Evaluation of Subclinical Myocardial Dysfunction Using Tissue Doppler Imaging Echocardiography in Children with Non-Alcoholic Fatty Liver Disease

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Abstract

Background: Pediatric Non-Alcoholic Fatty Liver Disease (NAFLD) is a global health problem worldwide and is considered the most common cause of chronic liver disease in pediatrics. Both NAFLD and heart failure are obesity-related conditions with high cardiovascular morbidity and mortality that have reached epidemic proportions.

Aim of Study: Evaluate subclinical myocardial dysfunction using Tissue Doppler imaging Echocardiography in a group of overweight/obese children and adolescents with NAFLD.

Patients and Methods: This prospective case-control study was carried out upon 80 children (40 cases with NAFLD, 20 cases obese without NAFLD and 20 healthy controls). Diagnosis of NAFLD was based on the finding of hepatic steatosis detected by abdominal ultrasonography. These children underwent full examination, lab investigations and TDI echocardiography.

Results: Using conventional echocardiography mean value of LV mass was significantly higher in patients with NAFLD compared to controls. Using TDI mean values of MPI was significantly higher in patients compared to controls, whereas other parameter showed no significant difference. Left ventricular mass by echo showed significant increase as the hepatic steatosis was advancing in severity.

Conclusion: Patients with NAFLD have evidence of subclinical myocardial dysfunction using TDI echocardiography. Although the TDI provides new insight into alterations in LV structure and function related to IR in NAFLD patients, it cannot be used for differentiation of steatosis grading.

Key Words: Non alcoholic fatty liver disease – Left ventricular mass – Tissue Doppler imaging – Myocardial performance index.

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Introduction

PARALLELING the epidemic of childhood obesity, pediatric Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a growing global health problem worldwide and is considered the most common cause of chronic liver disease in pediatrics, affecting an alarming number (3 8%) of obese children [1] . Both NAFLD and heart failure are obesity-related conditions with high cardiovascular morbidity and mortality that have reached epidemic proportions [2] studies have shown that mortality among patients with NAFLD is higher than that in general population, mainly due to Cardiovascular Disease (CVD) and liver dysfunction [3] . In fact, patients with NAFLD are more likely to die from complications of CVD than from liver-related death [4] . Growing evidence suggests that NAFLD is an independent risk factor for CVD and is associated with impaired endothelial function, [5] a higher prevalence of vulnerable coronary plaques [6] and with unfavorable levels of markers of subclinical atherosclerotic disease, including increased carotid intima media thicknes [7] and coronary artery calcification [8] . Given that NAFLD and metabolic syndrome features often coexist, any relationship between NAFLD and cardiac remodeling and dysfunction may be moderated by visceral adipose tissue volume, obesity, or other cardiometabolic risk factors [9] .

Conventional echocardiography provides assessment of the cardiac structure, function and hemodynamics. TDI is another useful echocardiographic technique employing the Doppler principle to measure the velocity of myocardial segments and other cardiac structures which is load independent.

Patients and Methods

This prospective case-control study was carried out upon three groups of children. The first group comprised 40 overweight/obese children and adolescents with ultrasound proven NAFLD, the second group involved 20 overweight/obese children and adolescents of matched age, sex, and BMI with normal levels of liver enzymes and lipid profile, with no evidence of steatosis by ultrasonography, whereas the third group included 20 healthy children of matched age and sex as a healthy control group. Diagnosis of NAFLD was based on the finding of hepatic steatosis detected by abdominal ultrasonography and appropriate exclusion of other causes of fatty liver. Children were selected from those attending the Outpatient Endocrinology Clinic of Pediatric Department at Tanta University Hospital during the period from June, 2017 to June, 2018.

Inclusion criteria: Overweight and obese children and adolescents with and without ultrasound proven NAFLD.

Exclusion criteria: Patients with known disorders to cause fatty liver, e.g. diabetes mellitus, glycogen storage disease and Wilson's disease, any patient with syndromatic obesity, patients receiving long term use of drugs known to cause steatosis, e.g. gulcocorticoids, patients with any other chronic liver disease such as viral hepatitis, autoimmune hepatitis, etc. were excluded by performing the appropriate investigations, children with congenital and those with acquired cardiac diseases and children with other systemic also diseases, metabolic or genetic diseases.

All the children in the study were subjected to detailed history, full clinical examination, laboratory investigations in the form of liver enzymes, blood cholesterol, triglycerides, LDL, HDL, fasting blood glucose level fasting serum insulin level, calculation of IR Troponin I (cardiac marker).

Abdominal ultrasonography: All patients were examined by abdominal ultrasound to detect the presence of liver fatty infiltration and to assess semi-quantitatively the degree of steatosis.

Echocardiographic examinations: Conventional, Tissue Doppler echocardiographic examination.

Equipment:

1- *Machine:* Echocardiographic studies were performed using a commercially available ultrasound transducer and equipment (Vivid 7 or Vivid 9, GE Healthcare, Horten, Norway).

2- *Transducers:* Data acquisition was performed with a 3.5MHz transducer, S7 and V3 matrix real-time 3 dimensional probes.

3- *Workstation:* Digital loops were stored on the hard disc of the echocardiography machine and transferred to a workstation (Echo PAC PC, 113; GE, and Horten, Norway) for offline analysis.

Technique:

1- Conventional echocardiographic examination:

Mitral inflow velocity was assessed using Pulsed-Wave (PW) Doppler in the apical four-chamber view, with a 3mm sample placed between the tips of the mitral leaflets. Diastolic indices that included mitral peak early LV filling velocity (E), peak late atrial filling velocity (A), were measured offline from the obtained recordings of inflow velocity pattern (cm/s) and averaged over 3 cardiac cycles. The ratios of trans-mitral early to late diastolic flow velocity (E/A ratio) as a measure of LV diastolic function were calculated [10].

2- Pulsed wave tissue Doppler imaging (PW-TDI):

A- Mitral valve annular velocities: Annular velocities by PW-TDI were obtained from the apical 4-chamber view during quiet respiration by placing a sample volume of 5.5mm at the lateral margin of the mitral valve annuli. The peak mitral annular systolic velocity (S), the peak early mitral annular diastolic velocities (E', cm/s) and peak late mitral annular diastolic velocities (A', cm/s) were measured offline from the time-myocardial velocity waveforms of 3 consecutive cardiac cycles and an average were recorded. The ratios of mitral early to late annular diastolic velocity (E'/A' ratio) as a measure of LV diastolic function was calculated [11].

B- Myocardial Performance Index (MPI) calculation: The intervals (a') between the end of the late diastolic annular velocity and the onset of the early diastolic annular velocity were equal to the sum of the isovolumetric contraction time (ICT), Isovolumetric Relaxation Time (IRT), and Ejection Time (ET). The ET (b') was measured as the duration of the systolic annular velocity (S). The sum of the ICT and IRT was obtained by subtracting (b') from (a'). Then the LV Tei index was calculated as (a'-b')/b'. All interval measurements in milliseconds were performed by TDI within one cardiac cycle [12].

Results

This prospective case-control study was carried out upon 80 children (40 cases with NAFLD, 20 cases obese without NAFLD and 20 healthy controls).

The mean values of age were significantly higher in obese patients with NAFLD compared to controls, there was insignificant male predominance in obese children and adolescents with NAFLD compared to controls and the frequency of patients with positive family history of obesity was significantly higher in obese patients (with and without NAFLD compared to controls.

The mean value of height was statistically insignificant between patients and controls, mean values of weight, BMI and WC were significantly higher in obese children with and without NAFLD compared to controls. But there were no differences between obese patients with and those without NAFLD.

The frequency of patients with acanthosis nigricans was significantly higher in obese children and adolescent with NAFLD compared to those without NAFLD, mean values of diastolic blood pressure were significantly higher in obese children and adolescent with NAFLD compared to controls with no difference between patients with and without NAFLD.

Mean values of ALT and GGT were significantly higher in obese patients with NAFLD compared to controls. But there were no difference between obese patients with and without NAFLD.

• Mean values of total cholesterol were significantly higher in obese patients with and without NAFLD compared to controls.

• Mean values of TG were significantly higher in obese patients with NAFLD compared to obese patients without NAFLD and to controls.

• Mean values of LDL were significantly higher in obese patients with NAFLD compared to controls.

• Mean value of HDL was significantly lower in obese patients with and without NAFLD compared to controls.

Mean values of fasting serum insulin level and insulin resistance were significantly higher in obese patients with and without NAFLD compared to controls.

Serum troponin I show no significant differences between patients and controls.

Analysis of echocardiographic results:

A- *Conventional echocardiography:* Mean values of LV Mass were significantly higher in obese children and adolescents with NAFLD compared to the controls, whereas mean values of EF show non-significant difference between patients and controls.

B- *Tissue Doppler imaging:* Mean value of mitral annulus systolic velocity (S') and E'/A' ratio shows insignificant difference between obese children and adolescents (with and without NAFLD) and controls.

Mean value of MPI was significantly higher in obese patients with and without NAFLD compared to controls. But there were no difference between obese patients with and without NAFLD.

There was semi-parallel increase in the percentage of cases with many abnormal laboratory data, with advance of the degree of hepatic echogenicity.

Tissue Doppler Imaging (TDI) data of NAFLD patients showed insignificant differences as the hepatic steatosis was advancing in severity. But LV mass by conventional echo showed significant increase as the hepatic steatosis was advancing in severity.

Table (1): Age, sex and family history of obesity of obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)						χ^2 p
	Obese with NAFLD (n=40)		Obese without NAFLD (n=20)		Control group (n=20)		
	N	%	N	%	N	%	
Age years:							
• Range	5.50-16.00		3.50-16.50		4.50-16.00		
• Mean ± SD	12.02±2.66		9.05±2.96		8.82±3.16		
F-value			11.616				
p			0.0001*				
Sex:							
• Males	24	60.0	11	55.0	9	45.0	0.545
• Females	16	40.0	9	45.0	11	5.0	1.212
Family history of obesity:							
• Positive	25	62.5	6	30.0	0	0	22.804
• Negative	15	37.5	14	70.0	20	100	0.0001*

*: Significant (*p*<0.05).

Table (2): Anthropometric measures of obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)			F-value p
	Obese with NAFLD (n=40) GI	Obese without NAFLD (n=20) GII	Control group (n=20) GIII	
Height (cm):				
• Range	97.00-173.00	96.50-163.00	97.00-170.00	1.912
• Mean ± SD	142.00±17.68	134.30±17.56	135.52±18.30	0.155
Weight (kg):				
• Range	30.00-150.00	25.40-103.00	16.00-58.00	16.744
• Mean ± SD	69.90±29.55	55.35±21.11	31.87±10.07	0.0001*
• Scheffe test	I vs. II & III p=0.093 & 0.0001*			
•p	II vs. III, p=0.011*			
BMI:				
• Range	22.30-54.40	22.90-40.20	13.20-20.00	50.666
• Mean ± SD	32.85±7.17	30.10±5.28	17.04±1.91	0.0001*
• Scheffe test	I vs. II & III p=0.231 & 0.0001*			
•p	II vs. III, p=0.0001 *			
WC (cm):				
• Range	68.00-140.00	55.50-118.00	24.00-62.00	54.501
• Mean ± SD	93.23±16.61	84.59±16.94	47.30±14.75	0.0001*
• Scheffe test	I vs. II & III p=0.159 & 0.0001*			
•p	II vs. III, p=0.0001 *			

* : Significant (*p*<0.05).   BMI : Body Mass Index.   WC : Waist Circumference.

Table (3): Clinical data of obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)						χ^2 p
	Obese with NAFLD (n=40)		Obese without NAFLD (n=20)		Control group (n=20)		
	N	%	N	%	N	%	
Acanthosis	27	67.5	13	65.0	0	0	26.700
Systolic BP:							0.0001*
• Range	80.0-145.00		80.00-140.00		80.00-120.00		
• Mean ± SD	104.62±15.74		100.25±16.26		96.75±11.39		
• F-value	1.959						
•p	0.148						
Diastolic BP:							
• Range	50.00-90.00		50.00-80.00		50.00-75.00		
• Mean ± SD	70.00-12.14		64.75±11.52		61.50±7.27		
• F-value	4.361						
•p	0.016*						
Scheffe test	I vs. II & III p=0.224 & 0.022*						
p	II vs. III, p=0.647						

* : Significant (*p*<0.05).
BP : Blood Pressure.

Table (4): Liver enzymes among obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)			F-value p
	Obese with NAFLD (n=40) GI	Obese without NAFLD (n=20) GII	Control group (n=20) GIII	
AST (U/L):				
• Range	7.00-96.00	6.00-40.00	6.00-55.00	2.803
• Mean ± SD	31.00±23.33	22.00±2.93	20.00±11.50	0.067
ALT (U/L):				
• Range	10.00-58.00	8.00-46.00	8.00-35.00	6.439
• Mean ± SD	29.00±13.37	24.00±10.46	19.00±7.84	0.003 *
• Scheffe test	I vs. II & III p=0.262 & 0.003*			
•p	II vs. III, p=0.264			
GGT (U/L):				
• Range	11.00-22.00	6.00-23.00	5.00-18.00	9.920
• Mean ± SD	15.00±2.73	14.00±4.67	11.00±4.01	0.0001*
• Scheffe test	I vs. II & III p=0.385 & 0.0001*			
•p	II vs. III, p=0.034*			

* : Significant (*p*<0.05).
ALT : Alanine Transferase.
AST : Aspartate Transferase.
GGT : Gamma Glutamyl Transferase.

Table (5): Lipid profile among obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)			F-value *p*
	Obese with NAFLD (n=40) GI	Obese without NAFLD (n=20) GII	Control group (n=20) GIII	
Total cholesterol (mg/dl):				
• Range	108.00-230.00	95.00-238.00	77.00-186.00	9.186
• Mean ± SD	167.40±34.10	161.55±38.61	127.45±31.64	0.0001*
• Scheffe test	I vs. II & III *p*=0.828 & 0.0001*			
•*p*	II vs. III, *p*=0.011 *			
TG (mg/dl):				
• Range	96.00-290.00	50.00-235.00	65.00-152.00	16.337
• Mean ± SD	166.70±37.20	122.81±52.83	109.95±29.24	0.0001*
• Scheffe test	I vs. II & III *p*=0.001 * & 0.0001*			
•*p*	II vs. III, *p*=0.599			
LDL (mg/dl):				
• Range	65.00-158.00	36.00-147.00	45.00-99.00	7.776
• Mean ± SD	102.40±21.72	93.46±27.83	78.55±15.41	0.001*
• Scheffe test	I vs. II & III *p*=0.341 & 0.001*			
•*p*	II vs. III, *p*=0.110			
HDL (mg/dl):				
• Range	30.00-89.00	30.00-97.00	41.00-95.00	12.801
• Mean ± SD	50.28±13.21	56.77±17.25	70.90±15.54	0.0001*
• Scheffe test	I vs. II & III *p*=0.287 & 0.0001*			
•*p*	II vs. III, *p*=0.014*			

*   : Significant (*p*<0.05).   LDL : Low Density Lipoprotein.
TG : Triglycerides.   HDL : High Density Lipoprotein.

Table (6): Fasting blood sugar, fasting serum insulin level and insulin resistance among obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)			F-value *p*
	Obese with NAFLD (n=40) GI	Obese without NAFLD (n=20) GII	Control group (n=20) GIII	
Fasting blood sugar (mg/dl):				
• Range	60.00-115.00	68.00-117.00	68.00-112.00	0.619
• Mean ± SD	88.30±13.29	89.10±12.20	84.95±12.60	0.541
Fasting serum insulin (mclu/ml):				
• Range	3.00-24.00	4.00-28.00	3.00-14.00	22.308
• Mean ± SD	15.37±5.07	13.80±5.15	6.93±3.01	0.0001*
• Scheffe test	I vs. II & III *p*=0.474 & 0.0001*			
•*p*	II vs. III, *p*=0.0001 *			
Insulin resistance:				
• Range	2.88-5.70	2.43-6.44	0.57-3.04	114.339
• Mean ± SD	4.42±0.71	4.40±0.84	1.47±0.75	0.0001*
• Scheffe test	I vs. II & III *p*=0.993 & 0.0001*			
•*p*	II vs. III, *p*=0.0001 *			

*: Significant (*p*<0.05).

Table (7): Serum Troponin I among obese children and adolescents (with and without NAFLD) and the control group.

Variables	The studied children and adolescents (n=80)		
	Obese with NAFLD (n=40) GI	Obese without NAFLD (n=20) GII	Control group (n=20) GIII
Serum Tropoin I (ng/ml):			
• Range	0.06-0.19	0.04-0.19	0.05-0.19
• Mean ± SD	0.12±0.03	0.12±0.04	0.13±0.03
•χ^2		0.354	
•*p*		0.838	

$\chi 2$ value of Kruskal Wallis test.

Table (8): Left ventricular mass (LV Mass) and Ejection Fraction (EF) measured by conventional echocardiography among obese children and adolescents (with and without NAFLD) versus the control group.

Conventional echocardiographic finding	The studied children and adolescents (n=80)		
	Obese with NAFLD (n=40)	Obese without NAFLD (n=20)	Control group (n=20)
LV mass:			
• Range	73-145	74-123	70.00-100.00
• Mean ± SD	105.15±17.03	99.05±16.12	89.80±8.80
• F-value		6.857	
•*p*		0.002*	
• Scheffe test		I vs. II & III *p*=0.345 & 0.002*	
•*p*		II vs. III, *p*=0.163	
EF (%):			
• Range	40.00-70.00	42.00-68.00	42.00-66.00
• Mean ± SD	52.80±5.95	51.85±6.94	53.60±6.23
• F-value		0.390	
•*p*		0.679	

*: Significant (*p*<0.05).

Table (9): Mitral annulus systolic velocity (S'), MPI and E'/A' ratio measured by tissue Doppler imaging among obese children and adolescents (with and without NAFLD) versus the control group.

Tissue Doppler Imaging (TDI)	The studied children and adolescents (n=80)		
	Obese with NAFLD (n=40)	Obese without NAFLD (n=20)	Control group (n=20)
Mitral annulus systolic velocity (S') (cm/sec):			
• Range	6.00-8.00	6.00-8.00	6.00-8.00
• Mean ± SD	6.95±0.78	6.60±0.82	6.75±0.64
• F- value		1.505	
•*p*		0.228	
E'/A' ratio:			
• Range	0.80-1.90	1.10-1.90	1.10-1.90
• Mean ± SD	1.60±0.24	1.58±0.28	1.54±0.22
• F-value		0.389	
•*p*		0.679	
MPI:			
• Range	0.16-0.90	0.40-0.80	0.30-0.50
• Mean ± SD	0.56±0.15	0.57±0.12	0.37±0.07
•$\chi 2$ value		16.240	
•*p*		0.0001*	
• Z-value		I vs. II & III *p*=0.945 & 0.0001*	
•*p*		II vs. III, *p*=0.0001*	

*: Significant (*p*<0.05): MPI, Myocardial Performance Index.
$\chi 2$ value of Kruskal Wallis test.
Z-value of Mann-Whitney U-test.

Table (10): Frequency of cases with abnormal laboratory data in relation to the degree of hepatic steatosis.

Abnormal laboratory data	Frequency of cases with abnormal laboratory data in relation to the degree of hepatic steatosis (n=40)						χ^2	*p*
	Mild (Grade I) (n=24)		Moderate & severe (Grade II & III) (n=16)		Total			
	N	%	N	%				
Hypercholesterolemia	6	25.0	2	12.5	8	(20%)	0.938	0.333
Hypertriglyceridemia	5	20.8	5	31.3	10	(25%)	0.556	0.456
Elevated LDL	5	20.8	0	0	5	(12.5%)	3.810	0.051
Low HDL	4	16.7	3	18.8	7	(17.5%)	0.029	0.865
Elevated ALT	2	8.3	4	25.0	6	(15%)	2.092	0.148
Elevated AST	4	16.7	4	25.0	8	(20%)	0.417	0.519
Elevated insulin resistance	23	95.8	16	100	39	(97.5%)	0.684	0.408

LDL : Low Density Lipoprotein.　　　　　ALT : Alanine Transferase.
HDL : High Density Lipoprotein.　　　　　AST : Aspartate Transferase.

Table (11): Tissue Doppler Imaging (TDI) data among NAFLD children and adolescents in relation to their degree of hepatic steatosis.

| Echocardiology (Tissue Doppler Imaging) (TDI) data | TDI data among NAFLD children and adolescents in relation to their degree of hepatic steatosis (n=40) | | *t*-test | *p* |
	Mild (Grade I) (n=24) Mean ± SD	Moderate & severe (Grade II & III) (n=16) Mean ± SD		
Mitral annulus systolic velocity (S)	6.87±0.95	6.75±0.68	0.454	0.652
E'/A' ratio	1.60±0.27	1.61±0.20	0.027	0.979
Myocardial Performance Index (MPI)	0.54±0.18	0.60±0.11	1.109	0.274
Left ventricular mass (LV Mass)	100.58±14.10	112.00±19.13	2.174	0.036*

Discussion

Most recent studies are conflicting and do not support an independent relation between NAFLD and CVD in pediatric patients. Despite that, some findings have shown that atherosclerosis is an early process beginning in childhood, as demonstrated by early subclinical atherosclerosis [flow-mediated vasodilatation; FMD, carotid artery intimal medial thickness (cIMT), arterial stiffness] and abnormalities in myocardial structure and function including LV dysfunction, increased LV mass, and epicardial adipose tissue thickness (EAT)) observed in obese children and adolescents [13].

The presence of intracellular cardiac troponin subunits T and I (cTnT and cTnI) in the blood is a sensitive and specific indicator for myocardial injury [14,15].

New noninvasive myocardial imaging including tissue Doppler (TDI), have been studied in evaluation of cardiac insult in systemic diseases [16,17].

In this study the mean values of age were significantly higher in obese patients with NAFLD compared to controls and there was insignificant male predominance. However, significant differences were reported in the prevalence of NAFLD in boys compared to girls, with boys having a higher prevalence (66.67%) in the SCALE study. In partial agreement with our results, Schwimmer et al., [18] suggested that NAFLD is consistently more prevalent in boys than in girls signifying that sex hormones are associated with the occurrence of pediatric NAFLD that is more prevalent in adolescents than in younger children where sex hormones and IR at puberty may be the cause of this finding. The disparate result of our study may be due to differences in selection criteria for enrollment.

The mean values of other anthropometric measures (weight, waist circumference and BMI) were significantly higher in obese children with and without NAFLD compared to controls. This finding is attributed to our selection criteria. But the finding of no differences between obese patients with and those without NAFLD in this study is not in agreement with that reported by Lee et al., [19] who found that NAFLD patients were more likely to be obese (58% vs. 16%) where measures of visceral and subcutaneous fat area, waist and hip circumferences are increased compared to those without NAFLD [19]. Our disparate result could be attributed to comparability of our obese patients (whether with or without NAFLD) in anthropometric measures.

NAFLD and obese patients had high WC exceeding the 95th percentile. WC is considered a surrogate measure of visceral fat and may predict the development of NAFLD in children [20] and it has been found to be associated with several metabolic impairments, including IR and NAFLD severity [20,21].

Frequency of patients with acanthosis nigricans was significantly higher in obese children and adolescent with NAFLD compared to those without NAFLD. This finding agreed with that reported by Louthan et al., [22] who observed acanthosis nigricans (a clinical marker of hyperinsulinemia) in one-third of the children with biopsy-proven NAFLD.

In the present study, the mean values of diastolic blood pressure were higher in NAFLD patients compared to controls whereas mean values of systolic blood pressure showed no significant difference between patients and controls. This finding partially agreed with that reported by Lee et al., [19] and Shwimmer et al., [23] who demonstrated that children with NAFLD. Obesity predisposes to hypertension because of metabolic and hemodynamic abnormalities, leading to inadequate lowering of systemic resistance and, to a more severe cardiovascular burden [24].

In the present study, the mean values of ALT and GGT were significantly higher in patients compared to controls. This could be due to presence of some degree of hepatic inflammatory reaction in children with NAFLD. This finding agreed with that reported by Lee et al., [19].

In this study, the mean levels of total serum cholesterol, Triglycerides (TG) and (LDL-C) were significantly higher in patients compared to controls, whereas mean levels of HDL-C were significantly lower in patients compared to controls. The dyslipidemic profile detected in the NAFLD patients of this study agreed with that reported by Romero et al., [25] and Sert et al., [26] who found higher levels of total cholesterol and LDL-C and lower levels of HDL-C in patients with NAFLD compared to patients without NAFLD. This is due to several metabolic impairments, including IR and NAFLD severity [20,21].

In this study, there is semi-parallel increase in the percentage of cases with abnormal laboratory data including dyslipidemic profile, with advancing degree of hepatic echogenicity. This result is in agreement with that reported by Duarte and Silva who found that the prevalence of hypercholesterolemia and hypertriglyceridemia was associated with the degree of steatosis [21]. These findings could be explained by the previous detection of severe metabolic impairments among overweight and obese children with NAFLD than those without NAFLD although unfavorable lipid profile was found in children with BMI greater than 85th percentile for age [27]. In this study the mean values of fasting serum insulin level and HOMA-IR were higher in obese patients (with and without NAFLD) compared to controls. This findings agreed with that reported by Sert et al., [26] who found that the NAFLD obese group had significantly higher HOMA-IR values than the non-NAFLD and control groups. Insulin resistance had a significant independent impact on LV remodeling in the absence of diabetes mellitus in patients with NAFLD.

It is well-established that the metabolic syndrome and insulin resistance affect LV geometry and function [28]. The presence of IR altered the cardiac structure and contractile function at the level of the myocyte in an animal study [29]. This finding has been also demonstrated in humans [28]. Whether or not the IR is independently associated with cardiac remodeling is unknown. Iacobellis et al., [28] reported that IR in obesity in the absence of diabetes was associated with an increased LVM and changes in LV geometry. However, not all studies in the non-diabetic population supported their results. When adjusted for BMI and BP, IR was not an independent determinant of LVM [30].

There is limited data on the influence of the metabolic syndrome on LV function, especially in patients without hypertension, diabetes, and obesity. A slight increase in plasma glucose levels was associated with abnormal diastolic function, independent from LV hypertrophy in non-diabetic patients with treated hypertension [30]. The effect of the metabolic syndrome on the LV diastolic function has also been demonstrated in the Strong Heart Study [31]. Changes in LV geometry and function correlated well with BMI in the previous studies that included patients with marked obesity. Recently, two studies in obese populations revealed that decreased systolic and early diastolic velocities on TDI and BMI were the only predictors of LV systolic and diastolic dysfunction [32,33].

Our study showed that there was no significant difference between patients and controls as regard the mean values of serum troponin I whereas the study reported by Elsaidi, et al., 2017 [34] demonstrated that troponin I showed a marked significant elevation in obese patients compared with controls. The difference between both studies could be attributed to patients characteristics, differences in methods of assay of troponin I in both studies and severity of NAFLD in both studies where patients in our study mostly belong to the mild grades of the disease (grades I and II as detected by abdominal ultrasound). Also, Elsaidi, et al., 2017 [34] and Di Salvo et al., [35] found no correlation between troponin I and LV diastolic function.

The conventional indices of global LV systolic and diastolic function, like EF and volumes have some disadvantages. These are load dependency, measurement errors, and insufficient image quality. TDI is another useful echocardiographic technique employing the Doppler principle to measure the velocity of myocardial segments and other cardiac structures which is load independent. But TDI also has some limitations, like angle dependency of the ultrasound beam, the complex rotational and translational movements of the heart [36].

Using TDI our study showed significant increase in mean values of LV myocardial performance index in NAFLD patients compared to controls. Sert et al., [26] found that non-NAFLD and NAFLD obese groups had regional systolic and/or diastolic myocardial functional abnormalities in the interventricular septum and LV lateral wall. In the basal, mid septal and mid lateral LV walls, the non-NAFLD and NAFLD obese groups had higher MPI values than the controls.

Reductions in indexes of systolic function were found only in patients with a considerable degree of obesity, suggesting that LV systolic function is affected late in the course of obesity [37]. In our study, no patient had LV systolic dysfunction by conventional echocardiography. We found abnormalities in LV structure, including increased LV wall thickness, LV mass, and LV mass index, in obese adolescents with NAFLD. Our study also provides evidence that obese adolescents with NAFLD exhibit abnormalities of LV structure and function (increased LV dimensions and LV mass as well as diastolic dysfunction) that can be identified by PW TDI. Our study is the first to show subtle LV dysfunction by pulsed-wave TDI, which conventional echocardiography cannot detect in obese adolescents with NAFLD.

In our study there was also significant increase in LV mass in obese children and adolescents with NAFLD compared to the controls. Previous studies showed a similar result which have shown that NAFLD has been associated with increased LV mass and changes in the cardiac geometry [38-40]. Goland et al., [40] reported that normotensive, nondiabetic patients with NAFLD in the absence of morbi d obesity, hypertension, and diabetes have mildly altered geometry (higher thickening of the intraventricular and posterior wall, increased LV mass indexed to height). However, they found that the EF and systolic velocities on tissue Doppler imaging were similar between groups. In addition, Fotbolcu et al., [39] showed that LV mass index, interventricular septum, and posterior wall thickness were higher in normotensive, nondiabetic NAFLD patients than normal individuals. They found significant systolic dysfunction detected by TDI in NAFLD patients, although ventricular dimensions and EF of the two groups were similar.

To summarize, multiple mechanisms contribute to LV dysfunction in obesity, including lipotoxicity associated with cardiac steatosis and lipoapoptosis, alterations in fatty acid metabolism, overproduction of cardioinhibitory cytokines, up-regulation of some neurohormones (especially angiotensin II), myocardial fibrosis and chronic overload with LV dilatation and hypertrophy, and increased oxygen consumption [41,42]. Insulin resistance may represent a link between obesity and LV dysfunction. Elevated insulin levels in patients with IR stimulate myocyte growth and interstitial fibrosis. Insulin also causes sodium retention and activates the sympathetic nervous system which can affect cardiac performance [42,43]. It is well-established that the metabolic syndrome and insulin resistance affect LV geometry and function [28].

The limitations of this study included small sample size and lack of histological examination with subsequent inability to assess NAFLD severity. Further, although ultrasonography is a practical approach commonly used to detect hepatic steatosis, it is not the gold standard technique for quantitative liver fat and it has several limitations for detection of steatosis.

Conclusion:

Patients with NAFLD have evidence of subclinical myocardial dysfunction using TDI echocardiography. Although the TDI provides new insight into alterations in LV structure and function related to IR in NAFLD patients, it cannot be used for differentiation of steatosis grading.

Conflicts of interest:

No conflicts of interest declared.

Authors' contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

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تقييم ضعف عضلة القلب تحت الإكلينيكى عن طريق فحص آنسجة القلب بالدوبلر فى الآطفال المصابين بمرض الكبد الدهنى غير الكحولى

تزامناً مع وباء السمنة لدى الآطفال فقد برز مرض الكبد الدهنى الغير كحولى كمشكلة صحية عالمية متزايدة. ويعتبر السبب الآكثر شيوعاً لآمراض الكبد المزمنة والتى تؤثر على ٣٨٪ من الآطفال البدناء. ويمثل مرض الكبد الدهنى الغير كحولى نطاقاً من الحالات التى تتراوح من تنكس كبدى بسيط إلى إلتهاب الكبد الدهنى الغير كحولى وتشمع الكبد القاتل. إن كلاً من مرض الكبد الدهنى الغير كحولى وفشل القلب هى آمراض متعلقة بالسمنة مع زيادة نسبة الآمراض القلبية المزمنة والوفيات إلى ان وصلت إلى معدلات وبائية. التروبونين قد يكون مفيداً للكشف التحت الإكلينيكى عن آمراض القلب والشرايين وتقييم مخاطر آمراض القلب والشرايين. ومع ذلك، فإن الإنتشار المنخفض للكشف مع فحوصات القياسية يحد من فائدة قياس التروبونين لهذه التطبيقات السريرية.

الهدف من البحث: هو تقييم عضلة القلب تحت الإكلينيكى عن طريق فحص آنسجة القلب بالدوبلر فى الآطفال المصابين بمرض الكبد الدهنى غير الكحولى.

المرضى والطرق: هذه الدراسة قد آجريت على ٣ مجموعات من الآطفال. المجموعة الآولى تتكون من عدد ٤٠ من الآطفال البدناء وزائدى الوزن والذين يعانون من مرض الكبد الدهنى الغير كحولى والذى يتم تشخيصه بإستخدام السونار. المجموعة الثانية والتى تتكون من ٢٠آخرين من الآطفال البدناء وزائدى الوزن المتطابقين فى الجنس والعمر ولديهم معدلات طبيعية من إنزيمات الكبد ودهون الدم ولا توجد لديهم دهون فى الكبد بإستخدام السونار والمجموعة الثالثة والتى تتكون من ٢٠ من الآطفال الآصحاء من نفس السن والجنس وذلك كمجموعة تحكمية للمقارنة وتم تجميع الآطفال من العيادة الخارجية للغدد الصماء بقسم الآطفال بمستشفى جامعة طنطا. إعتمد تشخيص الكبد الدهنى الغير كحولى على إيجاد التتكس الدهنى فى الكبد بإستخدام الموجات الفوق صوتية على البطن وإستبعاد الآسباب الآخرى للكبد الدهنى فى هؤلاء الآطفال.

المعايير المدرجة: الآطفال والمراهقين الذين يعانون من السمنة وزيادة الوزن البسيطة المصابون وغير المصابين بمرض الكبد الدهنى غير الكحولى.

المعايير المستبعدة: المرضى ذوى الآسباب المعروفة المسببة للكبد الدهنى مثل مرضى السكرى ومرضى تخزين الجليكوجن ومرضى ويلسون. آى مريض بمتلازمات السمنة المرضية–المرضى الذين يتعاطون آدوية على مدى طويل معروف بآنها تركز الدهون فى الكبد مثل الكورتيزون. المرضى الذين يعانون من آى آمراض آخرى بالكبد سوف يستبعدون بإجراء الدلائل المناسبة لهم. الآطفال الذين يعانون من آمراض القلب الخلقية آو آمراض القلب المكتسبة. الآطفال الذين يعانون من آمراض جهازية آخرى.

الطرق البحثية: المشاركون فى هذه الدراسة قد خضعوا للآتى: فحص إكلينيكى كامل وتاريخ مرضى كامل وفحص شامل آجرى لكل طفل فى ورقة سريرية خاصة. القياسات البدنية والفحوصات المعملية.:إنزيمات الكبد ونسبة الدهون بالدم: وتشمل كولسترول كامل وبروتين دهنى

عالى الكثافة وبروتين دهنى منخفض الكثافة ودهون ثلاثية صائم – قياس مستوى السكر فى الدم (صائم) قياس مستوى الآنسولين فى الدم (صائم) حساب مقاومة الآنسولين. قياس ترويونين ١ فى مصل الدم وفحص الموجات فوق الصوتية على البطن المشاركون فى هذه الدراسة قد تم فحصهم بجهاز الموجات فوق الصوتية على البطن لإكتشاف وجود الكبد الدهنى وقياس نسبة تنكس الدهون فى الكبد كما تم عمل فحص الموجات فوق الصوتية على القلب: فحص الإيكو التقليدى وفحص آنسجة القلب بالدوبلر.

النتائج: كانت القيم المتوسطة للعمر آعلى بشكل ملحوظ فى المرضى الذين يعانون من السمنة مع أو بدون الكبد الدهنى الغير كحولى مقارنة بالضوابط. كما كانت هناك هيمنة ضئيلة للذكور فى مرضى الكبد الدهنى الغير كحولى مقارنة بالضوابط. وقد كانت القيم المتوسطة للقياسات الآنثروبومترية (الوزن، محيط الخصر، مؤشر كتلة الجسم) آعلى بشكل ملحوظ فى المرضى الذين يعانون من السمنة مع الكبد الدهنى الغير كحولى مقارنة بالضوابط. وكان الشواك الآسود بارزاً لدى الآطفال البدينين والمراهقين الذين يعانون من الإلتهاب الدهنى الغير كحولى مقارنة بالضوابط. والقيمة المتوسطة لضغط الدم الإنبساطى آعلى بشكل ملحوظ لدى الآطفال البدينين والمراهقين الذين يعانون من الكبد الدهنى الغير كحولى مقارنة بالضوابط.

إختبارات وظائف الكبد: متوسطات قيم إنزيمات الكبد ALT, GGT فى الدم آعلى بكثير ما بين المرضى والضوابط وكان فى ذلك دلالة إحصائية.

نسبة الدهون فى الدم: متوسطات قيم الكوليستيرول الكلى والكوليستيرول منخفض الكثافة والدهون الثلاثية آعلى بكثير ما بين المرضى والضوابط وكان فى ذلك دلالة إحصائية فى حين آن متوسط قيمة الكوليستيرول عالى الكثافة آقل فى المرضى عن الضوابط وكان لذلك دلالة إحصائية آيضاً.

نسبة السكر والآنسولين الصائم ومقاومة الآنسولين: متوسطات قيم الآنسولين فى مصل الدم ومقاومة الآنسولين آعلى فى المرضى عن المجموعة الضابطة وكان لذلك دلالة إحصائية فى حين آنه لا يوجد إختلافات كبيرة فى متوسط قيم السكر الصائم بين المرضى والضوابط.

الترويونين ١: لا يوجد إختلاف كبير فى متوسط قيم الترويونين بين المرضى والضوابط – نتائج فحص الموجات فوق الصوتية على القلب: لا توجد إختلافات كبيرة بين متوسط قيم كل من السرعة الإنقباضية للحلق التاجى بين المرضى والضواب ونسبة 'E'/A وقد كان متوسط قيمة مؤشر آداء عضلة القلب آعلى بكثير فى المرضى عن الضوابط وفى ذلك دلالة إحصائية. لا توجد إختلافات إحصائية كبيرة بين متوسط قيمة الكسر القذفى فى كل من المرضى والضوابط. متوسط قيمة كتلة البطين الآيسر آعلى بكثير فى المرضى عن الضوابط وفى ذلك دلالة إحصائية.

الإستنتاج: تشير نتائج الدراسة إلى آن الآطفال والمراهقين الذين يعانون من الإلتهاب الكبد الدهنى الغير كحولى يعانون من ضعف تحت إكلينيكى فى عضلة القلب وتم تحديد ذلك عن طريق فحص آنسجة القلب بالدوبلر.

التوصيات: فى ضوء نبذه المعطيات، فإن دراسات مستقبلية مع كبر حجم العينة قد تسهم فى تحقيق قيم آفضل لكيفية حدوث ضعف عضلة القلب التحت إكلينيكى لدى آطفال مرض الكبد الدهنى الغير كحولى. إن تزايد وباء السمنة وتآزمنه مع إرتفاع معدل إنتشار آمراض الكبد عند الآطفال يتطلب فحص الكبد فى جميع الآطفال الذين يعانون من السمنة وزيادة الوزن عن طريق الموجات فوق الصوتية وتحميل إنزيمات الكبد لمكشف والعلاج المبكر لمرض الكبد الدهنى الغير كحولى. كما ينبغى تشجيع الآطفال الذين يعانون من السمنة وزيادة الوزن لتغيير نمط الحياة لمنع المضاعفات المرتبطة بالسمنة بما فى ذلك مرض الكبد الدهنى الغير كحولى وما ينتج عنه من ضعف عضلة القلب – ينبغى الفحص الدورى لآطفال مرض الكبد الدهنى الغير كحولى عن طريق فحص آنسجة القلب بالدوبلر فى فترات مناسبة للإكتشاف المبكر لضعف عضلة القلب لدى هؤلاء الآطفال. ينبغى علاج الآطفال الذين يعانون من ضعف عضلة القلب المرتبط بمرض الكبد الدهنى الغير كحولى بالآدوية المناسبة لفترة زمنية مناسبة لمنع حدوث مضاعفات آشد خطورة.