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Estimation of Glomerular Filtration Rate Using Serum Cystatin C as an Early Predictor of Renal Insufficiency in Overweight/ Obese Children and Adolescents with Non-alcoholic Fatty Liver Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: NAFLD is a clinical spectrum ranging from steatosis (fatty infiltration) to steatosis with inflammation, necrosis, fibrosis and cirrhosis resembling alcoholic hepatitis in the absence of alcoholic abuse. The aim of this work was to determine early renal functional alterations in overweight / obese children and adolescents with NAFLD, as assessed by estimated glomerular filtration rate using cystatin C, and to evaluate its relation to the degree and various clinic-laboratory parameters of NAFLD.
Methods: This case control research included 60 overweight and obese children and adolescent. The Cases were classified into two equal groups: group 1: overweight or obese children and adolescents with NAFLD and group 2: overweight or obese children and adolescents without NAFLD. Twenty healthy age-and-sex matched children with BMI less than the 85th percentile for age and sex were chosen as controls.

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Results: There was significantly positive correlation among serum cystatin C and weight, BMI, Waist/Hip ratio, ALT, AST, cholesterol, Hip circumference, Fasting plasma insulin and Insulin resistance. There was significantly negative correlation among serum cystatin C and eGFR. There were significant negative correlations between eGFR and weight z score, BMI z score, hip circumference, waist/hip ratio, ALT, AST, cholesterol, fasting plasma insulin, insulin resistance and cystatin C.

Conclusions: Serum Cystatin C correlated significantly to the degree of hepatic steatosis. Values of eGFR were significantly lower in NAFLD patients compared to those without NAFLD and controls. The reduction in eGFR was correlated significantly with the degree of hepatic steatosis. There was a statistically significant negative correlation between serum cystatin C and eGFR. Levels of eGFR were significantly correlated with weight, BMI, W/H ratio, ALT, AST, cholesterol and insulin resistance.

Keywords: Glomerular filtration rate; serum cystatin C; renal insufficiency; overweight/ obese children; NALFD.

ABBREVIATIONS

ALT : Alanine Aminotransferase
AST : Aspartate Aminotransferase
BMI : Body Mass Index
BUN : Blood Urea Nitrogen
CKD : Chronic Kidney Disease
CRP : C-Reactive Protein
eGFR : Estimated Glomerular Filtration Rate
GFR : Glomerular Filtration Rate
HDL-C : High Density Lipoprotein-Cholesterol
HRP : Horseradish Peroxidase
LDL-C : Low Density Lipoprotein- Cholesterol
NAFLD : Nonalcoholic Fatty Liver Disease
QC : Quality Controls
WC : Waist Circumference

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is becoming one of the most serious complications of obesity in children and adolescents. NAFLD emerged as a leading cause of chronic liver disorder [1].

NAFLD is a clinical spectrum ranged from steatosis (fatty infiltration) to steatosis with inflammation, fibrosis, necrosis, and cirrhosis like alcoholic hepatitis in the absence of alcoholic abuse. The incidence of the NAFLD is rising as the childhood obesity increases [2].

Emerging research recommends that NAFLD cases have a higher risk of chronic renal disease (CKD), as determined by a decrease in estimated glomerular filtration rate (eGFR) and/or microalbuminuria. Identifying the processes that link NAFLD and CKD is a significant health burden for two diseases and cause the development of innovative CKD prevention and treatment options [3].

The underlying mechanisms remain unclear. The most plausible explanation for the connection between NAFLD and CKD is that they share metabolic risk factors, such as insulin resistance and atherogenic dyslipideamia [4].

The possible molecular mediators connecting NAFLD, and CKD might involve the systemic release of several pathogenic factors from the steatotic liver like pro-inflammatory cytokines, pro-coagulant and oxidative stress factors [5].

Standardized evaluations of renal function, like levels of blood urea nitrogen (BUN) and serum creatinine, significantly increased only after substantial kidney injury happens and then with a time delay [6].

Therefore, novel biomarkers are needed for humans usage when early recognition of kidney injury will affect treatment and possibly morbidity and mortality [7].

eGFR allows rapid recognition of renal function degradation, avoidance of future deterioration, and care of CKD cases [8].

Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells. In healthy individuals, Plasma cystatin C is removed by glomerular filtration and digested entirely by the proximal tubules [9]. It was proposed as a new sensitive endogenous biomarker for assessment of GFR. In contrast to serum creatinine, serum cystatin C is independent of age, gender, inflammation, muscle mass or serum bilirubin level [10].

Nevertheless, no information on the connection between NAFLD and decreased renal function in

children are known. Recognizing the impact of NAFLD on renal function in the young will enable doctors to better comprehend this link, hence facilitating the initiation of successful treatment strategies at an earlier age [3].

This prompted us to investigate the possibility of renal functional alterations in overweight /obese children and adolescents with NAFLD as determined by estimated GFR (using cystatin C). The aim of this work was determined early renal functional alterations in overweight / obese children and adolescents with NAFLD, as assessed by eGFR using cystatin C, and to evaluate its relation to the degree and various clinic-laboratory parameters of NAFLD.

2. PATIENTS AND METHODS

This case control research included 60 overweight (BMI between 85th-95th percentile for age and sex) and obese (BMI above 95th percentile for age and sex) children and adolescent selected from those attending the outpatient clinics of the Pediatric Department of Tanta University Hospital. The study was performed from May 2018 to May 2020.

Exclusion criteria were known disorders to cause fatty liver. syndromic obesity (Prader -willi, Alstrom syndrome), patients receiving long term drugs known to cause steatosis (glucocorticoids), evidence of chronic liver diseases (viral hepatitis and autoimmune hepatitis), and known history, clinical, laboratory or imaging signs of renal disease.

The participants were classified (according to the presence of fatty liver) into two equal groups: Group 1: overweight or obese children and adolescents had NAFLD and group 2: overweight or obese children and adolescents had no NAFLD. Twenty healthy age-and-sex matched children with BMI less than the 85th percentile for age and sex were chosen as controls. Eligibility criteria included: no history of liver or renal diseases, normal abdominal ultrasound, and normal laboratory values.

All patients underwent to complete history taking, physical assessment (anthropometric measurements [body weight, height, BMI, waist circumference (WC)] and blood pressure) laboratory investigations, [fasting plasma insulin level, albumin/creatinine ratio, lipid profile, liver and renal function tests, serum cystatin C concentration and glomerular filtration rate] and abdominal ultrasound examination.

Assessment of serum cystatin C: By the quantitative sandwich enzyme immunoassay (ELISA technique).

Abdominal ultrasound examination: Full abdominal ultrasound examination was done for all participants using Toshiba Aplio device by a single operator. Grades of NAFLD were determined according to the degree of steatosis which diagnosed according to the following features [11].

2.1 Statistical Analysis

Statistical analysis was performed using SPSS v25 (IBM Inc., Chicago, IL, USA). Numerical data were represented as mean and standard deviation (SD) and were evaluated by paired Student's t- test for the same group. Categorical variables were represented as frequency and percentage (%). Linear Correlation coefficient (r) utilized for recognition of correlation between two numerical variables in one group. A two tailed P value < 0.05 was considered significant.

3. RESULTS

Table 1 shows insignificant difference in age, sex, clinical characteristics and height z score data between the studied cases and controls. There was a significantly increased in weight, BMI z score, waist, hip circumference and W/H ratio in NAFLD cases than controls. There was insignificantly different in height, weight, BMI z score, waist circumference, hip circumference and W/H ratio between NAFLD patients and those without NAFLD. There was a significant increase in weight, BMI z score, waist circumference, hip circumference and W/H ratio between those without NAFLD and controls. There was insignificantly different in height z score between those without NAFLD and controls.

There was increased serum level of ALT and AST in the NAFLD cases than those had no NAFLD and controls. There was not statistically difference found between the NAFLD patients and controls regarding values of bilirubin, alkaline phosphatase and prothrombin time. There was no difference found between those without NAFLD and controls regarding values of ALT and AST, bilirubin, alkaline phosphatase and prothrombin time. Mean values of cholesterol level showed significant increase in NAFLD cases than controls but there was insignificantly different between NAFLD and

those had no NAFLD groups. Mean values of HDL level showed significant decrease in NAFLD cases than controls but there was insignificantly different between NAFLD and those without NAFLD groups. Mean values of LDL level showed significant increase in NAFLD cases than controls but there was no significant difference between NAFLD and those without NAFLD groups. Mean values of triglycerides showed no significance difference between the studied groups Table 2.

There was insignificant difference between the studied cases and controls regarding fasting plasma glucose, microalbuminuria, blood urea and serum creatinine levels. There was a significantly increased in fasting plasma insulin level and insulin resistance in NAFLD cases than those had no NAFLD and controls. There was a significantly increased in fasting plasma insulin and insulin resistance in those had no NAFLD than controls. There was a significantly increased in cystatin C level in NAFLD cases than those had no NAFLD and controls. There was a significantly reduce of eGFR in NAFLD cases than those without NAFLD and controls. There was insignificantly different in cystatin C level and eGFR between those had no NAFLD and controls Table 3.

Table 1. Age, sex, clinical characteristics and anthropometric measurements of the studied cases and controls

		NAFLD (n=30)	Without NAFLD (n=30)	Controls (n=20)	P-value		
Age (years)		9.88±2.81	9.10±3.14	9.13±2.96	0.533		
Sex	Male	10(33.3%)	13(43.3%)	11(55.0%)	0.314		
	Female	20(66.7%)	17(56.7%)	9(45.0%)			
Clinical characteristics							
Systolic B.P(mm/Hg)		102.33±16.01	101.83±15.34	97.25±12.19	0.454		
Diastolic B.P (mm/Hg)		67.67±12.30	66.00±10.54	62.50±8.35	0.254		
Hypertension No		8	4	-			
Skin lesions No		6	3	-			
Hepatomegaly		7	-	-			
Splenomegaly No		-	-	-			
Edema No		-	-	-			
Ascites No		-	-	-			
Anthropometric measurements							
Height (z score)		0.92±1.43	0.79±1.67	0.64±1.05	0.797		
Weight (z score)		3.91±2.21	3.83±1.80	-0.08± (+0.67)	0.001*	P1	0.855
						P2	0.001*
						P3	0.001*
BMI (z score)		3.84±1.50	4.22±2.15	-0.27± (+0.73)	0.001*	P1	0.380
						P2	0.001*
						P3	0.001*
Waist circumference (cm)		93.88±18.42	84.68±19.34	47.30±14.75	0.001*	P1	0.051
						P2	0.001*
						P3	0.001*
Hip circumference (cm)		108.99±20.63	99.64±23.25	77.01±28.42	0.001*	P1	0.131
						P2	0.001*
						P3	0.001*
W/H ratio		0.86±0.05	0.87±0.05	0.63±0.10	0.001*	P1	0.692
						P2	0.001*
						P3	0.001*

*Data are presented as mean ± SD or frequency (%), * significant p>0.05, P1: NAFLD vs without NAFLD, P2: NAFLD vs controls, P3: Without NAFLD vs controls*

Table 2. Liver function tests of the studied patients and controls

	NAFLD(n=30)	Without NAFLD(n=30)	Controls (n=20)	P-value		
Total serum bilirubin (mg/dl)	0.51±0.15	0.55± 0.18	0.54±0.16	0.668		
ALT (U/L)	34.03±24.90	21.93± 9.28	19.80±9.27	0.005*	P1 P2 P3	0.007* 0.005* 0.664
AST (U/L)	29.63±11.98	24.00± 9.62	18.60±7.84	0.001*	P1 P2 P3	0.036* 0.001* 0.071
Alkaline phosphatase (U/L)	149.10±45.31	156.63±43.90	148.75±45.86	0.761		
PT (sec.)	11.34±1.27	11.28±1.34	11.58±1.25	0.719		
Serum albumin (g/dl)	4.2 ± 3.1	3.9± 2.8	4 ± 2.2	0.7		
Lipid Profile						
Cholesterol (mg/dl)	165.37±34.09	160.77±31.53	127.45±31.64	0.001*	P1 P2 P3	0.586 0.001* 0.001*
HDL (mg/dl)	50.53±14.69	51.28±13.80	70.90±15.55	0.001*	P1 P2 P3	0.843 0.001* 0.001*
LDL (mg/dl)	104.67±21.50	94.44±21.00	78.55±15.42	0.001*	P1 P2 P3	0.051 0.001* 0.007*
Triglycerides (mg/dl)	115.60±33.34	113.15±46.56	106.95±23.44	0.649		

*Data are presented as mean ± SD, * significant p>0.05, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, P1: NAFLD vs without NAFLD, P2: NAFLD vs controls, P3: Without NAFLD vs controls*

Table 3. Fasting plasma glucose, plasma insulin, insulin resistance, renal function tests, Cystatin C and estimated glomerular filtration rate of the studied patients and controls

	NAFLD (n=30)	Without NAFLD (n=30)	Controls (n=20)	p. value		
Fasting plasma glucose (mg/dl)	91.73±12.07	88.83±10.02	84.95±12.61	0.130		
Fasting plasma insulin (µU/L)	15.36±4.41	12.93±4.08	6.93±3.02	0.001*	P1 P2 P3	0.020* 0.001* 0.001*
Insulin resistance	4.57±0.70	3.94±0.89	1.47±0.75	0.001*	P1 P2 P3	0.003* 0.001* 0.001*
Renal function tests						
Blood Urea (mg/dl)	16.82±2.35	16.29±2.54	16.53±2.31	0.698		
Serum Creatinine (mg/dl)	0.77±0.11	0.75±0.10	0.75±0.10	0.537		
Microalbuminuria (mcg/mg)	6.82±3.29	6.40±2.71	6.10±2.59	0.189		
Cystatin C (mg/l)	0.71±0.09	0.68±0.03	0.67±0.02	0.037*	P1 P2 P3	0.047* 0.019* 0.554
eGFR (ml/min/1.73m^2)	114.10±14.15	118.47±5.89	120.45±4.82	0.046*	P1 P2 P3	0.041* 0.026* 0.481

*Data are presented as mean ± SD, * significant p>0.05, eGFR: Estimated glomerular filtration rate*

Table 4 indicates grades of hepatic fatty infiltration of NAFLD patients. Mean values of weight and BMI Z scores, waist circumference, hip circumference, W/H ratio, ALT and AST were higher with increasing the degree of steatosis. Mean values of cholesterol, HDL, LDL and microalbuminuria were higher with increasing degree of steatosis. Mean values of serum cystatin C were higher with increasing degree of steatosis. Mean values of eGFR were lower with increasing degree of steatosis. Mean values of fasting plasma insulin and insulin resistance were higher with increasing degree of steatosis.

There was significantly positive relationship among serum cystatin C and weight, BMI, Waist/Hip ratio, ALT, AST, cholesterol, Hip circumference, Fasting plasma insulin and Insulin resistance. There was significantly negative correlation between serum cystatin C and eGFR. While there was insignificant correlation between serum cystatin C and other studied data Table 5.

Table 4. Abdominal ultrasonographic grading of hepatic in NAFLD and Correlation between the degree of steatosis and the clinic-laboratory data (n=30)

Grades	**N**		**%**	
G I	19		63.33	
G II	8		26.67	
G III	3		10	
Total	**30**		**100.0**	
	G I (n=19)	**G II (n=8)**	**G III (n=3)**	**p. value**
Age	9.21±2.67	12.13±1.79	8.17±3.21	0.020
Systolic Bp	97.89±14.65	114.38±15.45	98.33±12.58	0.040
Diastolic Bp	64.21±11.46	75.00±11.95	70.00±13.23	0.048
Height Z score	1.02 ±1.41	0.48±0.89	1.42±2.83	0.561
Weight Z score	3.45±1.61	3.99±1.38	6.66±5.26	0.042*
BMI Z score	3.01±1.60	3.80±1.30	4.31±1.52	0.0 43*
Waist circumference	86.07±10.62	111.19±22.30	97.17±19.28	0.002*
Hip circumference	101.23±12.21	125.18±27.24	114.93±23.64	0.014*
W/H ratio	0.76±0.05	0.81±0.06	0.89±0.05	0.004*
ALT	22.47±10.00	49.13±32.04	67.00±26.21	0.001*
AST	26.47±11.06	32.13±12.71	43.00±5.20	0.042*
Total serum bilirubin	0.52±0.15	0.49±0.18	0.53±0.15	0.883
Alkaline phosphatase	148.32±44.93	157.88±44.94	130.67±60.91	0.685
Prothrombin Time	11.42±1.23	11.23±1.41	11.17±1.63	0.915
Cholesterol	138.21±36.36	164.13±34.98	182.33±13.65	0.015*
Triglycerides	105.25±25.46	120.75±35.75	130.33±36.56	0.030
HDL	52.58±17.16	47.13±9.80	34.67±5.77	0.001*
LDL	101.00±18.32	114.13±27.52	122.67±23.25	0.008*
Blood Urea	16.71±2.25	16.64±2.69	18.00±2.65	0.670
Serum Creatinine	0.76±0.10	0.79±0.14	0.90±0.10	0.138
Fasting plasma glucose	90.26±14.25	95.50±5.98	91.00±9.00	0.601
Fasting plasma insulin	13.35±3.88	17.93±2.78	21.28±1.50	0.001*
Insulin resistance	4.32±0.67	4.81±0.48	5.54±0.26	0.007*
Microalbuminuria	7.84±2.50	10.44±4.22	21.67±11.55	0.001*
Serum Cystatin C	0.66±0.02	0.77±0.07	0.91±0.01	0.001*
GFR	122.84±3.52	104.38±10.47	84.67±1.53	0.001*

*Data are presented as mean ± SD, * significant p>0.05, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GFR: glomerular filtration rate*

Table 5. Correlation between serum Cystatin C levels and the studied clinico-laboratory data

Variables	Cystatin C	
	r	P-value
Age	0.131	0.489
Systolic Bp	0.236	0.209
Diastolic Bp	0.313	0.092
Height Z score	-0.008	0.965
Weight Z score	0.451	0.012*
BMI Z score	0.575	0.001*
Waist circumference	0.217	0.096
Hip circumference	0.563	0.001*
Waist/Hip ratio	0.486	0.006*
ALT	0.755	0.001*
AST	0.577	0.001*
Total serum bilirubin	0.045	0.813
Alkaline phosphatase	-0.112	0.554
Prothrombin time	-0.131	0.492
Cholesterol	0.473	0.002*
Triglyceride	0.521	0.003
HDL	-0.199	0.292
LDL	0.175	0.356
Blood Urea	0.134	0.480
Serum Creatinine	0.416	0.122
Fasting plasma glucose	0.168	0.376
Fasting plasma insulin	0.643	0.001*
Insulin resistance	0.577	0.001*
Microalbuminuria	0.782	0.241
GFR	-0.996	0.001*

** Significant p>0.05, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GFR: glomerular filtration rate*

Table 6. Correlation between eGFR levels and the studied clinico- laboratory data

Variables	eGFR	
	r	P- value
Age	-0.156	0.411
Systolic Bp	0.411	0.164
Diastolic Bp	0.164	0.080
Height Z score	0.003	0.887
Weight Z score	-0.887	0.016*
BMI Z score	-0.016	0.001*
Waist circumference	-0.342	0.127
Hip circumference	-0.582	0.001*
Waist/Hip ratio	-0.001	0.003*
ALT	-0.001	0.001*
AST	-0.580	0.001*
Total serum bilirubin	0.001	0.833
Alkaline phosphatase	0.833	0.585
Prothrombin time	0.585	0.488
Cholesterol	-0.488	0.005*
Triglyceride	0.359	0.179
HDL	0.005	0.308
LDL	0.308	0.338
Blood Urea	0.338	0.523
Serum Creatinine	0.523	0.035
Fasting plasma glucose	0.035	0.302

Variables	eGFR	
	r	P- value
Fasting plasma insulin	-0.302	0.001*
Insulin resistance	-0.575	0.001*
Microalbuminuria	0.081	0.257
Cystatin C	-0.996	0.001*

** Significant p>0.05, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GFR: glomerular filtration rate*

There were significantly negative correlations between eGFR and weight z score, BMI z score, hip circumference, waist/hip ratio, ALT, AST, cholesterol, fasting plasma insulin, insulin resistance and cystatin C. While there was insignificant correlation among eGFR and other studied data Table 6.

4. DISCUSSION

Emerging data suggest that individuals with NAFLD have an increased risk of chronic kidney disease (CKD), as measured by a reduction in the estimated glomerular filtration rate (eGFR) and/or the presence of microalbuminuria [3].

The present work showed that there was an increase in liver enzymes (ALT, AST) concentrations in NAFLD cases than obese and control groups. Also, serum concentrations of ALT and AST were significant correlate with the degree of NAFLD.

In agreement, Agrawal et al. [12], observed that NAFLD patients had a ALT average value of 97.0±56.0 IU/l and AST average value of 75.0±50 IU/l. Nevertheless, several investigations have identified no connection between AST and ALT levels and NAFLD [13].

In this study, there was insignificantly different between NAFLD cases and controls regarding serum bilirubin and alkaline phosphatase levels. This coincides with that reported by, Bandaru et al. [14] who found insignificantly different between NAFLD cases and control groups as regard serum bilirubin concentration. Though, Puri et al. [15] indicated that total bilirubin was increased in NAFLD cases and growing in proportion to the degree of liver disease. In another study, elevated serum alkaline phosphatase levels were significantly associated with NAFLD than those had no NAFLD.

Results of the current study showed that serum total cholesterol concentrations were greater in NAFLD and obese groups than controls. Also, there was a significantly increased in LDL level in NAFLD cases than controls with insignificantly different between NAFLD cases and those had no NAFLD. Levels of HDL were significant decrease in cases with and without NAFLD than controls. Consistently, Borai et al. [16] found that lipid profile factors were significant increase (except for HDL-cholesterol, that was reduced) in NAFLD patients in comparison to controls.

Our study showed increasing total cholesterol and LDL and decreasing HDL levels with developing the degree of hepatic steatosis. However, Paredes-Turrubiarte et al. [17] described insignificant differences in the values of lipid profile than all various NAFLD grades.

The current research demonstrated that there was a significantly increased in fasting insulin and insulin resistance (IR) values in NAFLD and those without NAFLD patients compared to controls. The increase in IR paralleled with the degree of fatty liver infiltration.

These findings were also corroborated with a description by Hegazy MA et al. [18] that revealed a direct correlation between insulin and HOMA-IR with NAFLD grades.

Regarding measurement of urine albumin, our study did not demonstrate statistically significant differences in urine albumin levels between the control and obese with or without NAFLD groups. However, there was a strong association between microalbuminuria value and hepatic steatosis severity.

Similarly, Lin et al. [19] found low grade albuminuria in middle-aged patients with NAFLD. In contrast, some studies showed significant albuminuria in adult NAFLD patients.

The findings of the present investigation showed that serum cystatin C levels of NAFLD patients ranged from0.64 to0.92 mg/l with a mean value of 0.71±0.09 mg/l .Cystatin C of patients without NAFLD ranged from0.65 to 0.76 mg/l with a mean of 0.68±0.03 mg/l .Cystatin C of controls ranged from 0.64 to 0.73 mg/l with a mean of

0.67±0.02 mg/l .It appears that there was a significantly increased in serum cystatin C levels in NAFLD cases than those had no NAFLD and controls. Also, there was insignificantly increased of serum cystatin C in obese children without NAFLD than the controls. This likely suggests that no significant underlying renal injury in those studied obese children.

This in line with studies that found no effect of obesity in renal function [20]. However, previous studies had stated that serum cystatin C concentrations were elevated in obese adults. [21] This may reflect early renal disease in them, and obesity is an independent risk for the growth of CKD in these individuals.

The present study also showed that serum cystatin C levels correlated significantly with the degree of NAFLD. eGFR assessed by cystatin C-based formula in our study revealed a statistically significant reduction in eGFR in NAFLD patients compared to obese subjects without NAFLD and controls.

According to our knowledge, this study was the first to investigate cystatin C and cystatin C –based estimation of GFR in NAFLD children and adolescents as no data are available in children.

In the present study, a comparable eGFR results were observed between subjects without NAFLD and healthy children. This may indicate lack of detectable renal injury in the studied overweight/obese children.

Studies concerning eGFR variations in obese and normal weight children are conflicting. Some research indicate that obese children have a decreased eGFR [22] or no differences [20].

The finding that the decline in eGFR as the degree of NAFLD (as detected by ultrasonography) advancing was obvious in our study. Machado et al. [23] noticed that the occurrence and intensity of lobular inflammation in the liver correlated inversely with eGFR in obese patients with NAFLD.

Research by marawan et al. [24] proved that Cystatin C offered more effective outcomes than Cr in abnormal GFR assessments in comparison to 99 mTc diethylenetriamine Penta acetic acid (r=0.526, p=0.001).

There are a number of GFR measuring models, however none is recognised as the gold standard for GFR computation [25]. It is acknowledged that serum cystatin C provides more reliable GFR results than Cr-based techniques because it is less impacted by muscle mass and nutrition [26].

Roos et al. [27] analysed 24 studies involving cystatin C and Cr, enrolled 2,007 members. They discovered that at a 95% confidence interval and based on the Moses-Littenberg linear regression model, cystatin C was more interoceptive in detecting renal impairment than other biomarkers than Cr [cystatin C: 3.99 (3.41-4.57) versus Cr: 2.79 (2.12-3.4)].

In the present study, eGFR was significantly correlated with cystatin C. Therefore, serum cystatin C level could be assumed a good factor for predicting significant renal impairment in children with NAFLD. In agreement, Momtaz et al. [28] demonstrated a significantly negative association between cystatin C and GFR.

Correlation analysis, in our study, showed a significant association between eGFR (using cystatin C –based formula) and insulin resistance, total cholesterol, transaminases (ALT and AST) and waist/hip ratio.

These measured variables are considered risk factors contributing to the impairment of kidney function in the studied children and adolescents with NAFLD. This finding is supported by other authors studying NAFLD in children [29] and adults [30].

Finally, the positive result from our study indicates the capability of cystatin C measurement to detect changes in renal function in children had NAFLD and clearly valides the reliability of the cystatin C-based GFR-estimate.

5. CONCLUSIONS

Serum Cystatin C level was significant increases in NAFLD cases than those without NAFLD and controls. Serum Cystatin C correlated significantly to the degree of hepatic steatosis. Values of eGFR were significant decrease in NAFLD cases than those had no NAFLD and controls. The reduction in eGFR was correlated significantly with the degree of hepatic steatosis. There was a significantly negative correlation between serum cystatin C and eGFR. Levels of eGFR were significantly correlated with weight, BMI, W/H ratio, ALT, AST, cholesterol and insulin resistance.

ETHICAL APPROVAL AND CONSENT

The study was performed after approval from the Ethical Committee Tanta University. An informed written consent was obtained from the parents.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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