycerides, with the exception of total cholesterol. Similarly, the average level of fasting ALT, AST, GGT and insulin was significantly higher in NAFLD patients than in those in group 2. Finally, a significant difference was found in the HOMA test and the rest of the measurements (see Table 4).

Table 4. Biochemical and functional liver profile in infants with and without NAFLD

	With NAFLD		Without NAFLD		Student's t test
Variable	$\overline{X}$	DE	$\overline{X}$	DE	p
Glucose (mg/dl)	96.1	4.4	87.1	7.4	0.000
HbA1c	6.3	0.4	4.8	0.6	0.000
Total Cholesterol (mg/dl)	166.4	35.2	157.1	24.5	0.340
HDL Cholesterol (mg/dl)	30.6	4.1	42.9	13.3	0.000
LDL Cholesterol (mg/dl)	95.5	9.2	71.9	8.03	0.000
Triglycerides (mg/dl)	207.7	107.8	111.3	24.8	0.001
Fasting Insulin (microU/ml)	31.8	9.3	15.7	8.6	0.000
HOMA	7.5	2.2	3.4	1.9	0.000
QUICKI	1.4	0.09	1.6	0.2	0.000
ALT (u/l)	55.1	12.7	29.4	10.7	0.000
AST (u/l)	53.2	20.7	28.5	8.02	0.000
GGT (u/l)	43.3	5.5	21.5	5.01	0.000

HbA1c= Glycosylated hemoglobin, ALT= Alanine aminotransferase, AST= aspartate aminotransferase, GGT= Gamma-glutamyltransferase, C-HDL= high-density lipoprotein cholesterol, C-LDL= low-density lipoprotein cholesterol, HOMA= mathematical model for the assessment of glucose homeostasis, QUICKI= Quantitative Insulin Sensitivity Check Index

Discussion

In this study, the presence of NAFLD was more frequent in females than in males, but no significant difference was found (p<0.22). Similar results have been reported in other studies, with no difference in the presence of NAFLD between boys and girls.[20-21] However, these results are inconclusive and in some cases contradictory.[22] Several hypotheses have been put forward about these findings including differences in hormones, body composition, fat distribution and metabolic profile.[23] New evidence suggests that estrogen production and action may be the main factor creating the discrepancy and affecting one gender more than the other.[24]

The results found that BMI in group 1 was not significantly higher than in group 2 (p=0.63). Although BMI, when increased, does not determine whether it is predominantly fat or lean mass, it is widely used to diagnose overweight and obesity, as it is related to skin fat, close to 0.90. BMI is an indicator with high specificity to evaluate obesity in childhood and adolescence, but with low sensitivity to measure fat distribution. It is accepted that 90% of BMI variations

are due to changes in adipose mass, even considering that height presents genetic variation.[25] The need to measure body composition in infants from the Primary Care level is imperative due to the high incidence of childhood obesity, which has increased the demand for accurate methods to determine body fat in young children. In contrast to the BMI values, the fat mass found in group 1 was higher than in group 2, demonstrating this assertion with the presence of NAFLD (p=0.035). These data indicate that the alteration in some anthropometric indicators is closely related to NAFLD in infants.

The course of NAFLD can be completely asymptomatic and diagnosed incidentally by elevation of hepatic aminotransferases as markers of hepatocyte damage, increased hepatic fat and visceral fat.[26,27] Liver transaminases are routinely obtained because it is an available and inexpensive test for screening and initial evaluation of NAFLD. In the results of this study, ALT and AST values in group 1 patients were higher than in group 2, demonstrating an alteration in the presence of NAFLD.

On the other hand, elevated GGT levels in the pediatric population correlate directly with the hepatic fibrosis degree.[28] Hyperinsulinemia, caused by insulin resistance, is a determinant in the pathogenesis and is a predictor of NAFLD.[29] This information was verified in the results found in group 1 of the present study, in which all the patients with the presence of NAFLD diagnosed by ultrasound presented hyperinsulinemia and insulin resistance (assessed with the HOMA and QUICKI equations, respectively), evidence that highlights the alteration of insulin resistance in the presence of NAFLD.

The presence of hypertriglyceridemia has been considered as another biochemical marker frequently reported in children with obesity and the presence of NAFLD. The predominant pattern observed is combined dyslipidemia characterized by elevated LDL-C, triglycerides and decreased HDL-C.[30] This study also found that patients in group 1 had elevated triglyceride, LDL-C and abnormal HDL cholesterol values.

The evidence reported in this study shows that metabolic alterations that were thought to occur only in adults are now occurring in childhood, so it is important to consider an implementation of programs for early detection of NAFDL in Primary Care and to request laboratory tests such as those mentioned in this study for a timely detection of insulin resistance (acanthosis nigricans) and to initiate a dietary plan to help reduce weight and perform multidisciplinary management of the infant with obesity.

The study has some limitations that should be noted. NAFLD diagnosis was based on ultrasound imaging and the exclusion of other causes of chronic liver disease. It was based on parental report, such as having had viral hepatitis or alcohol consumption in adolescents which elevate liver aminotransferases; however, NAFLD was not confirmed by liver biopsy. It is known that none of the radiological features can distinguish between steatohepatitis and other forms of NAFLD and that only liver biopsy can assess the severity of damage and prognosis.[31] However, it would be impossible to perform a liver biopsy routinely in a large epidemiological study and it is not feasible to perform it in the pediatric population due to its invasive method that can have complications when taking the biopsy and high cost.

Conclusions

There are a series of alterations in anthropometric measurements, serum levels, biochemical profile and liver function in the presence of NAFLD. This highlights the importance of early and timely diagnosis of NAFLD in Primary Care through ultrasonography and liver function tests as accessible, non-invasive and safe diagnostic methods in children and adolescents with obesity.

It is important to inform parents and patients, as non-pharmacological measures, about the need to initiate an eating plan for weight reduction and to establish real short and long term goals. It is advisable to form support groups in which talks are given about the disease and the benefits of making changes in lifestyle, weight reduction through exercise and a good eating plan, as well as to follow up children with this disease to evaluate compliance with the given indications, since the presence of NAFLD in children is increasing as the onset of obesity increases.

It is important to inform parents and patients to make lifestyle changes and that weight reduction is essential to avoid the progression towards complications of this non-alcoholic fatty liver disease.

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