Cut Off Values of Visceral Adiposity for the Prediction of Non-alcoholic Fatty Liver Disease.

Hayam Kamal Nazif,[1] Moushira Erffan Zaki,[2] Wafaa Kandeel,[2] Heba Ahmed El-malt,[3] Khalda Amr,[4] Yasser EL-Hossary,[5] and Ramy Mohammed El-sherbini[2]

[1]Department of Childhood Medical Studies- Institute of Postgraduate Childhood Studies, [2]Biological Anthropology Department, National Research Center, [3]Biochemistry Department- National Research Center, [4]Human Molecular Genetics Department- National Research Center, [5]Internal Medicine Department- National Research Center

Abstract

Background: Non- alcoholic fatty liver disease includes a broad spectrum of liver tissue alterations, ranging from pure steatosis to non- alcoholic steatohepatitis to cirrhosis. Studies demonstrated that visceral adiposity is a risk factor for pediatric NAFLD and that visceral adiposity increases in parallel with the steatosis degree.

Aim: To determine the visceral adiposity thickness cut off points as a risk factor for the development of NAFLD in obese adolescents.

Results: No significant association was found between ALT and the ultrasonographic grades of NAFLD. No significant difference was found in AST across the different sonographic grades of NAFLD, Significant difference was found in BMI (Kg/m^2), hip circumference, waist circumference, abdominal skin fold thickness, fat mass, visceral fat thickness, serum cholesterol and blood glucose according to the different sonographic grades of the non- alcoholic fatty liver disease among patients. Where patients with grade 3 NAFLD had significant higher values than patients with grade 2 NAFLD and 1 NAFLD. Patients with grade 2 NAFLD had significant higher fat mass, abdominal skin fold thickness, waist and hip circumferences, and BMI than grade 1 NAFLD, Cut off points for visceral fat thickness is 3.55 cm for female patients and 3.9 cm for male patients, which can be predictive of NAFLD in obese adolescents.

Conclusion: Measurements of liver enzymes alone are insufficient, and liver ultrasonography is required for early identification of NAFLD, The expansion of visceral fat was associated with the severity of nonalcoholic fatty liver disease in obese adolescents. Visceral fat thickness above 3.55 cm for obese adolescents females and above 3.9 cm for obese adolescents males can be predictive of NAFLD.

Key words: Obese, Adolescents, NAFLD, and Visceral fat thickness

تعدد الاشكال من IL-6- 174G/C فى المراهقين البدناء

الذين يعانون من الكبد الغيركحولى وعلاقته بالمعلمات السريرية

الخلفية: تعد السمنة فى الأطفال وباء عالمي، لقد بينت الدراسات العلاقة بين السمنة والعديد من الامراض فى حياة الكبار، مثل ارتفاع ضغط الدم، ومرض السكرى النوع اثنين، السرطان وأيضا وفيات القلب والأوعية الدموية، والجديد بالذكر أن فائض الدهون فى الجسم متمثلا فى السمنة المركزية، يرتبط بشكل وثيق مع هذه الأمراض خاصة مرض الكبد الدهنى غير الكحولي. يشمل مرض الكبد الدهنى الغير كحولى على تعديلات واسعة الطيف من انسجة الكبد، بدأ من تنكس دهنى إلى تليف كبدى إلى التهاب الكبد الدهني. وفى تلك الدراسة تتماشى السمنة الحشوية بالتوازى مع زيادة درجة التنكس الدهنى للكبد، ولقد بينت الدراسات الأخيرة أن السمنة الحشوية هى عامل خطير لحدوث مرض الكبد الدهنى الغير كحولى فى الأطفال.

هدف الدراسة: تحديد النقاط للسمنة الحشوية كعامل خطر لحدوث الكبد الدهنى غير الكحولى فى المراهقين يعانون من السمنة المفرطة.

منهج الدراسة: تجرى الدراسة على ٧٠ مراهق مصاب بالسمنة (نسبة كتلة الجسم عند او اكثر من ٩٥ وفقا لمنحنيات النمو للمراهق المصرى) السن من (١٥- ١٨) عام من كلا الجنسين ويتم بمقارنة ٧٠ من المراهقين الأصحاء. ستجرى الدراسة فى عيادة الموجات فوق الصوتية بالمركز القومى للبحوث، سيتم عمل القياسات الأنثروبومترية الآتية (وزن الجسم، الطول، محيط الخصر. محيط منتصف الذراع الأعلى. محيط الفخذ). سمك الجلد فوق (العضلة ذات الرأسين، العضلة ذات الثلاث رؤوس، العضلة تحت لوح الكتف، أعلى الحرقفى والبطن). المؤشرات التى سيتم حسابها (معدل كتلة الجسم، نسبة الخصر الى الأرداف). قياس البنية الجسدية باستخدام جهاز المعاوقة الكهربائية، قياس ضغط الدم، التحاليل المعملية الدهون فى الدم ويتضمن: الكليستيرول الكلى- البروتين الشحمى عالى الكثافة HDL البروتين الشحمى منخفض الكثافة LDL الدهون الثلاثية، السكر الصائم الأنسولين، CRP, ALT, AST وسيتم حساب HOMA- IR الموجات فوق الصوتية للبطن لتقييم سمك الدهون الحشويه. سمك الدهون التى تحت الجلد، الكبد الدهني.

النتيجة: النقاط القاطعة للسمنة الحشوية كعامل خطر لحدوث الكبد الدهنى غير البدناء هى للذكور ٣,٥سم وللاناث ٣,٩سم.

Introduction:

Childhood obesity is a global epidemic. Rising trends in overweight and obesity are apparent in developed and developing countries (Flynn et al., 2006). Studies have shown the relationship between obesity and several diseases in adult life, such as arterial hypertension, type 2 diabetes mellitus, cancer, cardiovascular mortality, and also nonalcoholic fatty liver disease (NAFLD) (Bugianesi et al., 2005, Ong et al., 2005).

Several studies indicate however that (30- 40)% of obese subjects (Trombetta et al., 2005) and (28- 55)% of diabetics (Trombetta et al., 2005) have NAFLD.

NAFLD is an emerging clinical problem among obese patients of all ages (Federico et al., 2006). NAFLD includes a broad spectrum of liver tissue alterations, ranging from pure steatosis to non- alcoholic steatohepatitis (NASH) to cirrhosis (Angulo, 2002). NASH is defined by the presence of lobular necroinflammatory activity with or without the presence or perisinusoidal fibrosis that can evolve to cirrhosis and can be detected on liver biopsy (Loguercio et al., 2004, Palekar et al., 2006). Differentiating between the two is important because as many as 28% of patients with steatohepatitis, in contrast to those with simple steatosis, may progress to cirrhosis, but the only reliable method of differentiating them is by biopsy, which is costly and carries risks to patients (Harrison et al., 2004). Ultrasonography (US) is a cheap, non invasive and dependable technique to diagnose NAFLD and to measure the visceral fat commonly used in an ambulatory care setting Saadeh et al (2002). Visceral adiposity increased in parallel with the steatosis degree. In another study, Sabir et al. (2001) found a stronger correlation between visceral fat and steatosis than preperitoneal or subcutaneous fat analysed by ultrasonography.

Studies developed by Fishbein et al. (2006) demonstrated that visceral adiposity is a risk factor for paediatric NAFLD.

A previous study revealed that NAFLD was associated with visceral obesity, abnormal liver function tests, an adverse serum lipid profile, insulin resistance, and elevated blood pressure (Denzer et al., 2009).

A previous study revealed the unique association of insulin resistance and size of the visceral depot with the risk for fatty infiltration of the liver and development of suspected steatohepatitis in both genders (Denzer et al., 2009).

Aim Of The Study:

The aim of the study was to determine the visceral adiposity thickness cut off points as a risk factor for the development of NAFLD in obese adolescents.

Design Of The Study

Type of the study:

It is a case control study.

Subjects And Methods

Study Sample:

Seventy obese adolescents were recruited from the Ultrasonography Clinic of the National Research Center. They were 48 females and 22 males. They were included according to the inclusion criteria (BMI≥ 95th percentile, aged from (15- 18) years (late adolescents)), with non alcoholic fatty liver disease (NAFLD) diagnosed by ultrasonography.

Methods:

All patients and controls were subjected to:

1. Full medical history laying stress on:
   a. Personal history: age, sex, residence.
   b. Present history: onset, course, and progression.
   c. Past history: operations, blood transfusion, and medical conditions.
   d. Family history: obesity and chronic disease as: cardiovascular complications, diabetes, and hypertension.
   e. Thorough Clinical Examination:
      - General examination: Including:
        1. Head, neck, hands, and feet laying stress on: (acanthosis nigricans, acne, striae and dysmorphic features).
        2. Vital signs: Including temperature, heart rate, respiratory rate and laying stress on blood pressure measurement (National High Blood Pressure Education Program, 2004).
        3. Systemic examination: Laying stress on: Cardiac, chest, neurological and laying stress on abdominal examination: jaundice, striae, abdominal pain, edema and hepatomegaly.
        4. Auxology and growth assessment: Weight and height measurement were done using Egyptian growth charts (Ghalli et al., 2002). Waist circumference, hip circumference, mid upper arm circumference and skinfold thicknesses (triceps, abdominal, biceps, subscapular) (WHO, 2007) were assessed using standardized equipements and following recommendations of the international biologcal program (Hiernaux, J, Tanner, J, 1969)
      - Investigations:
        1. Laboratory Investigations:
           - Fasting lipid profile (LDL, HDL, Cholesterol, Triglycerides) was done by colorimetric method (National Cholesterol Education Program (NCEP), 2001).
           - High sensitivity C reactive protein, (IMMAGE immunochemistry systems, Beckman coulter INC., Fullerton, CA, USA.)
           - Fasting blood glucose by colorimetric method.
           - Fasting insulin level (Immulite serum insulin Code N: 23657505) (Matthews et al., 1985). Insulin resistance will be assessed by homeostasis model assessment insulin resistance index (HOMA- IR). HOMA- IR will be calculated by the fasting blood glucose (FBG) and the immunoreactive insulin (I): [FBG (mg/dl)×I (mU/l)]/ 405 (Mehmet et al., 2005).
           - Liver enzymes (Alanine Aminotransferase (ALT), Aspartate, Aminotransferase (AST).
        2. Ultrasonography: All abdominal ultrasonography procedures and measurements of visceral fat (The rectus muscle to spine and rectus muscle to aorta distances), subcutaneous fat tissue (The distance between skin to fat and fat to rectus muscle interfaces) and fatty liver was performed double blinded by the same physician specialized in diagnostic imaging using a 3.5 MHz multifrequency transducer (broad band) (SONOACEX8, SN: BO7900012301672). Visceral fat of obese adolescents was distributed in quartiles after ultrasound non alcoholic fatty liver disease diagnosis (Fishbein et al., 2006).
        3. Body composition assessment: Measuring fat% and fat free mass was done using body fat analyzer (Taneta (T5869) SN:

10010359v) by bioelectrical impedance (Bunc, 2007).

Results:

Table (1) Comparison of Clinical and Anthropometric Parameters between Patients and Control group.

		Patients Mean±SD	Control Mean±SD	t	P. Value
Age		16.43±1.399	16.83±1.370	10.983	0.46
Blood Pressure	Systolic blood pressure (mmhg)	115.07±17.120	100.24±13.559	1.805	0.001*
	Diastolic blood pressure (mmhg)	72.71±11.569	65.04±10.740	3.91	0.001*
	BMI (Kg/m^2)	38.09±5.493	19.65±3.763	3.084	0.001*
Anthropometric Data	Waist Circumference (Cm)	106.67±12.25	71.23±12.56	16.907	0.001*
	Hip Circumference (Cm)	123.20±9.48	89.77±10.78	19.487	0.001*
	Waist To Hip Ratio	0.8671±. 09074	0.7953±12320	3.929	0.001*
	Mid upper arm circumference (cm)	41.80±4.245	25.79±8.54	3.093	0.002*
	Triceps skin fold thickness (mm)	31.66±5.66	15.70±8.31	13.276	0.001*
	Biceps skin fold thickness (mm)	27.15±7.02	12.30±6.72	12.790	0.001*
	Abdominal skin fold thickness (mm)	33.95±8.07	15.12±7.74	14.093	0.001*
	Suprailiac Skin Fold Thickness (Mm)	19.17±597	8.66±4.43	11.828	0.001*
	Sub scapular skin fold Thickness (mm)	35.90±6.74	14.97±7.48	17.395	0.001*

Independent Samples Test, BMI= body mass index; BP= blood pressure; WHR= waist: hip ratio.

In table (1) it can be seen that patients have significantly higher systolic blood pressure, diastolic blood pressure and greater anthropometric measurements than control subjects (P< 0.05).

Table (2) Sex Distribution in Patients and Control.

	Patients No. (%)	Control No. (%)	X^2	P
Male	48 (68.5%)	45 (64.2%)	0.097	0.755
Female	22 (31.5%)	25 (35.8%)		
Total	70 (100%)	70 (100%)		

From table (2) it can be seen that sex distribution in patients is 48 (68.5%) males and 22 (31.5%) females, while in control subjects is 45 (64.2%) males and 25 (35.8%) females with no significant difference.

Table (3) Clinical Characteristics in Patients.

		Patients No. (%)
Percentiles (BMI)	95th<97th≤	10 (25.8%)
	97th≤	60 (74.2%)
Hepatomegally	Yes	24 (24.3%)
	No	46 (65.7%)
Splenomegally	Yes	57 (81.4%)
	No	13 (18.6%)
Acanthosis	Yes	30 (42.8%)
	No	40 (57.2%)
Striae	Yes	18 (25.7%)
	No	52 (74.3%)
Total		70 (100%)

Chi- Square Tests

From table (3) it can be seen that frequency distribution of the patient subjects according to clinical characteristics showed that 25.8% of the patients had BMI≤ 95th< 97th percentiles while 74.2% had BMI≤ 97th percentiles, 24.3% of the patients had splenomegally, 42.8% of the patients had acanthosis and 25.7% of the patients had striae.

Table (4) Comparison of Body Composition Data between Patients and Controls.

Body composition data by Tanita sc- 30	Patients Mean±SD	Control Mean±SD	t	P. Value
Fat Percentage	12.28±19.032	4.79±8.015	2.970	0.001*
Fat Mass	43.99±12.978	9.42±6.841	19.716	0.001*
Fat Free Mass	15.58951±59.4929	14.87113±42.0500	7.981	0.001*

Independent Samples Test

From table (4) it can be seen that patients have significantly higher fat percentage, fat mass, fat free mass than control subjects (P< 0.05).

Table (5) Comparison between Patients and Controls Regarding Laboratory Data.

Laboratory Data	Patients Mean±SD	Control Mean±SD	t	P. Value
Fasting blood glucose (mmol/L)	95.31±16.644	91.53±9.705	1.644	0.102
Fasting serum insulin (mmol/L)	21.03±12.387	3.94±1.306	11.476	0.001*
Homa- Ir	4.9743±3.09705	0.8888±0.30631	10.983	0.001*
CRP (ng/ml)	640.53±286.995	177.68±46.277	13.227	0.001*
AST (mg/dl)	25.19±11.379	24.64±8.302	0.322	0.748
ALT (mg/dl)	22.23±11.840	14.07±6.783	5.002	0.001*
Triglycerides (mmol/L)	123.49±69.631	80.36±46.889	4.298	0.001*
Cholesterol (mmol/L)	174.69±34.601	160.13±27.618	2.751	0.001*
LDL (mmol/L)	103.39±33.914	98.58±30.172	0.885	0.378
HDL (mmol/L)	46.77±19.063	49.00±20.601	-0.664-	0.508

Independent Samples Test, Insulin level: (normal value= (0.7- 0.9)mmo; /l) , Insulin resistence at HOMA- IR≥ 3.16, FPG= fasting plasma glucose; HDL= high- density lipoprotein; LDL=l ow density lipoprotein; HOMA- IR test (Homeostasis Model Assessment)= [fasting insulin (IU/ ml) fasting glucose (mmol/l)]/ 22.5: CRP= C reactive protein: AST= aspartate transaminases: ALT= alanine transaminases

From table (5) it can be seen that patients have significantly higher values of fasting serum insulin, HOMA- IR, CRP, ALT, triglycerides, cholesterol and lower HDL value than the control group (P< 0.05).

Table (6) Comparison between Patients and Controls Regarding Ultrasonographic Data.

Ultrasonographic Data	Patients Mean±SD	Control Mean±SD	t	P. Value
Subcutaneous fat thickness (cm)	3.04±0.962	1.15±0.530	14.372	0.001*
Visceral fat thickness (cm)	4.77±16.16	3.23±2.126	4.823	0.001*

Independent Samples Test

From table (6) it can be seen that patients have significantly higher visceral and subcutaneous fat thickness than the control subjects (P< 0.05).

Table (7) Comparing Anthropometric, Laboratory and Body Composition Data of Patients with Different Grades of Non- alcoholic Fatty Liver Disease

	Grade1 NAFLD Mean±SD No. (%) 40 (57.1%)	Grade2 NAFLD Mean±SD No. (%) 16 (22.8%)	Grade3 NAFLD Mean±SD No. (%) 14 (20.1%)	P Value
BMI (Kg/m^2)	36.32±4.992	37.24±1.745	44.68±5.460	0.000*
Hip Circumference (Cm)	120.92±9.802	122.29±5.676	131.38±8.392	0.002*
Waist Circumference (Cm)	102.30±11.964	109.24±9.344	116.7±79.867	0.000*
Biceps Skin Fold Thickness	25.35±6.041	30.11±7.963	28.85±7.324	0.008*
Abdominal skin fold thickness (mm)	31.56±8.082	36.13±6.688	38.46±7.401	0.010*
Fat Mass	40.18±11.743	44.07±7.211	55.62±15.996	0.001*
Fasting blood glucose (mmol/L)	94.02±12.721	90.18±12.660	106.00±26.204	0.025*
Cholesterol (mmol/L)	177.48±30.157	156.82±40.231	189.46±32.498	0.025*

Non alcoholic fatty liver disease, One Way Annova, BMI= Body Mass Index

From table (7) it can be seen that BMI, hip circumference, waist circumference, biceps skin fold thickness and abdominal skin fold thickness are statistically significant according to different sonographic grades of NAFLD (P< 0.05). None of the other parameters is statistically significant.

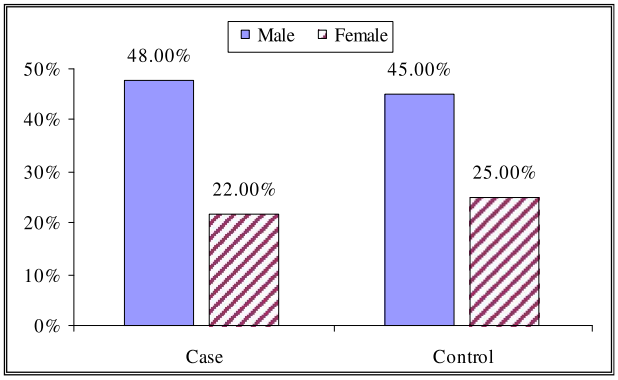


Figure (1) Sex distribution in cases and control.

Table (8) Comparison between Clinical Characteristics of Male and Female Patients.

		Female	Male	X^2	P Value
Percentiles (BMI)	≤95th<97	8 (16.7%)	2 (9.1%)	0.707	0.488
	≤97th	40 (83.3%)	20 (90.9%)		
Hepatomegally	Yes	19 (40.4%)	5 (22.7%)	2.069	0.183
	No	28 (59.6%)	17 (77.3%)		
Splenomegally	Yes	45 (93.8%)	12 (54.5%)	15.333	0.001*
	No	3 (6.2%)	10 (45.5%)		
Acanthosis	Yes	24 (50.0%)	6 (27.3%)	3.182	0.118
	No	24 (50.0%)	16 (72.7%)		
Striae	Yes	11 (22.9%)	7 (31.8%)	1.810	0.357
	No	37 (77.1)	15 (68.2)		

Chi- Square Test

From table (8) it can be seen that splenomegally is significantly more prevalent in the female patients compared to male patients. While the other parameters show no significant difference.

Table (9) Comparison between Clinical and Anthropometric Parameters of Male and Female Patients

		Male Mean±SD	Female Mean±SD	t	P. Value
Clinical Data	Systolic blood pressure (mmhg)	122.73±15.18	111.56±16.95	1.805	0.001*
Anthropometric Data	BMI (Kg/m²)	36.29±3.44	38.92±6.07	-1.897	0.001*
	Waist Circumference (Cm)	111.09±12.26	104.65±11.82	2.065	0.040*
	Hip Circumference (Cm)	120.23±6.60	124.56±10.31	1.805	0.038*
	WHR	0.9244±0.09488	0.8409±0.07632	3.933	0.001*
	Mid upper arm circumference (cm)	36.23±4.93	44.35±51.12	-0.741	0.281
	Triceps skin fold thickness (mm)	30.02±5.71	32.41±5.54	-1.660	0.109
	Subscapular skin fold thichness (mm)	34.50±7.08	36.54±6.55	-1.180	0.259
	Biceps skin fold thickness (mm)	28.41±7.60	26.58±6.74	1.013	0.339
	Abdominal skin fold thickness (mm)	36.92±6.5	32.59±8.40	2.137	0.23*
	Suprailiac skin fold thickness (mm)	17.89±5.85	19.76±5.99	- 1.219	0.225

Independent Samples Test, BMI= body mass index: WHR= waist: hip ratio.

From table (9), it can be seen that male patients have significant higher systolic blood pressure, waist circumference, abdominal skin fold thickness and waist/hip ratio than female patients (P< 0.05), also it can be seen that female patients have significant higher BMI and hip circumference than male patients (P< 0.05), and no significant difference in the other anthropometric parameters.

Table (10) Comparison Between Male And Female Patients Regarding Body Composition Parameters.

Body composition data by Tanita sc- 30	Male Mean±SD	Female Mean±SD	t	P. Value
Fat Mass	38.28±7.78	46.61±14.07	2.435	0.02*
Fat Percentage	1104.43±1626.50	1286.42±2036.50	-0.367	0.693
Fat Free Mass	72.2364±20.38988	53.6521±7.75741	-2.593	0.001*

Independent Samples Test

From table (10) it can be seen that female patients have significantly higher fat mass and male patients have significantly higher fat free mass (P< 0.05).

Table (11) Comparison between Male and Female Patients Regarding Laboratory Data

Laboratory Data	Male Mean±SD	Female Mean±SD	t	P. Value
Fasting blood glucose (mol/L)	95.05±12.07	95.44±18.48	-0.091	0.916
Fasting serum insulin (mmol/L)	21.14±15.17	20.98±11.07	0.049	0.966
Homa- Ir	4.9294±3.7138	4.9949±2.8138	-0.081	0.942
CRP	540.53±286.995	580.68±46.277	8.227	0.33
ALT (mg/dl)	26.27±10.60	20.38±12.02	1.975	0.044*
AST (mg/dl)	27.59±14.22	24.08±9.79	1.201	0.303
Cholesterol (mmol/L)	164.23±37.26	179.48±32.60	-1.737	0.107
Triglycerides (mmol/L)	145.00±99.81	113.63±48.48	1.777	0.173
HDL (mmol/L)	40.50±14.32	49.65±20.37	-1.898	0.035*
LDL (mmol/L)	95.46±36.49	107.02±32.42	-1.330	0.211

Independent Samples Test, HDL= high- density lipoprotein; LDL=l ow density lipoprotein HOMA- IR test (Homeostasis Model Assessment) = [fasting insulin (IU/ ml) fasting glucose (mmol/l)]/ 22.5: CRP= C reactive protein: AST= aspartate transaminases: ALT= alanine transaminases.

From table (11) it can be seen that male patients have significantly higher levels of serum ALT and lower levels of serum HDL than female patients (P< 0.05). While female patients showed a tendency to higher serum cholesterol, LDL, insulin and HOMA- IR with no significant difference.

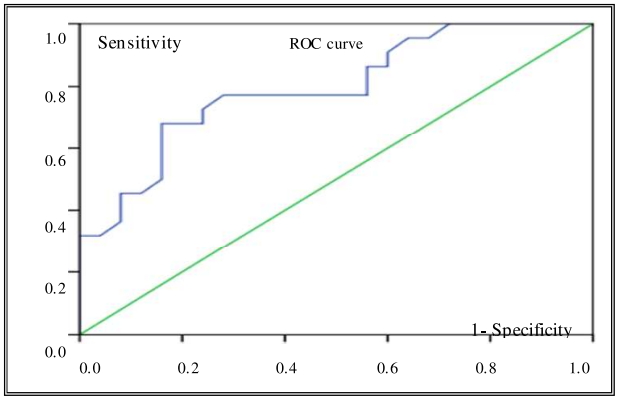
Table (12) Comparison Between Both Male And Female Patients Regarding Ultrasonographic Data.

Ultrasonographic Data	Male Mean±SD	Female Mean±SD	t	P. Value
Subcutanous fat thickness (cm)	2.66±0.85	3.21±0.97	-2.409	0.020*
Visceral fat thickness (cm)	4.92±1.72	4.29±1.37	1.539	0.139

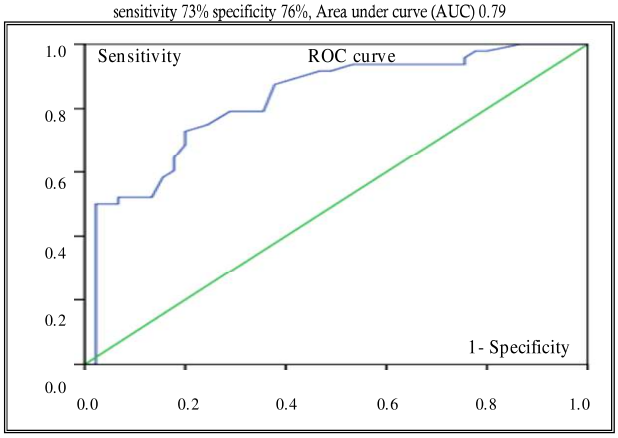
Independent Samples Test

From table (12) it can be seen that female patients have significantly higher subcutaneous fat thickness than male subjects while there is no significant difference in the visceral fat thickness.

Roc Curve: Visceral fat of obese adolescents was distributed in cut- off values using a Receiver Operating Characteristic Curve ROC curve. ROC curve was used to determine a cut- off that suggested the best accuracy of the visceral adiposity the computed risk score values to development the nonalcoholic fatty liver (NAFLD) given as area under the curve (AUC) and 95% confidence interval (CI). An AUC of 1.0 is characteristic of perfect discrimination, whereas an AUC of 0.5 indicates chance discrimination. In ROC analysis, the true- positive rate (sensitivity) is plotted against the false-positive rate (1- specificity) across a range of values from the diagnostic test. This provides an estimate of the cut- off that corresponds to the best tradeoff between sensitivity and 1- specificity (i.e., minimal false negative and false-positive cases), suggesting the NAFLD. The decision threshold for the best tradeoff is the criterion value with the highest accuracy that maximizes the sum of the sensitivity and specificity. One index reflecting the overall accuracy of the diagnostic test derived from an ROC analysis is the area under curve (AUC)



Diagonalsegments are producedby ties
Fig (2) Cut- off of visceral fat thickness for male patients is 3.9 cm, sensitivity 73% specificity 76%, Area under curve (AUC) 0.79



Diagonalsegments are producedby ties
Fig (3) Cut- off of visceral fat thickness for female patients is 3.55 cm, sensitivity 72.9% specificity 80% Area under curve (AUC) 0.83

Discussion:

NAFLD is a global public health problem. The prevalence of NAFLD is increased in first- degree relatives of individuals with NAFLD, particularly if they are obese, (Schwimmer et al., 2009) and this suggests a potential cascade of population risk. Serum alanine aminotransferase (ALT) levels are frequently used to define NAFLD (Ruhl& Everhart, 2003; Booth et al., 2005; Schwimmer et al., 2008); however, ALT is relatively insensitive and nonspecific for NAFLD (Bedogni et al., 2005).

NAFLD comprises a disease spectrum ranging from simple steatosis to steatohepatitis (NASH), with varying degrees of inflammation and fibrosis, progressing to end- stage liver disease with cirrhosis (Loomba et al., 2009).

The aim of the present study was to determine the visceral adiposity thickness cut off points as a risk factor to develop NAFLD in obese adolescents.

Seventy obese adolescents were included. They were recruited from the ultrasonography clinic of the national research center; their age ranged from (15- 18) years. Seventy age and sex matched control subjects were also included for comparison.

The enrolled subjects were subjected to full history taking, general examination, anthropometric measurements, laboratory and ultrasonographic evaluation

In agreement with other more recent studies (Ayonrinde et al., 2011; Santomauro et al., 2012; Alp et al., 2013; Anna et al., 2013), the present study shows that when comparing patients to controls that patients had significantly higher serum insulin (3.94± 1.306 versus 21.03± 12.387, p= 0.001), HOMA-IR (0.8888± 0.30631 versus 4.9743± 3.09705, p= 0.001), higher ALT (14.07± 6.783 versus 22.23± 11.840, p= 0.001), higher triglycerides (80.36± 46.889 versus 123.49± 69.631, p= 0.001), higher cholesterol (160.13± 27.618 versus 174.69± 34.601, p= 0.001), lower HDL (49.00± 20.601 versus 46.77± 19.063, p= 0.001), higher systolic blood pressure (115.07± 17.120 versus 100.24± 13.559, p= 0.001) and diastolic blood pressure (65.04± 10.740 versus 72.71± 11.569, p= 0.001)

It has been reported that the typical obese adolescents with NAFLD will usually manifest several components of metabolic syndrome as lipid abnormalities, hypertension and glucose metabolism alteration (Duarte et al., 2011, Montazerifar et al., 2014)

In agreement with other more recent studies (Ayonrinde et al., 2011; Santomauro et al., 2012; Alp et al., 2013; Anna et al., 2013), the patients of the present study when compared to the control group had significantly higher visceral fat thickness (3.23± 2.126 versus 4.77± 16.16, p= 0.001) and higher subcutaneous fat thickness (1.15± 0.530 versus 3.04± 0.962, p= 0.001),

A recent study by Ayonrinde et al. (2011) has been suggested that visceral adiposity is more influential than body mass index in predicting fatty liver disease (Ayonrinde et al., 2011). Accordingly, Dˆamaso et al. (2008) demonstrated that the group of adolescents with NAFLD presented significantly higher values of BMI, visceral and subcutaneous fat, insulin, and HOMA- IR in both genders, comparing with non- NAFLD patients.

There has been increasing interest in the last few years in the role of visceral adipose tissue and NAFLD. In fact, studies have shown that visceral adipose tissue, originally considered a passive depot for energy storage, is able to secrete a variety of substances that regulate metabolism and inflammation, also participating in the pathogenesis of NAFLD (Dˆamaso et al., 2008; Petta et al., 2012).

In agreement with other more recent studies (Ayonrinde et al., 2011; Santomauro et al., 2012; Alp et al., 2013; Anna et al., 2013, Montazerifar et al., 2014), the present study demonstrated that patients had significantly higher ALT than the control group (14.07± 6.783 versus 22.23± 11.840, p= 0.001).

Clinical studies showed that ALT levels are sensitive in the detection of NAFLD and have also been associated with an increased risk of metabolic syndrome, diabetes mellitus, and cardiovascular disease (Gonz´alez- Gil et al., 2009; Takahashi and Fukusato, 2010). Another study mentioned that unexplained alanine aminotransferase (ALT) elevation is a frequently used surrogate for the presence of NAFLD in children and adults (Devadason and Scheimann, 2012).

The present study showed significant difference of BMI across the different sonographic grades of NAFLD, where patients with grade 3 NAFLD had significantly higher BMI than grade 1 and 2 NAFLD. It was suggested that BMI measurement is helpful for evaluation of NAFLD (Fassio et al., 2004; Rocha et al., 2005) Several studies showed that BMI is predictor of NAFLD severity and was significantly higher in the patients with fatty liver (Novakovic et al. 2013 Abangah et al., 2014).

In contrast to the present study which showed no significant difference in AST across the different sonographic grades of NAFLD, other studies (Abangah et al., 2014) showed that AST had a prediction role in the severity of disease and U. S grade. However, other studies showed that it has not been a reliable finding, because AST level changed in many conditions such as systemic disorder (Kotronen et al., 2010; Ye er al., 2010).

In agreement with the present study, another study by Abangah et al. (2014) could not find any significant association between ALT and the grade of U. S (Abangah et al., 2014).

In contrast to the present study which showed no significant difference in ALT, HOMA- IR, triglycerides, HDL across the grades of NAFLD, Chen-Chung Fu et al (2009) showed significant difference of these parameters. In contrast to the present study Chen- Chung Fu et al. (2009) suggested that the higher ALT, HOMA- IR, cholesterol, triglyceride and lower HDL- C as the severity of fatty liver increased indicates that a higher ALT and degree of abnormal lipid levels are predictive of severe NAFLD graded by ultrasound. This indicates that an increased severity of obesity causes more fat to be accumulated in the liver, resulting in more severe NAFLD, also other researchers showed that elevated ALT is a predictor of NAFLD (Bellentani et al., 2000, Chan et al., 2004, Fishbein et al., 2006). Another recent study supported that elevated aminotransferases have been correlated with the presence of hepatic fat on imaging (Ghamar- Chehreh et al., 2012, Anna et al., 2013). Another study mentioned that serum ALT is not sensitive enough to detect low levels of hepatic fat accumulation, and heavy fat infiltration is required for abnormalities in serum aminotransferases to occur (Lai et al., 2002).

In agreement with the present study Ayonrinde et al. (2011) suggested that there were significant difference in visceral fat thickness across the sonoggraphic grades of NAFLD (Ayonrinde et al., 2011).

The present study found that visceral fat to be associated with the severity of hepatic steatosis. Conventionally, visceral adiposity is considered to be more important than subcutaneous adiposity with respect to the risk of NAFLD (Fishbein et al., 2006; Damaso et al., 2008; Fan& Farrell, 2008).

The visceral fat cut- off points found were 3.5 cm for the girls and 3.9cm for the boys. The statistical power of the adjusted model employed was demonstrated by the high- sensitivity values obtained for the girls and boys (72.9% and 73%), resp. the specificity of the adjusted model was 80% for the girls and 76% for the boys.

Another study detected that the visceral fat cut- off points were 4.47 cm for the girls and 4.21 cm for the boys with high- sensitivity values obtained for the girls and boys (78.9% and 50.0%) resp., the specificity of the adjusted model was 74.3% for the girls and 70.0% for the boys (Anna et al., 2013).

A previous study demonstrated that each 1 cm increase in visceral adiposity, when evaluated by abdominal ultrasonography, was associated with a 2- fold greater risk of NAFLD in obese adolescents (D'amaso et al. 2008).

Conclusion:

So from the results of the present study it can be concluded that:

1. Measurements of liver enzymes alone are insufficient, and liver ultrasonography is required for early identification of NAFLD.
2. The expansion of visceral fat was associated with the severity of nonalcoholic fatty liver disease in obese adolescents. Visceral fat thickness above 3.55 cm for obese adolescents female patients and above 3.9 cm for obese adolescents male patients can be predictive of NAFLD.

Recommendations:

1. Liver ultrasonography should be introduced as part of the routine procedure required for early diagnosis of NAFLD complementary to laboratory investigations as measurements of liver enzymes alone are insufficient to allow the detection of NAFLD at an early stage. We recommend the use of ultrasonography for assessment of visceral fat thickness as it is a noninvasive, cheap, accurate, safe and convenient for follow up
2. Use of the developed cut off points for visceral fat thickness which is 3.55 cm for female patients and 3.9 cm for male patients as determined by the ROC curve, which can be predictive of NAFLD in obese adolescents.

References:

1. Ana Paula Grotti Clemente, Bárbara DalMolin Netto, Aline di Piano Ganen, Lian Tock, Danielle Arisa Caranti, Marco Túlio de Mello, Sergio Tufik, and Ana R. Dâmaso. Cut- Off Values of Visceral Adiposity to Predict NAFLD in Brazilian Obese Adolescents. **Journal of Nutrition and Metabolism** Volume 2013, Article ID 724781, 8 pages.
2. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos Nutrition and Liver Study. **Hepatology** 2005;42:44- 52.
3. Booth ML, George J, Denney- Wilson E, Okely AD, Hardy LL, Aitken R, et al. The population prevalence of adverse concentrations and associations with adiposity of liver tests among Australian adolescents. **J Paediatr Child Health** 2008;44:686- 691.
4. Bugianesi E, Fagotto U, Manini R, Vanni E, Gastaldelli A, de Iasio R, et al. Plasma adiponectin in nonalcoholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity. **J Clin Endocrinol Metab** 2005;90:3498- 504.
5. Bunc V. **Prospects of body composition analysis by bioimpedance method in children**. Cas Lek Cesk. 2007; 146 (5) : 492- 6.
6. C. A. Devadason and A. O. Scheimann, "Overview of screening methods for fatty liver disease in children", **World Journal of Hepatology**, vol. 4, no. 1, pp. 1- 4, 2012.
7. Damaso AR, do Prado WL, de Piano A, Tock L, Caranti DA, Lofrano MC, et al. Relationship between nonalcoholic fatty liver diseas prevalence and visceral fat in obese adolescents. **Dig Liver Dis** 2008; 40: 132- 139.
8. Denzer C, Thiere D, Muche R, Koenig W, Mayer H, Kratzer W, Wabitsch M. Gender- specific prevalences of fatty liver in obese children and adolescents: roles of body fat distribution, sex steroids, and insulin resistance. **J Clin Endocrinol Metab**. 2009 Oct; 94 (10) : 3872- 81.
9. Durate MA, Silva GAP. Hepatic steatosis in obese children and adolescents. **J Pediatr (Rio J)** 2011; 87:150- 6.
10. E. M. Gonz´alez- Gil, G. Bueno- Lozano, O. Bueno- Lozano et al., "Serum transaminases concentrations in obese children and adolescents", **Journal of Physiology and Biochemistry**, vol. 65, no. 1, pp. 51- 60, 2009.
11. Farzareh Montazerifar, Mansour karjibani, Ali Reza Ansari Moghaddir. Relationship between fatty liver disease and biochemical factors in obese adolescents**. J Pediatr** 2014; 15- 18
12. Federico A, Trappoliere M, Loguercio C. Treatment of patients with nonalcoholic fatty liver disease: current views and perspectives. **Dig Liver Dis** 2006; 38:789- 801.
13. Fishbein MH, Mogren C, Gleason T, Stevens WR. Relationship of hepatic steatosis to adipose tissue distribution in pediatric nonalcoholic fatty liver disease. **J Pediatr Gastroenterol Nutr** 2006;42:83- 88.
14. Flynn MA, McNeil DA, Maloff B, Mutasingwa D, Wu M, Ford C, et al. Reducing obesity and related chronic dsisease rik in children and youth: a synthesis of evidence with best practice recommendations. **Obes** Rev 2006;

7 (Suppl. 1) : 1- 5.

15. Ghalli I, Salah N, Hussien F, Erfan M, El- Ruby M, Mazen I, Sabry M, Abd El- Razik M, Saad M, Hossney S, Ismaail and Abd El- Dayem S (2002): **Egyptian growth curves for infants, children and adolescents**. Published in: Crecere nel mondo. Satorio A, Buckler JMH and Marazzi N (2008), Ferring Publisher, Italy.
16. H. Alp, S. Karaarslan, B. Selver Eklioglu et al., "Association between nonalcoholic fatty liver disease and cardiovascular risk in obese children and adolescents", **Canadian Journal of Cardiology**, vol. 29, no. 9, pp. 1118- 1125, 2012.
17. Harrison SA, Neuschwander- Tetri BA. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. **Clin Liver Dis** 2004;8:861- 79.
18. Hiernaux, J., Tanner, JM. Growth and physique: anthropometry. In: Weiner JS, Lourie JA, eds. **Human biology, a guide to field methods**. Philadelphia, FA Davis Company, 1969; 2- 42.
19. J. B. Schwimmer, R. Deutsch, T. Kahen, J. E. Lavine, C. Stanley, and C. Behling, "Prevalence of fatty liver in children and adolescents", **Pediatrics**, Vol. 118, no. 4, pp. 1388- 1393, 2006.
20. Loguercio C, De Simone T, D'Auria MV, de Sio I, Federico A, Tuccillo C, et al. Non- alcoholic fatty liver disease: a multicentre clinical study by Italian Association for the Study of the Liver. **Dig Liver Dis** 2004; 36:398- 405.
21. Mehmet Keskin,Selim Kurtolgu, Mustafa Kendirci, Emre Atabek and Cevat Yazici. Homeostasis Model Assessment Is More Reliable Than the Fasting Glucose/Insulin Ratio and Quantitative Inslulin Sensitivity Check Index for assessing Insulin Resistance Among Obese Children and Adolescents. **Pediatrics**. 2005; 115: e500- e503.
22. Mercedes Santomauroa, Mariela Paoli- Valeri a, Maricelia Fernándeza, Nolis Camachob, Zarela Molinab, Rosanna Cicchettib, Lenin Valeri a, Evila Dávila de Campagnaroc, Gabriela Arata- Bellabarbad. Non-alcoholic fatty liver disease and its association with clinical and biochemical variables in obese children and adolescents: Effect of a one-year intervention on lifestyle. **Endocrinol Nutr**. 2012;59 (6) : 346-353
23. National Cholesterol Education Program (NCEP).T hird Report of the National Cholesterol Education Program (NCEP). Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) Final report. **Circulation** 2002; 106:3143- 421.
24. National High Blood Pressure Education Program. W orking Group on High Blood Pressure in Children and Adolescents. T he fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. **Pediatrics** 2004; 114 (2 Suppl 4th Report) : 555- 76.
25. Ong JP, Younossi ZM. Approach to the diagnosis and treatment of nonalcoholic fatty liver disease. **Clin Liver Dis** 2005;9:617- 34.
26. Oyekoya T. Ayonrinde, John K. Olynyk, Lawrence J. Beilin, Trevor A. Mori, Craig E. Pennell, Nicholas de Klerk, Wendy H. Oddy, Peter Shipman, and Leon A. Adams. **Gender Specific Differences in Adipose Distribution and Adipocytokines Influence Adolescent Nonalcoholic Fatty Liver Disease**
27. Palekar NA, Naus R, Larson SP, Ward J, Harrison AS. Clinical model for distinguishing nonalcoholic steatohepatitis from simple steatosis in patients with nonalcoholic fatty liver disease. **Liver Int** 2006;26:151- 6
28. R. Loomba, C. B. Sirlin, J. B. Schwimmer, and J. E. Lavine, "Advances in pediatric nonalcoholic fatty liver disease", **Hepatology**, Vol. 50, No. 4, pp. 1282- 1293, 2009.
29. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. **Gastroenterology** 2003; 124:71- 9.
30. S. Petta, M. C. Amato, V. Di Marco et al., "Visceral adiposity index is associated with significant fibrosis in patients with non- alcoholic fatty liver disease", **Alimentary Pharmacology and Therapeutics**, vol. 35, No. 2, pp. 238- 247, 2012.
31. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. **Gastroenterology** 2002; 123:745e50.
32. Sabir N, Sermez Y, Kazil S, Zencir M. Correlation of abdominal fat accumulation and liver steatosis: importance of ultrasonographic and anthropometric measurements. **Eur J Ultrasound** 2001;14:121- 8.
33. Schwimmer JB, Celedon MA, Lavine JE, Salem R,Campbell N, Schork NJ, et al. Heritability of nonalcoholic fatty liver disease. **Gastroenterology** 2009; 136: 1585- 1592.
34. Schwimmer JB, Pardee PE, Lavine JE, et al. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. **Circulation** 2008;118:277- 83.
35. Trombetta M, Spiazzi G, Zoppini G, Muggeo M. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. **Aliment Pharmacol Ther** 2005; 22 (Suppl. 2) : 24- 7.
36. Y. Takahashi and T. Fukusato, "Pediatric nonalcoholic fatty liver disease: overview with emphasis on histology", **World Journal of Gastroenterology**, Vol. 16, No. 42, pp. 5280-5285, 2010.